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IMMEDIATE MESSAGE TO:

1. Directors of Pharmacy
2. Medical Directors NHS Boards

28 November 2022

Dear Healthcare Professional

CAS DRUG ALERT – No. 14 – Immediate Effect - Treatments For Highest Risk Non-Hospitalised Patients (Adults And Children) With Covid-19

Please see attached CMO letter about the updated UK-wide policy (with Immediate Effect) to provide access to antiviral treatment options for eligible individuals, based on a review of the latest available evidence.

This policy applies to non-hospitalised patients with COVID-19 who are symptomatic and showing no evidence of clinical recovery and covers the following treatment options: • First-line: nirmatrelvir plus ritonavir (antiviral) • Second-line: remdesivir (antiviral) • Third-line: molnupiravir (antiviral) Sotrovimab (neutralising monoclonal antibody (nMAB)): may be considered by exception where the available antiviral treatments above are contraindicated or determined to be unsuitable following multi-disciplinary team (MDT) assessment. Further information on selecting the most appropriate treatment can be found in the Clinical Guide which accompanies this policy. Combination treatment with an antiviral and a nMAB is NOT routinely recommended. Where patients are ineligible for treatment under this policy, recruitment to the PANORAMIC trial, which is building the evidence for novel oral antivirals in a broader cohort of at risk patients, should be supported

Could Medical Directors and Directors of Pharmacy please forward this alert to relevant healthcare professional colleagues, including any clinicians and clinical teams involved in treatment for Highest Risk Non-Hospitalised Patients (Adults and Children) with Covid-19.

Thank you for your co-operation.

Yours sincerely

Grace Jamieson
Medicines Policy Team

Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2022/014 28 November 2022

Treatments for Highest Risk Non-Hospitalised Patients (Adults and Children) with COVID-19

Summary

The published UK-wide policy has been updated, effective with immediate effect, to provide access to antiviral treatment options for eligible individuals, based on a review of the latest available evidence.

Treatment options under the policy for eligible patients are now:

- First-line**:** nirmatrelvir/ritonavir (Paxlovid), administered orally
- Second-line: remdesivir, administered intravenously over three sequential days
- Third-line: molnupiravir, administered orally

Exceptionally, sotrovimab may be considered where the above treatments are deemed unsuitable and its use is supported following MDT assessment.

Non-hospitalised patients are eligible for treatment under the policy if:

- SARS-CoV-2 infection is confirmed by either:
  - Lateral flow test (ideally registered via gov.uk or NHS 119)

  OR
  - Polymerase chain reaction (PCR) testing

  AND
- They are symptomatic with COVID-19 and are showing no signs of clinical recovery

  AND
- The patient is a member of a 'highest risk' group (as defined in the Department of Health and Social Care)

Eligible children and adolescents may only be considered for treatment with remdesivir (of all ages weighing 40kg and above) or sotrovimab (for those aged 12 years and above AND weighing 40kg and above). For paediatric/adolescent patients paediatric multi-disciplinary

team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.

Further details, including medicine specific guidance, may be found in the clinical policy. Further information on selecting the most appropriate treatment may be found in the accompanying clinical guide.

Action

Commissioned COVID Medicine Delivery Units (CMDUs) and their devolved administration equivalents are asked to:

1. Consider prescribing an antiviral to non-hospitalised patients eligible under the published policy, noting that the groups of adult and paediatric patients potentially eligible under the policy are defined within the report published by the Department of Health and Social Care (DHSC). Exceptionally, sotrovimab may be considered where the above treatments are determined to be unsuitable and supported following MDT assessment.

   Eligible children and adolescents may only be considered for treatment with remdesivir (of all ages weighing 40kg and above) or sotrovimab (for those aged 12 years and above AND weighing 40kg and above). For paediatric/adolescent patients, paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.

2. In England, continue to use Blueteq to confirm pre-authorisation for individual patients.

3. Note that neither nirmatrelvir/ritonavir nor molnupiravir are recommended during pregnancy. All individuals of childbearing potential who are prescribed molnupiravir should be advised to use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir. The 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.

4. Ensure that any patients who receive a COVID antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 (available 9:00am to 5:00pm, Monday to Friday, excluding bank holidays) so that they can be followed up. For more information, go to https://www.medicinesinpregnancy.org/COVID-19-Antivirals-Pregnancy-Registry/.

5. **Noting the important role of surveillance, treating clinicians are asked to support testing and / or data requirements as recommended under country specific or UK wide surveillance programmes, where laboratory capacity and resourcing allows.** Sequencing is an important part of surveillance activities to monitor for the development of new variants and drug resistance. Genotype results do not form part of the eligibility criteria for any treatment under this policy and treatment should not be delayed pending these results.

6. Ensure adequate arrangements are in place to provide dosing adjustment where nirmatrelvir/ritonavir is prescribed for patients with stage 3 chronic kidney disease (CKD

3). This will typically require dispensing pharmacies to remove tablets from packs and ensure clear explanatory advice is provided to the patient.

7. Ensure letters to primary care, and other handovers of clinical care, explicitly record the treatment that has been given, together with the dose and date of administration. The following **SNOMED codes should be used to support evaluation and to inform subsequent treatment decisions**:

   Provision of nirmatrelvir/ritonavir

   Procedure code: 427314002 |Antiviral therapy (procedure)|

   Presentation:
   - 30 tablet pack - 40325111000001108

   Administration of remdesivir

   Procedure code: 47943005 |Administration of anti-infective agent (procedure)|

   Presentation:
   - 100mg powder for solution for infusion, 1 vial - 38376311000001103

   Provision of molnupiravir

   Procedure code: 427314002 |Antiviral therapy (procedure)|

   Presentation:
   - Molnupiravir 200mg capsules, 40 capsule – 40251211000001109

   Administration of sotrovimab

   Procedure code: 47943005 |Administration of anti-infective agent (procedure)|

   Presentation:
   - Sotrovimab 500mg/8ml solution for infusion vials – 40219011000001108

8. Adhere to the guidance which has been developed by the Specialist Pharmacy Service (SPS) to support the administration of antivirals or monoclonal antibodies.

9. Provide regular stock updates to trust / hospital and regional pharmacy procurement lead / chief pharmacists. Providers should enter the products onto stock control and prescribing systems as described below:

   - Paxlovid, nirmatrelvir (150mg tablets) plus ritonavir (100mg tablets), 30 tablet pack
   - Remdesivir 100mg powder for concentrate for solution for infusion
   - Molnupiravir 200mg capsules, 40 capsules
   - Sotrovimab 500mg/8ml solution for infusion vials

Product Details

Molnupiravir (Lagevrio) is an oral (capsule) based antiviral treatment supplied by Merck Sharp and Dohme (UK) Limited. It works by stopping the virus that causes COVID-19 from growing and spreading. It has a conditional market authorisation in both Great Britain (under the Medicines and Healthcare products Regulatory Authority (MHRA)) and in Northern Ireland (under the European Medicines Agency (EMA)) for the treatment of mild to moderate coronovirus disease 2019 (COVID-19) in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness.

Nirmatrelvir plus ritonavir (Paxlovid) is a combination oral antiviral supplied by Pfizer that works by inhibiting a protease required for viral replication. It is supplied as a pack providing a five-day treatment course containing both nirmatrelvir (150mg tablets) and ritonavir (100mg tablets). Nirmatrelvir plus ritonavir has a conditional market authorisation in Great Britain (under the Medicines and Healthcare products Regulatory Authority (MHRA)), and in Northern Ireland (under the European Medicines Agency (EMA)), 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 (Veklury) is supplied by Gilead. Delivered intravenously, it has market authorisations for use as a treatment for COVID-19 in both Great Britain (under the Medicines and Healthcare products Regulatory Authority (MHRA)) and in Northern Ireland (under the European Medicines Agency (EMA)) for 1) adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), and 2) 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.

Sotrovimab (Xevudy) is supplied by GlaxoSmithKline and Vir Biotechnology. Delivered intravenously, sotrovimab has a conditional marketing authorisation in Great Britain (England, Scotland and Wales) and a marking authorisation in Europe (under the European Medicines Agency) for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection. Access to sotrovimab in Northern Ireland is through a Regulation 174 approval or the European Medicines Agency marketing authorisation.

Co-Administration

For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

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 record that an antiviral has been given, together with the dose and date of administration. SNOMED codes (see action section, above) should be used in discharge letters to primary care.

Healthcare professionals are asked to report any suspected adverse reactions (including congenital malformations and or neurodevelopmental delays following treatment during pregnancy) via the United Kingdom Yellow Card Scheme www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Distribution

- NHS Trusts (NHS boards in Scotland and Wales)
- Primary Care (including out of hours providers)
- Community Pharmacies
- National / Regional Medical Directors
- National / Regional Chief Pharmacists
- Lead/Senior Pharmacists and Regional Procurement Pharmacy Leads
- Trust/Hospital Pathology Directors (to circulate to pathology networks and laboratory staff)
- Trust / Hospital Medical Directors (to circulate to medical and nursing staff managing admitted patients infected with COVID-19)

Enquiries

England
Enquiries from NHS trusts in England should in the first instance be directed to your trust pharmacy team who will escalate issues to the Regional Chief Pharmacist and national teams if required. Further information can be requested from the dedicated email address: england.spoc-c19therapeutics@nhs.net.

Northern Ireland
Enquiries from hospitals in Northern Ireland should in the first instance be directed to your hospital pharmacy team who will escalate issues to the Regional Pharmaceutical Procurement Service or Pharmaceutical Directorate at the Department of Health if required Further information can be obtained by contacting RPHPS.Admin@northerntrust.hscni.net

Scotland
Enquiries from hospitals in Scotland should in the first instance be directed to your hospital pharmacy team who will escalate issues to either NHS National Procurement or the Scottish Government's Medicines Policy Team if required. Contact should be made using the following emails: nss.nhssmedicineshortages@nhs.scot or medicines.policy@gov.scot

Wales
Enquiries from hospitals in Wales should in the first instance be directed to the health board's Chief Pharmacist who will escalate issues to the Pharmacy and Prescribing Team at Welsh Government if required. Enquiries to the Welsh Government should be directed to: COVID-19.Pharmacy.Prescribing@gov.wales.

Rapid Policy Statement

Interim Clinical Commissioning Policy: Treatments for non-hospitalised patients with COVID-19

Published on: 28 November 2022

Effective from: 28 November 2022

Commissioning position

The following treatments are recommended to be available for non-hospitalised adults and children with COVID-19 treated in accordance with the criteria set out in this document.

This policy applies to non-hospitalised patients with COVID-19 who are symptomatic and showing no evidence of clinical recovery and covers the following treatment options:

- First-line**:** nirmatrelvir plus ritonavir (antiviral)
- Second-line: remdesivir (antiviral)
- Third-line: molnupiravir (antiviral)

Sotrovimab (neutralising monoclonal antibody (nMAB)): may be considered by exception where the available antiviral treatments above are contraindicated or determined to be unsuitable following multi-disciplinary team (MDT) assessment.

Further information on selecting the most appropriate treatment can be found in the Clinical Guide which accompanies this policy.

Combination treatment with an antiviral and a nMAB is **NOT** routinely recommended.

Where patients are ineligible for treatment under this policy, recruitment to the PANORAMIC trial, which is building the evidence for novel oral antivirals in a broader cohort of at risk patients, should be supported.

Background

Antiviral medications inhibit viral replication and prevent progression of infection. 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.

Evidence suggests that antivirals significantly improve clinical outcomes in non-hospitalised patients with COVID-19 who are at high risk of progression to severe disease and/or death. The World Health Organization (WHO) updated its 'Therapeutics and COVID-19: Living Guideline'

on 16 September 2022 and the WHO recommendations (conditional and strong) have been considered in the development of this policy. (WHO, September 2022).

1) Nirmatrelvir/ritonavir

Evidence

Final results from the EPIC HR trial indicate that the dual oral antiviral nirmatrelvir/ritonavir 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).

Marketing authorisation

Nirmatrelvir/ritonavir administered orally has conditional marketing authorisation in Great Britain (England, Scotland and Wales) 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. Access to nirmatrelvir/ritonavir in Northern Ireland for this indication is through a Regulation 174 approval or the European Medicines Agency marketing authorisation.

2) Remdesivir

Evidence

A three-day intravenous course of remdesivir within 7 days of COVID-19 symptom onset for non-hospitalised patients with 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).

Marketing authorisation

Remdesivir delivered intravenously has conditional marketing authorisation for use as a treatment for COVID-19 in Great Britain (under the Medicines and Healthcare Products Regulatory Authority (MHRA)) and a full marketing authorisation in Northern Ireland (under the European Medicines Agency (EMA)) for the following indications:

- treatment of COVID-19 in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), for a treatment duration of 5-10 days.
- 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.

3) Molnupiravir

Evidence

Final results from the Phase 3 MOVe-OUT trial show that the oral antiviral molnupiravir administered within 5 days of COVID-19 symptom onset to high-risk, non-hospitalised patients resulted in a relative risk reduction of 30% in the composite primary outcome of hospitalisation or death at day 29 (Bernal et al, 2021). The WHO has made a conditional recommendation for molnupiravir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022).

Marketing authorisation

Molnupiravir administered orally has conditional marketing authorisation in Great Britain

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

Sotrovimab

Evidence

In relation to nMABs, interim analysis of the COMET-ICE trial, which studied sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression, showed a relative risk reduction in hospitalisation or death at day 29 by 85% in patients treated with sotrovimab compared with placebo (Gupta et al, 2021a). The final analysis of this study has shown a relative risk reduction in hospitalisation or death at day 29 by 79% in patients treated with sotrovimab compared with placebo (Gupta et al, 2021b). In September 2022, the WHO made a strong recommendation against the use of sotrovimab in non-hospitalised patients (WHO).

Having taken account of existing evidence and pharmacokinetic and pharmacodynamic data (PK/PD), sotrovimab should only be used as described in this policy.

Marketing authorisation

Sotrovimab delivered intravenously has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for the treatment of symptomatic adults, and adolescents (aged 12 years and over and weighing at least 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. Access to sotrovimab in Northern Ireland for the above indication is through a Regulation 174 approval or via the European Medicines Agency marketing authorisation.

Eligibility criteria

Non-hospitalised patients are eligible for treatment with any one of the four medicines if:

- SARS-CoV-2 infection is confirmed by either:
    - Lateral flow test (registered via gov.uk or NHS 119) OR
    - Polymerase chain reaction (PCR) testing

AND

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

AND

- The patient is a member of a ‘highest’ risk group (as defined in the Department of Health and Social Care commissioned Independent Advisory Group Report)

Available treatment options for eligible patients are:

- First-line**:** nirmatrelvir/ritonavir (antiviral)
- Second-line: remdesivir (antiviral)
- Third-line: molnupiravir (antiviral)

  Sotrovimab (nMAB) (by exception) following MDT assessment

Further information on selecting the most appropriate treatment can be found in the accompanying Clinical Guide associated with this policy.

Combination treatment with an antiviral and nMAB is **NOT** routinely recommended.

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.

Remdesivir may be used in all children weighing over 40kg in patients with no supplemental oxygen requirement.

Children and adolescents aged 12-17 years inclusive may be considered for treatment with sotrovimab.

For paediatric/adolescent patients, paediatric MDT assessment should be used to determine clinical capacity to benefit from a treatment. Additional criteria can be found in the Department of Health and Social Care commissioned Independent Advisory Group Report.

Exclusion criteria

Where patients are ineligible for treatment under this policy, recruitment to the PANORAMIC trial, which is building the evidence for novel oral antivirals in a broader cohort of at risk patients, should be supported.

Patients would not be eligible for treatment if any of the following apply:

- Requirement for hospitalisation for COVID-19
- New supplemental oxygen requirement specifically for the management of COVID-19 symptoms
- Known hypersensitivity reaction to the active substances or to any of the excipients of the medications below as listed in their respective Summary of Product Characteristics.

Nirmatrelvir/ritonavir

If the initial criteria above are met, patients may be considered for treatment with **nirmatrelvir/ritonavir** if:

- Treatment is commenced within 5 days of symptom onset[1]

AND

- The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease (CKD)[2]

AND

- Nirmatrelvir/ritonavir treatment has been deemed safe following guidance from the appropriate specialty team(s) – see the accompanying Clinical Guide for treatment with antivirals and nMABs

The following additional **exclusion criteria** apply if considering treatment with nirmatrelvir/ritonavir:

- Children aged less than 18 years
- Pregnancy
- The patient is taking any of the medications listed as ‘do not use’ in the Specialist Pharmacy Service (SPS) guidance for nirmatrelvir/ritonavir.

[1] Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated (treatment commencement beyond 5 days from symptom onset is off-label).
[2] Nirmatrelvir/ritonavir may be considered in non-hospitalised patients with stage 3 CKD, if providers can assure themselves that the required dose modification can be delivered safely. See the Summary of Product Characteristics and the section on dosing in the policy for more information

Remdesivir

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

- Treatment with nirmatrelvir/ritonavir is contraindicated or not possible

AND

- Treatment is commenced within 7 days of symptom onset.

The following additional **exclusion criteria** apply if considering treatment with remdesivir:

- Children weighing less than 40kg
- Estimated glomerular filtration rate (eGFR) <30 mL/min (except in patients with end-stage renal disease on haemodialysis)
- Alanine transaminase (ALT) ≥ 5 times the upper limit of normal.

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 outlined in the UK Clinical Commissioning Policy for remdesivir in patients hospitalised due to COVID-19.

Molnupiravir

If the initial criteria above are met, patients should only be considered for treatment with

molnupiravir if:

- Treatment with nirmatrelvir/ritonavir or remdesivir are contraindicated or not possible

AND

- Treatment is commenced within 5 days of symptom onset[1].

The following additional **exclusion criteria** applies if considering treatment with molnupiravir:

- Children aged less than 18 years
- Pregnancy.

Sotrovimab

If the initial criteria above are met and the above antiviral medicines are contraindicated or not deemed suitable patients may be considered for treatment with **sotrovimab** by exception if**:**

- Endorsement of treatment has been sought and approved by a relevant MDT

AND

- Treatment is delivered within 5 days of symptom onset[1].

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 in the context of the case-by-case basis described above.

The following additional **exclusion criteria** apply if considering treatment with sotrovimab:

- Children aged under 12 years
- Adolescents (aged 12-17) weighing less than 40kg.

Dose and administration

Nirmatrelvir/ritonavir

The recommended dose of nirmatrelvir/ritonavir 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/ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days. The remaining tablet of nirmatrelvir should be disposed of in accordance with local requirements.

Nirmatrelvir/ritonavir 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[1]. Clinicians should assure themselves that patients are able to swallow the oral tablets.

Refer to the Specialist Pharmacy Services guidance and University of Liverpool COVID-19 Drug Interactions Checker for further information.

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 hospitalisation 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

The recommended dose of remdesivir for this 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.

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

Molnupiravir

The recommended dose of molnupiravir is 800mg (four 200mg capsules) taken orally every 12 hours for 5 days. Treatment must not be extended beyond 5 days. Molnupiravir should be commenced as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset[1]. Clinicians should assure themselves that patients are able to swallow the oral capsules.

If a patient missed a dose within 10 hours of the time it is usually taken, they should take as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

To reduce the possibility of emerging resistance, patients should be advised to complete the whole course of treatment even if their symptoms improve and/or they feel better. If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with molnupiravir, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.

Sotrovimab

The recommended dose of sotrovimab is 500mg to be administered as a single intravenous infusion[3]. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset[1].

8mls of sotrovimab (62.5mg/ml) should be added to a 100ml pre-filled infusion bag containing 0.9% sodium chloride and administered over 30 minutes. Preparation and administration of sotrovimab should be initiated and monitored by a qualified healthcare provider using aseptic technique. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored post intravenous infusion according to local medical practice.

Refer to the Specialist Pharmacy Services institutional readiness document for further information on the handling, reconstitution and administration of the product. Sotrovimab should not be infused concomitantly in the same intravenous line with other medication.

Cautions

Please refer to the Summary of Product Characteristics (SmPC) for nirmatrelvir/ritonavir, remdesivir (Great Britain and Northern Ireland), molnupiravir and sotrovimab, for special warnings and precautions for use.

Nirmatrelvir/ritonavir

Nirmatrelvir/ritonavir has a risk of serious adverse reactions due to interactions with other medicinal products (see the SPS guidance for a list of these products).

Initiation of nirmatrelvir/ritonavir, 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, 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
- Loss of therapeutic effect of nirmatrelvir/ritonavir 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[4].

Remdesivir

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,

[3] No dose adjustment is recommended in patients with renal or hepatic impairment.
[4] Unless as part of a formal clinical trial.

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.

Patients receiving remdesivir in an outpatient setting should be monitored according to local medical practice.

Molnupiravir

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

Sotrovimab

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.

COVID-19 vaccines

Sotrovimab is 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 an nMAB is available at the following sites:

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

Pregnancy and women of childbearing potential

Clinicians should refer to the SmPCs for the relevant products for further information on use in pregnancy and women of childbearing potential. All healthcare professionals are asked to ensure that any patients who receive a COVID antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 (available 9:00am to 5:00pm, Monday to Friday, excluding bank holidays) so that they can be followed up. For more information, go to https://www.medicinesinpregnancy.org/COVID-19-Antivirals-Pregnancy-Registry/. Clinicians are advised to refer to the SmPC nirmatrelvir/ritonavir and molnupiravir for more information on use during pregnancy or lactation.

Nirmatrelvir/ritonavir

There are no human data on the use of nirmatrelvir/ritonavir during pregnancy to inform the drug-associated risk of adverse developmental outcomes, women of childbearing potential should avoid becoming pregnant during treatment with nirmatrelvir/ritonavir. Nirmatrelvir/ritonavir 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 nirmatrelvir/ritonavir.

Remdesivir

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

Molnupiravir

There are no data from the use of molnupiravir in pregnant women. Studies in animals have shown reproductive toxicity. Molnupiravir is **not recommended** during pregnancy. Individuals of childbearing potential should use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir.

Sotrovimab

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

Co-administration

Please see the SPS guidance for potential interactions involving nirmatrelvir/ritonavir.

There is no interaction expected between remdesivir, molnupiravir or sotrovimab and other commissioned treatments for COVID-19. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Please refer to other published UK clinical commissioning policies setting out available COVID-19 treatments here.

Safety reporting

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

Governance

Data collection requirement

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

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

Effective from

This policy will be in effect from 28 November 2022

Policy review date

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

Surveillance and service evaluation

There is an urgent need to generate more evidence and greater understanding around the use of antivirals and nMABs 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 antiviral and nMAB treatment; the impact of antiviral and nMAB treatment in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of antiviral and nMAB use, such as generation of new mutations and/or variants.

Treating clinicians are asked to ensure that all PCR tests undertaken as part of routine clinical care should do this through the hospital laboratory where these samples should be retained for sequencing. Please note that during times of high prevalence, labs will prioritise sending samples from clinical priority groups only. To aid with this, clinicians should ensure PCR samples from clinical priority groups are clearly labelled as such. Further serial sampling for specific patient groups may be requested as part of UKHSA genomic surveillance purposes, or country specific programmes.

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

Equality statement

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

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

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

References

1. Bernal AJ, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Non-hospitalised Patients [published online ahead of print, 2021 Dec 16]. N Engl J Med. 2021; 10.1056/NEJMoa2116044. doi: 10.1056/NEJMoa2116044

2. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med*. 2021;NEJMoa2116846. doi:10.1056/NEJMoa2116846

3. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 2021;10.1056/NEJMoa2107934. doi:10.1056/NEJMoa2107934

4. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022;10.1056/NEJMoa2118542. doi:10.1056/NEJMoa2118542

5. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of the Neutralizing SARS-CoV-“ Antibody Sotrovimab in Preventing Progression of COVID-19: A Randomized Clinical Trial. Preprint available at: https://www.medrxiv.org/content/10.1101/2021.11.03.21265533v1

6. World Health Organization (WHO), 2022. Therapeutics and COVID-19: Living guideline. Available at: Therapeutics and COVID-19: Living guideline (who.int)

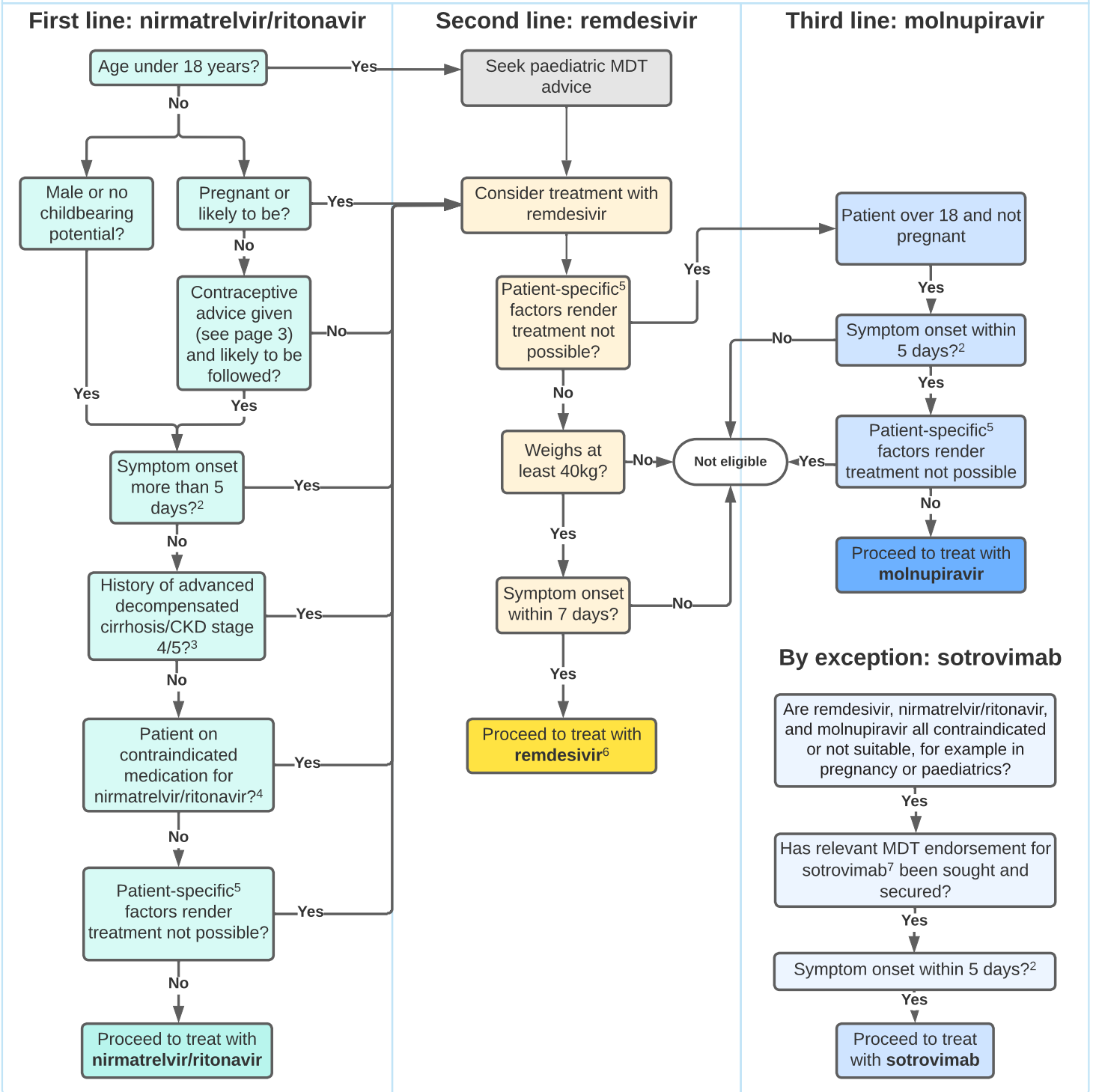
UK Interim Clinical Commissioning Policy

Therapies for symptomatic non-hospitalised adult and paediatric patients with COVID-19

Consider access to this clinical pathway under the following conditions:

- Onset of symptoms of COVID-19 within the last 5 days (for nirmatrelvir/ritonavir[1], molnupiravir and sotrovimab) or 7 days (for remdesivir), remains symptomatic and with no signs of clinical recovery
- SARS-CoV-2 infection is confirmed by either lateral flow test or PCR (registered via gov.uk or NHS 119)
- The patient is a member of a 'highest' risk group (as defined in the Department of Health and Social Care commissioned Independent Advisory Group report)
- The patient is not hospitalised for COVID-19 and is not requiring new supplemental oxygen specifically for the management of COVID-19 symptoms

Treatment options under the policy for eligible patients are now: First-line: nirmatrelvir/ritonavir(Paxlovid), administered orally. Second-line: remdesivir, administered intravenously over three sequential days. Third-line: molnupiravir, administered orally



[1] May also be known as paxlovid
[2] Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated (this would be off-label)
[3] Nirmatrelvir/ritonavir may be considered in patients with stage 3 CKD. Dose modification is required. See the Summary of Product Characteristics and the section on dosing in the policy for more information.
[4] See Specialist Pharmacy Service (SPS) guidance for nirmatrelvir/ritonavir and University of Liverpool COVID-19 Drug Interactions checker
[5] Patient-specific factors could include needle phobia and inability to receive intravenous treatment (for remdesivir) or swallowing difficulties with oral tablets (nirmatrelvir/ritonavir)
[6] Please see remdesivir specific exclusion criteria in the clinical commissioning policy
[7] Please see sotrovimab specific exclusion criteria in the clinical commissioning policy

Clinical Guide: Therapy characteristics when deciding on treatment choice

Use this guide to assist in decision making on which therapeutic option to use:

- Two products have similar relative risk reduction of reducing hospitalisation: nirmatrelvir/ritonavir and remdesivir
- Molnupiravir has a substantially lower level of efficacy - reserve when the others cannot be used
- Medicines availability will be monitored nationally and regionally, so unless otherwise directed do not consider supply issues in your decision making

Nirmatrelvir/ritonavir (Paxlovid)	Remdesivir (Veklury)	Molnupiravir (Lagevrio)
Antiviral (dual therapy)	Antiviral (monotherapy)	Antiviral (monotherapy)
Administered **orally**: 3 tablets twice a day for 5 days	Administered **intravenously**: one infusion every 24 hours for 3 days	Administered **orally**: 4 capsules twice a day for 5 days
Adults only (aged 18 years and over)	Adults and paediatric patients (weighing at least 40 kg)	Adults only (aged 18 years and over)
Evidence based on treatment within **5** days of symptom onset	Evidence based on treatment within **7** days of symptom onset	**Not recommended in pregnancy**
Not recommended in pregnancy	May be used in **pregnancy** where benefits of treatment outweigh risks	Breast-feeding should be discontinued during treatment and for 4 days after last dose
Breast-feeding should be discontinued during treatment and for 7 days after last dose	No specific advice on discontinuation of breast-feeding during treatment	May be used in severe liver and kidney disease (no dose adjustment recommended)
Contraindicated in severe liver and kidney disease	Not recommended in individuals with ALT ≥5 times the upper limit of normal or eGFR <30ml/min	No significant drug-drug interactions
Multiple significant drug-drug interactions (see SPS guidance)	No significant drug-drug interactions	30% Relative Risk Reduction of hospitalisation
88% Relative Risk Reduction of hospitalisation	87% Relative Risk Reduction of hospitalisation	

Sotrovimab (Xevudy)	
Neutralising monoclonal antibody	May be used in **pregnancy** although there is no safety data available
Administered **intravenously**: single infusion	No specific advice on discontinuation of breast-feeding during treatment
Adults and adolescents (aged 12 years and over and weighing at least 40kg)	No dose adjustment recommended in liver or renal impairment*
Evidence based on treatment within **5** days of symptom onset	No significant drug-drug interactions

For the key publications of trial results and licence click here

- Nirmatrelvir/ritonavir NEJM Feb 2022
- Nirmatrelvir/ritonavir SmPC
- Remdesivir NEJM Dec 2021
- Remdesivir SmPC
- Sotrovimab NEJM Nov 2021
- Sotrovimab SmPC
- Molnupiravir NEJM Dec 2021
- Molnupiravir SmPC

*there are limited/no data on the use of sotrovimab in patients with a creatinine clearance of <30ml/min/1.73m^2 and those with severe elevations ALT (5 - <10 x upper limit of normal)

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/1.73m^2 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

[1]This advice may also apply to individuals with other chromosomal abnormalities affecting immune competence.