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

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

‘neutralises’ the virus particle. Antiviral medications inhibit viral replication and prevent progression of infection.

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:

- Clinical judgement deems that an nMAB is the preferred option

[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

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.

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

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

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

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

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

References

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

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3. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab [published online ahead of print, 2021 Oct 27]. N Engl J Med. 2021;10.1056/NEJMoa2107934. doi:10.1056/NEJMoa2107934

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
Everolimus	Cancer or immunosuppressant	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
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 can be used for a range of conditions	Ciclosporin Everolimus Sirolimus Tacrolimus	Do not use* 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)	• 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

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