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URGENT MESSAGE TO:

1. Directors of Pharmacy
2. Medical Directors NHS Boards

27 January 2022

Dear Healthcare Professional,

COVID THERAPEUTIC ALERT – ANTIVIRALS OR NEUTRALISING MONOCLONAL ANTIBODIES (NMABS) FOR NON-HOSPITALISED PATIENTS WITH COVID-19

Please see attached CMO letter about the updated UK-wide clinical commissioning policy (for implementation from 10 February 2022) which applies to non-hospitalised patients with COVID-19 who are symptomatic and showing no evidence of clinical recovery for dissemination to relevant healthcare professionals for onward transmission as detailed below:-

Could all Directors of Pharmacy please forward this alert to:-

- Community Pharmacists
- Hospital Pharmacists
- Primary Care Pharmacists

Please could Medical Directors arrange to forward this alert on to:-

- General Practitioners
- Accident & Emergency Departments
- Nurses
- Consultants in Communicable Diseases
- Directors of Public Health
- Relevant Clinics
- Chief Executives of NHS Board

Thank you for your co-operation.

Yours sincerely

IRENE FAZAKERLEY
Medicines Policy Team

Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2022/001 27 January 2022

Antivirals or neutralising monoclonal antibodies (nMABs) for non-hospitalised patients with COVID-19

Summary

Antiviral treatments inhibit the development and replication of viruses such as SARS-CoV-2. Neutralising monoclonal antibodies (nMABs) 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 neutralising monoclonal antibodies (nMABs) 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 updated UK-wide clinical commissioning policy **(for implementation from 10 February 2022)** applies to non-hospitalised patients with COVID-19 who are symptomatic and showing no evidence of clinical recovery. It provides the following treatment options:

- First-line**:** PF-07321332(Nirmatrelvir) plus Ritonavir (antiviral) OR Sotrovimab (nMAB), as clinically indicated
- Second-line: Remdesivir (antiviral)
- Third-line: Molnupiravir (antiviral)

Either PCR tests or formally registered positive lateral flow tests[1] (registered via gov.uk or via 119) may now be considered to meet the eligibility requirement on confirmed COVID infection.

Further information on selecting the most appropriate treatment can be found in the clinical guide associated with this policy.

Please also refer to the published (revised) policy for a summary of the supporting evidence, further details on eligibility (and exclusion criteria) and for additional guidance.

Action

[1] Individuals who are symptomatic, and those with a positive lateral flow test result are strongly encouraged to continue to take a confirmatory PCR test.

Providers locally commissioned to provide **C**OVID **M**edicines **D**elivery **U**nit (CMDU) services and any equivalent arrangements in the devolved nations are asked to:

1. **Consider prescribing and administering an antiviral or monoclonal antibody treatment in line with the published policy and associated clinical guide to non-hospitalised patients where*:***

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

    AND

    - Symptomatic with COVID-19[2] and showing no signs of clinical recovery

    AND

    - The patient is member of the 'highest' risk group as set out in the policy

    Children aged 12-17 years may only be considered for treatment with sotrovimab or remdesivir. For paediatric/adolescent patients (aged 12-17 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.

2. PF-07321332(nirmatrelvir) plus ritonavir, and molnupiravir, are **not 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 Paxlovid.

3. 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 so that they can be followed up. For more information, go to http://www.uktis.org/.

4. Where possible, take samples for relevant serology testing prior to planned treatment with sotrovimab. However, serology results are **not** a requirement for treatment with nMABs under the criteria specified in the policy.

5. **Support additional testing or data requirements where requested under country specific or UK wide surveillance programmes, in line with current guidance.**

[2] 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

6. Ensure clinicians prescribing remdesivir for individuals aged 12-17 years, as an off-label product, follow local governance procedures in relation to the prescribing of off-label medicines.

   Further guidance on the prescribing of off-label medicines can be found below:

   - https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities
   - https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines
   - https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Professional%20standards/Prescribing%20competency%20framework/prescribing-competency-framework.pdf

7. Ensure discharge letters to primary 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 PF-07321332(Nirmatrelvir) plus 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

   Administration of Sotrovimab

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

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

   Provision of Molnupiravir

   Procedure code: 427314002 |Antiviral therapy (procedure)|

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

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. In England, trusts who have not yet done so should register (by site) to participate in COVID-19 (and medicine) specific supply arrangements, via Blueteq™. Blueteq should also then be used to confirm pre-authorisation for individual patients and to capture a limited dataset essential for surveillance of antiviral resistance. Training for antimicrobial stewardship teams will be provided via webinar by UKHSA jointly with NHS England and NHS Improvement. HSC Trusts in Northern Ireland should liaise with the Regional Pharmaceutical Procurement Service to register interest. In Scotland, Health Board Directors of Pharmacy should notify NHS National Procurement if they wish to participate. Health Boards in Wales should notify the All Wales Specialist Procurement Pharmacist of their intention to participate.

10. Note that following initial nationally determined allocations to participating sites, ongoing supply will be replenished on the basis of relative use / need. Ongoing ordering will be through existing (business as usual) routes, supported by volume-based caps (reflecting estimated eligible patient volumes) if required.

11. Note that initial supply of COVID medicines may be available within 'emergency supply' packaging, which differs from the planned Great Britain (GB) packaging / labelling aligned to the product's GB licence (or the equivalent product packaging / labelling aligned to a Regulation 174 authorisation or European Medicines Agency marketing authorisation as applicable in Northern Ireland). **To preserve available supply, providers must ensure that packs with shorter use by dates are used first**.

12. 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:

    - PF-07321332(nirmatrelvir) (150mg tablets) plus Ritonavir (100mg tablets), 30 tablet pack
    - Remdesivir 100mg powder for concentrate for solution for infusion
    - Sotrovimab 500mg/8ml solution for infusion vials
    - Molnupiravir 200mg capsules, 40 capsules

Co-Administration

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

COVID treatments should not be infused concomitantly in the same IV line with other medications.

Monitoring, tracking and follow-up

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

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 the treatment that 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.

Department of Health & Social Care | The Scottish Government Riaghaltas na h-Alba | Llywodraeth Cymru Welsh Government | Department of Health An Roinn Sláinte Männystrie O Poustie | NHS

Rapid Policy Statement

Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies for non-hospitalised patients with COVID-19

Published on: 27 January 2022

Effective from: 10 February 2022

Commissioning position

The proposal is: Antivirals or neutralising monoclonal antibodies (nMABs) are recommended to be available as a treatment option through routine commissioning for non-hospitalised adults 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**:** PF-07321332 (may also be known as nirmatrelvir) plus ritonavir (Paxlovid, antiviral)[1] OR sotrovimab (nMAB), as clinically indicated
- Second-line: Remdesivir (antiviral)
- Third-line: Molnupiravir (antiviral)

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

Combination treatment with an nMAB and an antiviral 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

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

[1] This therapy will be referred to in this document as PF-07321332 (nirmatrelvir) plus ritonavir

Recent evidence suggests that antivirals and neutralising monoclonal antibodies (nMABs) 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 following products have conditional marketing authorisation for the treatment of non-hospitalised patients with COVID-19:

1) **PF-07321332 (nirmatrelvir) plus ritonavir**

Evidence

Final results from the EPIC HR trial indicate that the dual oral antiviral PF-07321332 (nirmatrelvir) plus 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.

Marketing authorisation

PF-07321332 (nirmatrelvir) plus 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 PF-07321332 (nirmatrelvir) plus ritonavir in Northern Ireland for this indication is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

Sotrovimab

Evidence

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).

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 conditional marketing authorisation.

2) **Remdesivir**

Evidence

A three-day intravenous course of remdesivir administered within 7 days of COVID-19 symptom onset to 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).

Marketing authorisation

Remdesivir delivered intravenously has conditional marketing authorisation in the UK for the following indications:

- treatment of COVID-19 in adults, and adolescents (aged 12 years and over and weighing at least 40kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), for a treatment duration of 5-10 days.

- treatment of COVID-19 in adults 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.

Use of remdesivir under this policy in children aged 12-17 years would be off-label.

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).

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 a licensing determination by the European Medicines Agency.

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:
  - Polymerase chain reaction (PCR) testing OR
  - Lateral flow test (registered via gov.uk or NHS 119)[2]

  AND
- Symptomatic with COVID-19[3] and showing no signs of clinical recovery

  AND
- The patient is a member of a 'highest' risk group (as defined in Appendix 1)

Available treatment options for eligible patients are:

- First-line**:** PF-07321332 (nirmatrelvir) plus ritonavir (antiviral) OR sotrovimab (nMAB), as clinically indicated
- Second-line: Remdesivir (antiviral)
- Third-line: Molnupiravir (antiviral)

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

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

[2] A confirmatory PCR test is recommended to support surveillance activities

[3] 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

Children aged 12-17 years may only be considered for treatment with sotrovimab or remdesivir. For paediatric/adolescent patients (aged 12-17 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.

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.

Exclusion criteria

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

PF-07321332 (nirmatrelvir) plus ritonavir

If the initial criteria above are met, patients may be considered for treatment with **PF-07321332 (nirmatrelvir) plus ritonavir** if:

- Clinical judgement deems that an antiviral is the preferred option

  AND

- Treatment is commenced within 5 days of symptom onset[4]

  AND

- The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 3-5 chronic kidney disease[5] [6]

  AND

- PF-07321332 (nirmatrelvir) plus 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 PF-07321332 (nirmatrelvir) plus ritonavir:

- Children aged less than 18 years
- Pregnancy
- The patient is taking any of the medications listed in Appendix 2 (see accompanying Clinical Guide for advice)

Sotrovimab

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

[4] 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)
[5] If PF-07321332 (nirmatrelvir) plus ritonavir is being considered for the treatment of patients with advanced decompensated liver cirrhosis or stage 3-5 chronic kidney disease, the treatment decision will need to be discussed with the responsible specialist clinical team
[6] Dose modification in stage 3 chronic kidney disease is not recommended in non-hospitalised patients

- Clinical judgement deems that an nMAB is the preferred option

  AND

- Treatment is delivered within 5 days of symptom onset[4]

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 previously received treatment with an nMAB and who meet the eligibility criteria above may receive a repeat course for a subsequent infective episode, if clinically appropriate.

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.

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

- Children aged under 12 years
- Adolescents (aged 12-17) weighing 40kg and under

Remdesivir

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

- Clinical judgement deems that an antiviral is the preferred option

  AND

- Treatment with PF-07321332 (nirmatrelvir) plus 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 aged under 12 years
- Adolescents (aged 12-17) weighing 40kg and under

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 with COVID-19.

Molnupiravir

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

- Treatment with PF-07321332 (nirmatrelvir) plus ritonavir, remdesivir AND sotrovimab are contraindicated or not possible

  AND

- Treatment is commenced within 5 days of symptom onset[4]

The following additional **exclusion criteria** applies if considering treatment with PF-07321332 (nirmatrelvir) plus ritonavir:

- Children aged less than 18 years
- Pregnancy

Dose and administration

PF-07321332 (nirmatrelvir) plus ritonavir

The recommended dose of PF-07321332 (nirmatrelvir) plus ritonavir is 300mg (two 150mg tablets) PF-07321332 (may also be known as nirmatrelvir) with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days. PF-07321332 (nirmatrelvir) plus 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[3]. Clinicians should assure themselves that patients are able to swallow the oral tablets.

Refer to the Specialist Pharmacy Services guidance 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 PF-07321332 (nirmatrelvir) plus ritonavir, 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[7]. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset[4].

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.

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[4]. Clinicians should assure themselves that patients are able to swallow the oral capsules.

[7] No dose adjustment is recommended in patients with renal or hepatic impairment.

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.

Cautions

Please refer to the Summary of Product Characteristics (SmPC) for PF-07321332 (nirmatrelvir) plus ritonavir, sotrovimab, remdesivir and molnupiravir for special warnings and precautions for use.

PF-07321332 (nirmatrelvir) plus ritonavir

PF-07321332 (nirmatrelvir) plus ritonavir has a risk of serious adverse reactions due to interactions with other medicinal products (see Appendix 2 for a list of these products).

Initiation of PF-07321332 (nirmatrelvir) plus ritonavir, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving PF-07321332 (nirmatrelvir) plus 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 PF-07321332 (nirmatrelvir), 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 PF-07321332 (nirmatrelvir) plus ritonavir.
- Loss of therapeutic effect of PF-07321332 (nirmatrelvir) plus 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 PF-07321332 (nirmatrelvir) plus ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

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.

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, 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).

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-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/. Clinicians are advised to refer to the SmPC for PF-07321332 (nirmatrelvir) plus ritonavir and molnupiravir for more information on use during pregnancy or lactation.

PF-07321332 (nirmatrelvir) plus ritonavir

There are no human data on the use of PF-07321332 (nirmatrelvir) plus ritonavir during pregnancy to inform the drug-associated risk of adverse developmental outcomes, women of childbearing potential should avoid becoming pregnant during treatment with PF-07321332 (nirmatrelvir) plus ritonavir. PF-07321332 (nirmatrelvir) plus 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 PF-07321332 (nirmatrelvir) plus ritonavir.

Sotrovimab

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

Remdesivir

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

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.

Co-administration

Please see Appendix 2 for potential interactions involving PF-07321332 (nirmatrelvir) plus ritonavir.

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

Corticosteroids

The UK CAS Alert on the use of corticosteroids in patients with COVID-19 can be found here. Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Please refer to the recommendation on the use of corticosteroids in the National Institute for Health and Care Excellence (NICE) Rapid Guideline on Managing COVID-19[8]. nMABs and antivirals should not be regarded as an alternative to corticosteroids.

Remdesivir

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

IL-6 inhibitors

The Clinical Commissioning Policies for the use of IL-6 inhibitors in hospitalised patients with COVID-19 who require supplemental oxygen can be found 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).

Clinical outcome reporting

Where available, hospitals managing COVID-19 patients are strongly encouraged to submit data through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as

[8] Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found here.

coordinated by the COVID-19 Clinical Information Network (CO-CIN) (https://isaric4c.net/protocols/).

Effective from

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

Policy review date

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

This policy will be reviewed, if required, as further data emerge on the population prevalence of the omicron variant and any impact it may have on the efficacy of COVID-19 therapies.

Surveillance and service evaluation

There is an urgent need to generate more evidence and greater understanding around the use of nMABs and antivirals in the treatment of patients with COVID-19. Both surveillance and service evaluation are necessary to gain knowledge around the following: factors of relevance in determining nMAB and antiviral treatment; the impact of nMAB and antiviral treatment in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of nMAB and antiviral use, such as generation of new mutations.

Treating clinicians are asked to ensure that all PCR tests undertaken as an inpatient and/or in the community where any patient who is receiving ongoing PCR testing as part of secondary care (for example, through an outpatient clinic) should do this through the hospital laboratory where these samples should be retained for sequencing. Further serial sampling for specific patient groups may be requested as part of UKHSA genomic surveillance purposes, or country specific programmes.

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

Equality statement

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

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

Definitions

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

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4. 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

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)[9].

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

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

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

Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who:
	  ○ Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin)
	  ○ Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals
	  ○ Not been vaccinated prior to transplantation
	• Non-transplant patients who have received a comparable level of immunosuppression
	• Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression

Patients with liver disease	• Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease). • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) • Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders (IMID)	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable disease on corticosteroids*, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID with stable disease on either corticosteroids*, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Immune deficiencies	• Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • Severe Combined Immunodeficiency (SCID) • Autoimmune polyglandular syndromes/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Primary immunodeficiency associated with impaired type I interferon signalling • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias) • Any patient with a secondary immunodeficiency

	receiving, or eligible for, immunoglobulin replacement therapy
HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 <350 cells/mm3 and stable on HIV treatment or CD4>350 cells/mm3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	• Multiple sclerosis • Motor neurone disease • Myasthenia gravis • Huntington's disease

Appendix 2: Drug-drug interactions involving PF-07321332 (nirmatrelvir) plus ritonavir[10]

Table 1 below lists medicines in alphabetical (by generic name) order indicating that concurrent prescribing of PF-07321132 (nirmatrelvir) plus ritonavir is not an appropriate option. This list is not comprehensive. If a medicine is not listed also check University of Liverpool COVID-19 Drug Interaction checker (https://covid19-druginteractions.org/checker).

The last column gives an indication of when advice to not prescribe together applies or where risks and benefits need careful consideration taking account of the practicalities of managing such patients in a CMDU or non-specialist setting.

Table 1: Alphabetical (by generic name) list of medicines indicating that PF-07321132 (nirmatrelvir) plus ritonavir is not an appropriate option to be prescribed together.

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Abemaciclib	Cancer	Consider risks and benefits
Acalabrutinib	Cancer	Consider risks and benefits
Alfuzosin	Prostate gland enlargement	Do not use
Aliskiren	High blood pressure (hypertension)	Do not use*
Amiodarone	Irregular heartbeats	Do not use
Apalutamide	Cancer	Consider risks and benefits
Apixaban	Treating or preventing blood clots	Do not use
Avanafil	Erection problems	Do not use
Bedaquiline	Infections	Consider risks and benefits
Bosentan	Pulmonary arterial hypertension	Do not use
Budesonide (inhaled, nasal spray)	Relieving asthma or COPD, or cold-like symptoms caused by allergic rhinitis	Consider risks and benefits
Carbamazepine	Epilepsy, nerve pain or trigeminal neuralgia	Do not use
Ceritinib	Cancer	Consider risks and benefits
Ciclosporin	Immunosuppressant	Do not use
Cisapride	Gastrointestinal motility problems	Do not use
Clonazepam	Epilepsy or anxiety	Do not use
Clopidogrel	Treating or preventing blood clots	Do not use*
Clozapine	Schizophrenia	Do not use
Colchicine	Gout	Do not use
Contraception, hormonal	Contraception	Consider risks and benefits
Dabigatran	Treating or preventing blood clots	Consider risks and benefits
Delamanid	Infections	Consider risks and benefits
Dexamphetamine	Narcolepsy or attention deficit hyperactivity disorder (ADHD)	Consider risks and benefits
Diazepam	Anxiety, muscle spasms or fits	Do not use
Digoxin	Irregular heartbeats or heart failure	Consider risks and benefits
Dihydroergotamine	Cluster headaches	Do not use
Disopyramide	Irregular heartbeats	Do not use*
Dronedarone	Irregular heartbeats	Do not use
Eletriptan	Migraines	Consider risks and benefits
Encorafenib	Cancer	Consider risks and benefits
Enzalutamide	Cancer	Consider risks and benefits
Eplerenone	Heart failure	Do not use*
Ergotamine	Cluster headaches	Do not use

[10] The information in this appendix is based on SPS guidance and is correct at the time of publication. Please refer to the SPS guidance for the most up to date information.

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Everolimus	Cancer or immunosuppressant	Do not use
Exviera (contains dasabuvir)	Hepatitis C	Consider risks and benefits
Fentanyl	Pain	Consider risks and benefits
Flecainide	Irregular heartbeats	Do not use
Flurazepam	Anxiety or problems sleeping	Do not use
Fluticasone propionate (inhaled or nasal spray)	Relieving asthma or COPD Cold-like symptoms caused by allergic rhinitis	Consider risks and benefits
Fostamatinib	Blood disorder	Consider risks and benefits
Fusidic acid (oral)	Infections	Do not use
Ibrutinib	Cancer	Consider risks and benefits
Illegal drugs	Substance abuse	Check advice in University of Liverpool COVID-19 Drug Interaction checker
Ivabradine	Heart failure or angina	Do not use*
Ketoconazole	Infections	Consider risks and benefits
Lamotrigine	Epilepsy or bipolar disorder	Consider risks and benefits
Lercanidipine	High blood pressure (hypertension)	Do not use*
Letermovir	Transplant	Consider risks and benefits
Levothyroxine	Underactive thyroid (hypothyroidism)	Consider risks and benefits
Lomitapide	Lowering cholesterol	Do not use
Lurasidone	Schizophrenia	Do not use
Maviret (contains glecaprevir and pibrentasvir)	Hepatitis C	Do not use
Methadone	Heroin dependence	Consider risks and benefits
Methylphenidate	Narcolepsy or attention deficit hyperactivity disorder (ADHD)	Consider risks and benefits
Midazolam	Epilepsy	Do not use
Neratinib	Cancer	Do not use
Pethidine	Pain	Do not use
Phenobarbital	Epilepsy	Do not use
Phenytoin	Epilepsy	Do not use
Pimozide	Schizophrenia	Do not use
Piroxicam	Pain	Do not use
Propafenone	Irregular heartbeats	Do not use
Propoxyphene	Analgesics	Do not use
Quetiapine	Bipolar disorder, depression, schizophrenia	Do not use
Quinidine	Antiarrhythmic	Do not use
Ranolazine	Heart failure or angina	Do not use
Rifabutin	Infections	Consider risks and benefits
Rifampicin	Infections	Do not use
Riociguat	Pulmonary arterial hypertension	Consider risks and benefits
Rivaroxaban	Treating or preventing blood clots	Do not use
Rosuvastatin	Lowering cholesterol	Consider risks and benefits
Salmeterol (inhaled)	Relieving asthma or COPD	Do not use
Sildenafil	Erection problems or pulmonary arterial hypertension	Do not use
Simvastatin	Lowering cholesterol	Do not use
Sirolimus	Immunosuppressant	Do not use*
Sodium fusidate (oral)	Infections	Do not use
St. John's Wort (Hypericum perforatum)	Herbal medicine	Do not use
Tacrolimus	Immunosuppressant	Do not use

Specific medicines	Medicine used for	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Tadalafil	Erection problems or pulmonary arterial hypertension	Do not use
Theophylline	Relieving asthma or COPD	Consider risks and benefits
Ticagrelor	Treating or preventing blood clots	Do not use*
Vardenafil	Erection problems	Do not use
Valproic acid	Bipolar disorder, epilepsy or migraine	Consider risks and benefits
Venetoclax	Cancer	Do not use
Viekirax (contains ombitasvir, paritaprevir and ritonavir)	Hepatitis C	Consider risks and benefits
Vinblastine	Cancer	Consider risks and benefits
Vincristine	Cancer	Consider risks and benefits
Voriconazole	Infections	Consider risks and benefits
Warfarin	Treating or preventing blood clots	Consider risks and benefits
Zepatier (contains elbasvir and grazoprevir)	Hepatitis C	Do not use*

*Not listed in PF-07321132 (nirmatrelvir) plus ritonavir SmPC but use NOT advised by *COVID-19 Drug Interaction checker*

Table 2 below lists medicines by what they are used for indicating when PF-07321132 (nirmatrelvir) plus ritonavir is not an appropriate option to be prescribed concurrently. This list is not comprehensive. If a medicine is not listed also check University of Liverpool COVID-19 Drug Interaction checker (https://covid19-druginteractions.org/checker).

The last column gives an indication of when advice to not prescribe together applies or where risks and benefits need careful consideration taking account of the practicalities of managing such patients in a CMDU or non-specialist setting.

Table 2: Medications interacting with PF-07321332 (nirmatrelvir) plus ritonavir listed by use.

What the medicine is used for	Specific medicines	Use of PF-07321132 (nirmatrelvir) plus ritonavir
Underactive thyroid (hypothyroidism)	Levothyroxine	Consider risks and benefits
Lowering cholesterol	Lomitapide Rosuvastatin Simvastatin	Do not use Consider risks and benefits Do not use
Treating or preventing blood clots	Apixaban Clopidogrel Dabigatran Rivaroxaban Ticagrelor Warfarin	Do not use Do not use* Consider risks and benefits Do not use Do not use* Consider risks and benefits
Relieving asthma or COPD (inhaled or oral)	Budesonide Fluticasone propionate Salmeterol Theophylline	Consider risks and benefits Consider risks and benefits Do not use Consider risks and benefits
Bipolar disorder, schizophrenia, epilepsy, migraine or cluster headaches	Carbamazepine Clonazepam Clozapine Dihydroergotamine Eletriptan Ergotamine Lamotrigine Lurasidone Phenobarbital Phenytoin	Do not use Do not use Do not use Do not use Consider risks and benefits Do not use Consider risks and benefits Do not use Do not use Do not use

	Pimozide Quetiapine Valproic acid Midazolam	Do not use Do not use Consider risks and benefits Do not use
Erection problems	Avanafil Sildenafil Tadalafil Vardenafil	Do not use Do not use Do not use Do not use
Contraception, hormonal	Elicit name of medication and check COVID-19 Drug Interaction checker.	Consider risks and benefits
Irregular heartbeats	Amiodarone Digoxin Disopyramide Dronedarone Flecainide Propafenone Quinidine	Do not use Consider risks and benefits Do not use* Do not use Do not use Do not use Do not use
High blood pressure (hypertension)	Aliskiren Lercanidipine	Do not use* Do not use*
Prostate gland enlargement	Alfuzosin	Do not use
Cold-like symptoms caused by allergic rhinitis (nasal spray)	Budesonide Fluticasone propionate	Consider risks and benefits Consider risks and benefits
Pain	Fentanyl Midazolam Pethidine Propoxyphene Piroxicam	Consider risks and benefits Do not use Do not use Do not use Do not use
Nerve pain or trigeminal neuralgia	Carbamazepine	Do not use
Heart failure or angina	Eplerenone Ivabradine Ranolazine Digoxin	Do not use* Do not use* Do not use Consider risks and benefits
Gout	Colchicine	Do not use
Heroin dependence	Methadone	Consider risks and benefits
Substance abuse	Various illicit drugs	Check COVID-19 Drug Interaction checker
Herbal medicines	St. John's Wort (Hypericum perforatum)	Do not use
Infections	Bedaquiline Delamanid Fusidic acid/ sodium fusidate (oral) Ketoconazole Rifabutin Rifampicin Voriconazole	Consider risks and benefits Consider risks and benefits Do not use Consider risks and benefits Consider risks and benefits Do not use Consider risks and benefits
Pulmonary arterial hypertension (PAH)	Bosentan Riociguat Sildenafil (Revatrio) Tadalafil	Do not use* Consider risks and benefits Do not use Do not use
Anxiety, problems sleeping, muscle spasms, fits, attention deficit hyperactivity disorder (ADHD) or narcolepsy	Diazepam Flurazepam Clonazepam St John's Wort Dexamphetamine Methylphenidate	Do not use Do not use Do not use Do not use Consider risks and benefits Consider risks and benefits
Immunosuppressant medicines which	Ciclosporin	Do not use*

can be used for a range of conditions	Everolimus Sirolimus Tacrolimus	Do not use* Do not use* Do not use*
Transplant	Letermovir	Consider risks and benefits
Hepatitis C	Exviera (contains dasabuvir) Maviret (contains glecaprevir and pibrentasvir) Viekirax (contains ombitasvir, paritaprevir and ritonavir) Zepatier (contains elbasvir and grazoprevir)	Consider risks and benefits Do not use Consider risks and benefits Do not use*
Cancer	Abemaciclib Acalabrutinib Apalutamide Ceritinib Encorafenib Enzalutamide Everolimus Ibrutinib Neratinib Venetoclax Vinblastine Vincristine	Consider risks and benefits Consider risks and benefits Consider risks and benefits Consider risks and benefits Consider risks and benefits Consider risks and benefits Do not use Consider risks and benefits Do not use Do not use Consider risks and benefits Consider risks and benefits
Blood disorders	Fostamatinib	Consider risks and benefits

*Not listed in PF-07321132 (nirmatrelvir plus ritonavir SmPC but use NOT advised by *COVID-19 Drug Interaction checker*

Appendix 3: Chemotherapy agents (Groups B and C)

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

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

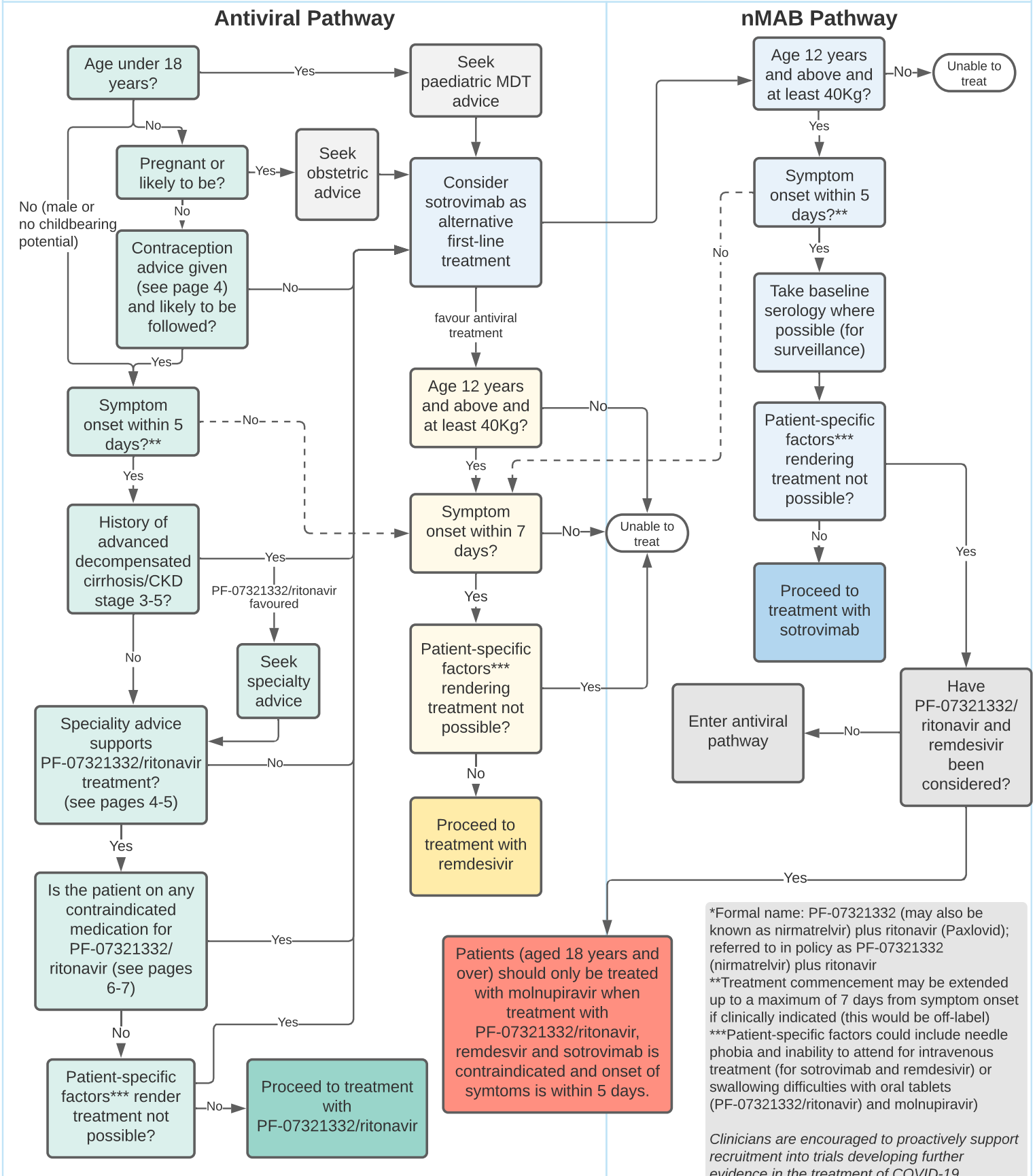
cisplatin (ESHAP) • Cyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD) • Dacarbazine-based regimens • Lomustine • Magalizumab • Brentuximab vedotin • Asparaginase-based regimens	

UK Interim Clinical Commissioning Policy:
Therapies for symptomatic non-hospitalised patients with COVID-19

Consider access to this clinical pathway for patients under the following conditions:

- Onset of symptoms of COVID-19 within the last 5 days (for PF-07321332/ritonavir*, sotrovimab and molnupiravir) or 7 days (for remdesivir), remains symptomatic and with no signs of clinical recovery
- SARS-CoV-2 infection is confirmed by either PCR or lateral flow test (registered via gov.uk)
- The patient is a member of a 'highest' risk group (see page 2)
- The patient is not hospitalised for COVID-19 and is not requiring new supplemental oxygen specifically for the management of COVID-19 symptoms

Consider the clinical suitability of antiviral or neutralising monoclonal antibody. PF-07321332/ritonavir and sotrovimab are first-line options and remdesivir is second-line. Molnupiravir should be considered a third-line treatment options. (see page 3 for further information on choosing between antiviral and nMAB).



*Formal name: PF-07321332 (may also be known as nirmatrelvir) plus ritonavir (Paxlovid); referred to in policy as PF-07321332 (nirmatrelvir) plus ritonavir

**Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated (this would be off-label)

***Patient-specific factors could include needle phobia and inability to attend for intravenous treatment (for sotrovimab and remdesivir) or swallowing difficulties with oral tablets (PF-07321332/ritonavir) and molnupiravir)

Clinicians are encouraged to proactively support recruitment into trials developing further evidence in the treatment of COVID-19

Clinical Guide: The 'highest risk' cohort for access to treatment

The following cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC). Patients in these cohorts are determined to be at highest risk of adverse outcomes from COVID-19 and are to be prioritised for treatment with nMABs and antivirals.

Cohort	Definition
Down's syndrome	All patients with Down's syndrome
Patients with a solid cancer	Active metastatic cancer and active solid cancers (at any stage) • All patients receiving chemotherapy within the last 3 months • Patients receiving group B or C chemotherapy 3-12 months prior (see Appendix 3) • Patients receiving radiotherapy within the last 6 months
Patients with haematological disease and stem cell transplant recipients	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs host disease (GVHD) regardless of time from transplant (including (HSCT for non-malignant diseases) • Autologous HSCT recipients in the last 12 months (including (HSCT for non-malignant diseases) • Individuals with haematological malignancies who have ◦ received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months. or ◦ radiotherapy in the last 6 months • Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months except patients with chronic phase chronic myeloid leukaemia (CML) in molecular response; or first or second line tyrosine kinase inhibitors (TKI) • All patients with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g.chronic lymphocytic leukaemia, follicular lymphoma) or myelodysplastic syndrome (MDS) who do not fit the criteria above. • All patients with sickle cell disease. • Individuals with non-malignant haematological disorder (e.g.aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (e.g.anti-CD20, anti-thymocyte globulin [ATG] andalemtzumab) within the last 12 months.
Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who: ◦ Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin) ◦ Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals ◦ Not been vaccinated prior to transplantation • Non-transplant patients who have received a comparable level of immunosuppression • Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression
Patients with liver disease	Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease) • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable OR stable disease on corticosteroids (equivalent to ≥10mg/day of prednisolone for at least the 28 days prior to a positive PCR result), cyclophosphamide, tacrolimus, cyclosporin or mycophenolate • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Immune deficiencies	• Primary immunodeficiency associated with impaired type I interferon signalling • Good's syndrome (thymoma plus B-cell deficiency) • X-linked agammaglobulinaemia (and other primaryagammaglobulinaemias) • Any patient with a secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy • Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Severe Combined Immunodeficiency (SCID) • Autoimmune polyglandular syndromes /autoimmunepolyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 <350 cells/mm3 and stable on HIV treatment or CD4>350 cells/mm3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	Multiple sclerosis Motor neurone disease Myasthenia gravis Huntington's disease

Clinical Guide: Therapy characteristics when deciding on treatment choice

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

- Three products have similar relative risk reduction of reducing hospitalistion: PF-07321332/ritoniavir, remdesivir; and sotrovimab
- 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

PF-07321332/ritonavir (Paxlovid)	Remdesivir (Veklury)	Sotrovimab (Xevudy)
Antiviral (dual therapy)	Antiviral (monotherapy)	Neutralising monoclonal antibody
Administered **orally**: 3 tablets twice a day for 5 days	Administered **intravenously**: one infusion every 24 hours for 3 days	Administered **intravenously**: single infusion
Adults only (aged 18 years and over)	Adults and adolescents (aged 12 years and over and weighing at least 40kg)	Adults and adolescents (aged 12 years and over and weighing at least 40kg)
Evidence based on treatment within **5** days of symptom onset	Evidence based on treatment within **7** days of symptom onset	Evidence based on treatment within **5** days of symptom onset
Not recommended in pregnancy	May be used in **pregnancy** where benefits of treatment outweigh risks	May be used in **pregnancy** although there is no safety data available
Breast-feeding should be discontinued during treatment and for 7 days after last dose	No specific advice on discontinuation of breast-feeding during treatment	No specific advice on discontinuation of breast-feeding during treatment
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 dose adjustment recommended in liver or renal impairment*
Multiple significant drug-drug interactions (see page 4)	No significant drug-drug interactions	No significant drug-drug interactions
88% Relative Risk Reduction of Hospitalisation	87% Relative Risk Reduction of Hospitalisation	85% Relative Risk Reduction of Hospitalisation

Molnupiravir (Lageviro)

Antiviral (monotherapy)	Breast-feeding should be discontinued during treatment and for 4 days after last dose
Administered **orally**: 4 capsules twice a day for 5 days	May be used in severe liver and kidney disease (no dose adjustment recommended)
Adults only (aged 18 years and over)	No significant drug-drug interactions
Not recommended in pregnancy	
30% Relative Risk Reduction of Hospitalisation	

For the key publications of trial results and licence click here

PF-07321332/ritonavir publication due	PF-07321332/ritonavir SmPC
Remdesevir 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)

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

Specialty-specific advice on the management of patients within each of the highest-risk cohorts (particularly around the use of PF-07321332/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	PF-07321332/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 PF-07321332/ritonavir. If blood tests are available a bilirubin >50 at any time is a contraindication to PF-07321332/ritonavir, if the jaundice is due to liver disease. Patients receiving rifaximin (only used in very advanced liver disease) should not receive PF-07321332/ritonavir.
Solid organ transplant (non-renal)	PF-07321332/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 PF-07321332/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. PF-07321332/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 PF-07321332/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 PF-07321332/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 pages 6-7, avoid concurrent use of PF-07321332/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 PF-07321332/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 PF-07321332/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 PF-07321332/ritonavir and should be temporarily suspended following discussion with an MND physician. **Huntington's Disease** • In addition to the medicines listed in pages 6-7, avoid concurrent use of PF-07321332/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 PF-07321332/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 on pages 6-7 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 PF-07321332/ritonavir.
Paediatrics	For paediatric/adolescent patients (aged 12-17 year inclusive), paediatric multidisciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from treatment.

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

Specialty-specific advice on the management of patients within each of the highest-risk cohorts (particularly around the use of PF-07321332/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. Specialty 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 PF-07321332/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 PF-07321332/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	• 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 PF-07321332/ritonavir e.g.:
	  • For heart conditions and high blood pressure
	  • Antipsychotic, antidepressants, anxiolytics A
	  • Anticonvulsants (anti-epileptics)
	  • Statins
	• PF-07321332/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

Clinical Guide: Medicines where PF-07321332/ritonavir is NOT an appropriate option

These tables show the medicines where there are contraindications with PF-07321332/ritonavir and cautions that are not easily managed. If a patient is currently prescribed any of these medicines, then PF-07321332/ritonavir is NOT a treatment option. Please refer to SPS Guidance here.

What the medicine is used for	Specific Medicines
Irregular heartbeats	Digoxin, Disopyramide, Amiodarone, Quinidine, Dronedarone, Flecainide, Propafenone
Treating and preventing blood clots	Apixaban, Dabigatran, Rivaroxaban, Warfarin, Clopidogrel, Ticagrelor
High blood pressure (hypertension)	Aliskiren, Lercanidipine
Lowering cholesterol	Rosuvastatin, Simvastatin, Lomitapide
Erection problems	Avanafil, Sildenafil, Tadalafil, Vardenafil
Inhalers Inhaled or oral medicines to relieve asthma and COPD	Salmeterol, Budesonide, Fluticasone Propionate, Theophylline
Cold-like symptoms caused by allergic rhinitis (nasal spray)	Budesonide, Fluticasone propionate
Underactive thyroid (hypothyroidism)	Levothyroxine
Prostate gland enlargement	Alfuzosin
Heart failure or angina	Ranolazine, Ivabradine, Eplerenone, Digoxin
Pain	Fentanyl, Midazolam, Pethidine, Piroxicam, Propoxyphene
Heroin dependence	Methadone
Bipolar disorder, schizophrenia, epilepsy, migraine or cluster headaches	Carbamazepine, Clozapine, Eletriptan, Lamotrigine, Lurasidone, Phenobarbital, Phenytoin, Quetiapine, Ergotamine, Dihydroergotamine, Valproic acid, Pimozide, Midazolam, Clonazepam
Nerve pain or trigeminal neuralgia	Carbamazepine
Gout	Colchicine
Pulmonary arterial hypertension (PAH)	Sildenafil, Bosentan, Riociguat, Tadalafil
Herbal medicines	St. John's Wort
Anxiety, problems sleeping, muscle spasms, fits, narcolepsy and ADHD	Flurazepam, Diazepam, Clonazepam, St John's Wort, Methylphenidate, Dexamphetamine

Clinical Guide: Medicines where PF-07321332/ritonavir is NOT an appropriate option

These tables show the medicines where there are contraindications with PF-07321332/ritonavir and cautions that are not easily managed. If a patient is currently prescribed any of these medicines, then PF-07321332/ritonavir is NOT a treatment option. Please refer to SPS Guidance here.

What the medicine is used for	Specific Medicines
Cancer	Abemaciclib, Acalabrutinib, Ceritinib, Encainide, Encorafenib, Enzalutamide, Everolimus, Apalutamide, Ibrutinib, Neratinib, Venetoclax, Vinblastine, Vincristine
Infections	Bedaquiline, Delamanid, Ketoconazole, Rifabutin, Rifampicin, Voriconazole, Fusidic acid / sodium fusidate
Transplant	Letermovir
Immunosuppressant medicines which can be used for a range of conditions	Ciclosporin, Sirolimus, Tacrolimus, Everolimus
Hepatitis C	Maviret (contains glecaprevir and pibrentasvir), Zepatier (contains elbasvir and grazoprevir), Exviera (contains dasabuvir), Viekierax (contains ombitasvir, paritaprevir and ritonavir)
Blood Disorder	Fostamatinib
Hormonal contraception	Check COVID-19 Drug Interaction Checker
Illegal substances	

A-Z: All medicines where PF-07321332/ritonavir is NOT an appropriate option

DO NOT USE | CONSIDER RISKS AND BENEFITS

Abemaciclib, Acalabrutinib, Alfuzosin, Aliskiren, Amiodarone, Apalutamaide, Apixaban, Avanafil, Bedaquiline, Bosentan, Budesonide, Carbamazepine, Ceritinib, Ciclosporin, Cisapride, Clonazepam, Clopidogrel, Clozapine, Colchicine, Contraception, hormonal, Dabigatran, Delamanid, Dexamphetamine, Diazepam, Digoxin, Dihydroergotamine, Disopyramide, Dronedarone, Elbasvir/grazoprevir (Zepatier), Eletriptan, Encorafenib, Enzalutamide, Eplerenone, Ergotamine, Everolimus, Exviera, Fentanyl, Flecainide, Flurazepam, Fluticasone, Fostamatinib, Fusidic acid, Glecaprevir/pibrentasvir (Maviret), Ibrutinib, Ivabradine, Ketoconazole, Lamotrigine, Lercanidipine, Letermovir, Levothyroxine, Lomitapide, Lurasidone, Methadone, Methylphenidate, Midazolam, Neratinib, Pethidine, Phenobarbital, Phenytoin, Pimozide, Piroxicam, Propafenone, Propoxyphene, Quetiapine, Quinidine, Ranolazine, Rifabutin, Rifampicin, Riociguat, Rivaroxaban, Rosuvastatin, Salmeterol, Sildenafil, Simvastatin, Sirolimus, Sodium fusidate, St. John's Wort, Tacrolimus, Tadalafil, Theophylline, Ticagrelor, Valproic acid, Vardenafil, Venetoclax, Viekirax, Vinblastine, Vincristine, Voriconazole, Warfarin

More detail of drug/drug interactions in found on the Liverpool COVID Drug Interaction Checker - Click Here