

# Guideline for the treatment of hospitalised adult patients with COVID-19 not on oxygen (Group 2)

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| Target audience: | Health care professionals (nurses/doctors/pharmacists) |

**Scope**

This document provides guidance for healthcare professionals using antivirals or neutralising monoclonal antibodies (nMAbs) for the treatment of COVID-19 in hospitalised patients. It follows recommendations from the CMO alert [CEM/CMO/2022/015](https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103219) dated 28th November 2022.

The World Health Organization (WHO) updated its [’Therapeutics and COVID-19: Living guideline’](https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.5) on 16 September 2022 and the recommendations have been considered in the development of the commissioning policies, on which this guidance is based.

Antiviral medications inhibit viral replication and prevent progression of infection. Evidence suggests that antivirals significantly improve clinical outcomes in patients with COVID-19 who are at high risk of progression to severe disease and/or death.

* **PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®):** nirmatrelvir is an orally active 3C-like protease inhibitor. It binds directly to the catalytic cysteine residue of the cysteine protease enzyme. Ritonavir slows down the metabolism of nirmatrelvir via cytochrome enzyme inhibition, increasing the circulating concentration of the main drug.
* **Remdesivir:** adenosine nucleotide prodrug that is metabolised intracellularly to form the pharmacologically active substrate remdesivir triphosphate which inhibits SARS-CoV-2 RNA polymerase and perturbs viral replication.

nMAbs are synthetic monoclonal antibodies that bind to the spike protein of SARS-CoV-2, preventing subsequent entry of the virus into the host cell and its replication. This effectively ‘neutralises’ the virus particle. The following nMAb have conditional marketing authorisation for use in the treatment of COVID-19 in the UK:

* **Sotrovimab (Xevudy®)**: an nMAB that both blocks viral entry into healthy cells and clears cells infected with SARS-CoV-2.

The guidance applies Trust-wide but some elements are site-specific. Please ensure you are following advice for the relevant site: Royal Sussex County Hospital (RSCH), Princess Royal Hospital (PRH), Worthing or St Richards Hospital (SRH).

**Evidence summary**

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 day of symptom onset) and 88% (within 5 days of symptom onset) compared to placebo in non-hospitalised, high-risk adults with COVID-19. (Hammond 2022). The WHO has made a strong recommendation for nirmatrelvir-ritonavir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022).

Remdesivir administered intravenously for 3 days to non-hospitalised patients within 7 days of COVID-19 symptom onset who had risk factors for disease progression, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (absolute risk reduction 5.3% to 0.7%) (Gottlieb RL*,* 2021). The WHO has made a conditional recommendation for remdesivir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022).

Interim analysis of the COMET-ICE trial, which studied sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression, showed a relative risk reduction in hospitalisation or death at day 29 by 85% in patients treated with sotrovimab compared with placebo (Gupta et al, 2021a). The final analysis of this study has shown a relative risk reduction in hospitalisation or death at day 29 by 79% in patients treated with sotrovimab compared with placebo (Gupta et al, 2021b). In September 2022, the WHO made a strong recommendation against the use of sotrovimab patients with COVID-19 (WHO).

**Indication**

Patients with hospital-onset COVID-19 or COVID-19 positive on admission but hospitalised for indications other than for the management of acute symptoms of COVID-19 – may be treated with either PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir or sotrovimab (with MDT approval). Further information on selecting the most appropriate treatment below.

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

**Patients hospitalised for acute COVID-19 illness (Group 1)**

When a patient is admitted to hospital for the treatment of COVID-19 infection and has a new oxygen requirement they may be eligible for treatment with Dexamethasone, Remdesivir, Baricitinib or an IL-6 Inhibitor. Please see the [Guidance for Hospitalised Adults with COVID-19 on Oxygen](https://viewer.microguide.global/BSUH/COVIDBSUH#content,f69d4343-226f-4d37-a2a7-0020bb1b9219).

All the patients hospitalised for acute COVID-19 illness (Group 1) should be offered the opportunity to take part in the RECOVERY trial if available.

**Patients with hospital-onset COVID-19 or COVID-19 positive on admission but hospitalised for another condition (Group 2)**

When a patient in hospital acquires COVID-19 infection or is admitted with COVID-19 but is not unwell enough to need hospital treatment for COVID-19 disease, they may be eligible for treatment with first line PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) orally 300/100mg BD for 5 days, second line remdesivir IV infusion for 3 days or third line sotrovimab 500mg single IV infusion (with MDT approval).

If the patient experiences clinical deterioration such that hospitalisation and supplemental oxygen is required, the patient may be considered for treatment under the [Guidance for Hospitalised Adults with COVID-19 on Oxygen](https://viewer.microguide.global/BSUH/COVIDBSUH#content,f69d4343-226f-4d37-a2a7-0020bb1b9219).

Patients must meet **all** of the following **inclusion criteria** and none of the exclusion criteria**:**

* SARS-CoV-2 infection confirmed by PCR or LFT. In the case of a LFT result only a confirmatory PCR test is recommended to support surveillance activities.
* Symptomatic[[1]](#footnote-1) with COVID-19 and showing no signs of clinical recovery.
* The patient meets one of the following options:
  + Member of the ‘highest risk’ group (appendix 1).
* COVID-19 infection presents a material risk of destabilising a pre-existing condition or illness or compromising recovery from surgery or other hospital procedure, determined by MDT assessment (see below for members).

**Treatment choices for Group 2**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Order of preference** | **Drug** | **Symptom onset** | **Dose** | **Other information** |
| First line | PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) | ≤ 5 days\* | PF-07321332 (nirmatrelvir) 300mg (2x150mg tablets) plus ritonavir 100mg taken together BD for 5 days | Oral tablets, see [guidance](https://liverpool-covid19.s3.eu-west-2.amazonaws.com/23f1r1d370m1163mi33609uololl?response-content-disposition=inline%3B%20filename%3D%22Covid_PaxlovidCrushing_Nov28.pdf%22%3B%20filename%2A%3DUTF-8%27%27Covid_PaxlovidCrushing_Nov28.pdf&response-content-type=application%2Fpdf&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Credential=AKIAI7XER5GUPWKQNOYA%2F20221205%2Feu-west-2%2Fs3%2Faws4_request&X-Amz-Date=20221205T114048Z&X-Amz-Expires=300&X-Amz-SignedHeaders=host&X-Amz-Signature=48c2ef019f25a59552e247bd7e7a8ab738d011cf60f6cc99fc28cdffe559d467)[[2]](#footnote-2) for crushing/feeding tubes  See below for numerous cautions, contraindications and interactions. The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 4-5 CKD. Renal dose below. |
| Second line | Remdesivir | ≤ 7 days | 200mg stat IV infusion on day 1 then 100mg OD on day 2 and 3 | Monitor renal and hepatic function throughout treatment. |
| By exception, only with MDT approval | Sotrovimab | ≤ 5 days\* | 500mg stat IV infusion only | May be considered by exception where the available antiviral treatments above are contraindicated or determined to be unsuitable following multi-disciplinary team (MDT) assessment. |

\* 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).

**Exclusion criteria for Group 2**

* Require hospital-level care for the management of acute COVID-19 illness.
* New supplemental oxygen requirement specifically for the management of COVID-19 symptoms ([treat as per group 1](https://viewer.microguide.global/BSUH/COVIDBSUH#content,f69d4343-226f-4d37-a2a7-0020bb1b9219)).
* Children aged under 18 (guideline only applies to adults).
* Known hypersensitivity reaction to the active substances or to any of the excipients of the products as listed in the respective Summary of Product Characteristics.
* The pattern of clinical presentation indicates that there is recovery rather than risk of deterioration from infection.

**Additional exclusion criteria**

**PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®)**

* Children aged less than 18 years old.
* Pregnancy.
* The patient is taking any of the medications listed in Appendix 2 and the interaction cannot be otherwise managed (e.g. cessation of interacting medication or benefits outweigh risks). If taking of these medications that in raised concentrations could be associated with serious/life threatening reactions PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) would be contraindicated.
* Severe renal (eGFR < 30 ml/min). See below for renal dosage adjustment.
* History of advanced decompensated liver cirrhosis

**Remdesivir**

* Treatment with PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) is contraindicated or not possible
* Estimated glomerular filtration rate (eGFR) <30 mL/min (except in patients with end-stage

renal disease on haemodialysis)

* Alanine transaminase (ALT) ≥ 5 times the upper limit of normal.

**Cautions and Drug Interactions**

**Hepatic Impairment**

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 (Paxlovid®)** to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

For **remdesivir** the patient’s alanine aminotransferase (ALT) must be below 5 times the upper limit of normal at baseline. Remdesivir should also be discontinued in patients who develop either of the following during treatment:

* ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal).
* ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

**Renal Impairment**

In patients with moderate renal impairment (eGFR 30 – 59 ml/min), the dose of **PF 07321332/ritonavir (Paxlovid®)** should be reduced to 150 mg/100 mg (1 tablet of each) twice daily for 5 days.

**Remdesivir** should not be given to patients with an eGFR/CrCl < 30 mL/min (except in patients with end-stage renal disease on haemodialysis).

It should be discontinued in patients who develop an eGFR < 30 mL/min (except in patients with end-stage renal disease on haemodialysis), while on treatment.

**Drug Interactions**

**PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®)** has a risk of serious adverse reactions due to interactions with other medicinal products (see appendix 2). It is a CYP3A inhibitor which may result in increased concentrations of concurrent medications that are metabolised by CYP3A.

Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), respectively.

These interactions may lead to:

* Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
* Clinically significant adverse reactions from greater exposures of PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®).
* Loss of therapeutic effect of PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) and possible development of viral resistance.

Please check the [Paxlovid Interaction Guide](https://viewer.microguide.global/BSUH/COVIDBSUH#content,033d17b1-66d9-45eb-a2c0-185dec8ef706) on Microguide or [the University of Liverpool COVID-19 drug interactions](https://www.covid19-druginteractions.org/) website

No significant drug interactions have been described for **sotrovimab**. For up to date information check [the University of Liverpool COVID-19 drug interactions](https://www.covid19-druginteractions.org/) website.

Drug-drug interaction trials of **remdesivir** have not been conducted in humans. *In vitro*, remdesivir is a substrate/inhibitor for enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for P-glycoprotein (P-gp) transporters. The clinical relevance of these *in vitro* drug assessments has not been established.

For up to date information check [the University of Liverpool COVID-19 drug interactions](https://www.covid19-druginteractions.org/) website.

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

**Pregnancy & Breastfeeding**

**Pregnancy**

There are no human data on the use of **PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®)** 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 (Paxlovid®). PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®).

There are limited 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).

There is no data from the use of **sotrovimab** in pregnant women. Sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus.

**Breastfeeding**

There are no human data on the use of **PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®)** in breastfeeding. It is unknown whether PF-07321332 (nirmatrelvir) is excreted in human or animal milk, and the effects of it on the breast fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or the effects of the medicinal product on milk production. A risk to the newborn/infant cannot be excluded. Breast feeding should be discontinued during treatment with Paxlovid and for 7 days after the last dose of Paxlovid.

It is unknown whether **remdesivir** is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production. In animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given remdesivir. Therefore, excretion of remdesivir and/or metabolites into the milk of lactating animals can be assumed. Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

There are no data on the excretion of **sotrovimab** in human milk. The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known. Decisions on whether to breastfeed during treatment or to abstain from sotrovimab therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

**Approval & Governance**

A decision to prescribe PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir or sotrovimab must be made by a **multi-disciplinary team (MDT)** consisting of:

1. The consultant who has responsibility for the patient’s care
2. Infection specialist
   * RSCH/PRH: ext. 65207 during working hours (or out of hours on-call consultant via switchboard)
   * Worthing: ext. 85398 during working hours (or out of hours on-call microbiologist via switchboard)
   * SRH: ext. 33547 during working hours (or out of hours on-call microbiologist via switchboard)
3. Pharmacy
   * RSCH/PRH: infection/critical care specialist pharmacist via their bleep during working hours (or out of hours and weekends on-call pharmacist via switchboard)
   * Worthing/SRH: ward pharmacist via their bleep (or on-call pharmacist at weekends after 2pm via switchboard)

For patients in ITU, PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir and sotrovimab will be available at all times.

For patients who have hospital onset COVID-19 or have mild disease (Group 2) and eligible for PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir or sotrovimab, this will be available during normal working hours of 9.00am to 6.00pm. Spike antibody tests should be conducted promptly on these patients before administering. Sotrovimab may be given before the results are reported.

Completion of a Blueteq form is mandatory for approval and supply of PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir and sotrovimab:

RSCH/PRH

PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir and sotrovimab Blueteq forms must be completed by the specialist pharmacist for all requests. The pharmacist supplying the medication should inform the infection specialist pharmacist via email or on bleep 8033.

Worthing/SRH

PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir and sotrovimab Blueteq forms must be completed by the prescribing clinician and processed by the ward pharmacist. This is available on the [intranet](http://nww.westernsussexhospitals.nhs.uk/departments/pharmacy/covid-19-treatment/). Blueteq forms must be emailed to [uhsussex.COVIDdrugforms@nhs.net](mailto:uhsussex.COVIDdrugforms@nhs.net) and [uhsussex.research@nhs.net](mailto:uhsussex.research@nhs.net) by the ward pharmacist to be reviewed by the antimicrobial pharmacists.

**Continuing care**

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals) must explicitly mention that PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir or sotrovimab has been given and the date of administration. The GP should also be informed on the discharge summary that the above has been prescribed specifying the date of administration.

**Dose**

* The recommended dose of **PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®)** is 300mg (two 150mg tablets) PF-07321332 (also known as nirmatrelvir) with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days. See Renal section for patients with an eGFR of 30 – 59 ml/min.
* The recommended dose of **remdesivir** for this cohort is 200mg intravenously on day 1 followed by 100mg intravenously once daily on days 2 and 3. Please see the Injectable Medicines Guide (Medusa) for administration as there are two preparations.
  + If the patient experiences clinical deterioration such that low flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of remdesivir. Please see [group 1 guidance](https://viewer.microguide.global/BSUH/COVIDBSUH#content,f69d4343-226f-4d37-a2a7-0020bb1b9219).
* The recommended dose of **sotrovimab** is 500mg to be administered as a single intravenous infusion. This is different to the dose in the recovery trial.

**Administration**

**Administration of PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®)**

PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms. Clinicians should assure themselves that patients are able to swallow the oral tablets. Refer to University of Liverpool, Liverpool Drug Interactions Group: [Crushing nirmatrelvir and ritonavir tablets](https://liverpool-covid19.s3.eu-west-2.amazonaws.com/23f1r1d370m1163mi33609uololl?response-content-disposition=inline%3B%20filename%3D%22Covid_PaxlovidCrushing_Nov28.pdf%22%3B%20filename%2A%3DUTF-8%27%27Covid_PaxlovidCrushing_Nov28.pdf&response-content-type=application%2Fpdf&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Credential=AKIAI7XER5GUPWKQNOYA%2F20221205%2Feu-west-2%2Fs3%2Faws4_request&X-Amz-Date=20221205T114048Z&X-Amz-Expires=300&X-Amz-SignedHeaders=host&X-Amz-Signature=48c2ef019f25a59552e247bd7e7a8ab738d011cf60f6cc99fc28cdffe559d467) for further guidance.

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospital-based care due to severe or critical COVID-19 after starting treatment with nirmatrelvir/ritonavir, the patient should complete the full 5-day treatment course at the discretion of their healthcare provider.

Patients should be advised of the possible gastro-intestinal side-effects of treatment with nirmatrelvir/ritonavir (e.g. nausea, vomiting). If such side-effects are experienced, anti-emetics should be considered that are not contra-indicated. If nirmatrelvir/ritonavir treatment cannot be tolerated, an alternative treatment can be considered within the options and criteria of this policy.

**Remdesivir**

Remdesivir 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.

**Monitoring during administration of remdesivir**

Infusion-related reactions (fever, chills, hypotension, tachycardia, dyspnoea, angioedema, rash, vomiting) can occur with remdesivir. Slower infusion rates, with a maximum infusion time of up to 120 minutes, may prevent these signs and symptoms but if clinically significant hypersensitivity occurs immediately discontinue remdesivir and manage the reaction appropriately.

**The patient should be monitored closely during infusion and for one hour after the infusion** for signs and symptoms of hypersensitivity, including anaphylaxis.

**Continued daily monitoring for Remdesivir**

Renal and hepatic function should be monitored **daily throughout treatment.**

* Discontinue remdesivir if ALT ≥ 5 times upper limit of normal or ALT elevation with signs or symptoms of liver inflammation or increasing bilirubin, alkaline phosphatase or INR.
* Discontinue remdesivir if CrCl <30mL/min or renal replacement therapy required.

**Sotrovimab**

* Two qualified members of staff are needed to prepare this infusion.
* To prepare
  + Remove the vial from the fridge and check it is free from particulate matter. Allow the vial to reach room temperature, protected from light, prior to dilution (about 15 minutes). Gently swirl the vial several times before use; do not shake as air bubbles may form.
  + Add 8mls (500mg) of sotrovimab (62.5mg/ml) to a 100ml pre-filled infusion bag containing 0.9% sodium chloride.
  + Gently rock the bag back and forth 3 to 5 times. Do NOT invert the bag.
* Sotrovimab should be **administered over 30 minutes** using a filter which will be supplied by pharmacy with the vials.
  + **For RSCH/PRH pharmacy**: the filters are profiled on WellSky as “Paclitaxel Pump Admin Set” or “Infliximab Filter 0.2 microns”.
  + **For Worthing/SRH pharmacy**: suitable filters are available on the wards (COVID-red wards and gastroenterology).
* Sotrovimab should not be infused concomitantly in the same intravenous line with other medication.
* Sotrovimab **should not be prepared or administered by pregnant members of staff or staff members actively trying to conceive.** The second check can be completed by a pregnant member of staff. A disposable apron, gloves, FFP3 mask and eye protection should be worn by both members of staff when preparing and administering.
* In order to improve the traceability of biological medicines, the batch number should be recorded on EPMA or the patients drug chart.

**Monitoring during administration of sotrovimab**

Serious hypersensitivity reactions including anaphylaxis have been reported with infusion of sotrovimab. **The patient should be monitored closely during infusion and for one hour after the infusion** for signs and symptoms of hypersensitivity, including anaphylaxis. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

If an IRR (Infusion-related reaction) occurs, consider interrupting, slowing or stopping the infusion (if severe) and administer appropriate medications and/or supportive care. IRRs observed with IV administration of casirivimab and imdevimab include nausea, chills, dizziness (or syncope), rash, urticaria and flushing. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion.

**Additional Surveillance required by UKHSA**

All patients treated with PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®), remdesivir or sotrovimab will need additional PCRs for genomic surveillance. These will be sent to the UKHSA for sequencing, and it will need to highlight that these samples are from individuals prioritised for treatment.

* Pre-treatment PCR
* Day 5 after the start of treatment (or on discharge if before day 5)
* Day 14 for patients in high risk groups (Appendix 1) if they remain an inpatient

**Safety reporting**

PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) administered orally has conditional marketing authorisation in Great Britain for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

Remdesivir delivered intravenously has conditional marketing authorisation in the UK for the 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.
* in adults and adolescents (aged 12 to less than 18 years 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.

Sotrovimab delivered intravenously has conditional marketing authorisation in Great Britain for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection.

Any suspected adverse drug reactions for patients receiving Paxlovid®, remdesivir or sotrovimab must be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: <https://coronavirus-yellowcard.mhra.gov.uk/>**.**

**References**

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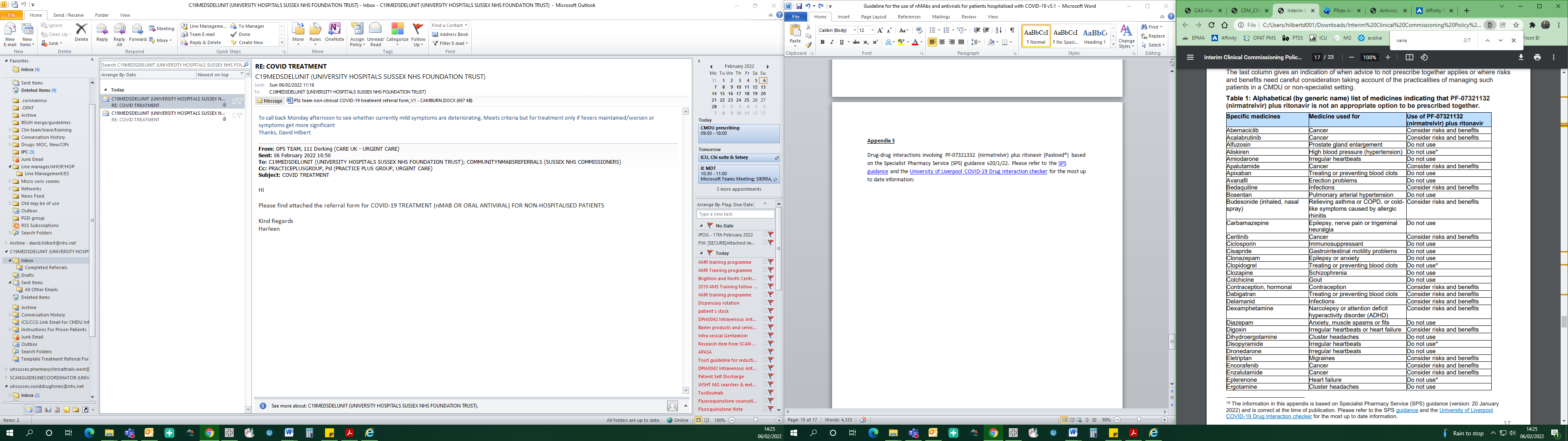
**Appendix 1**

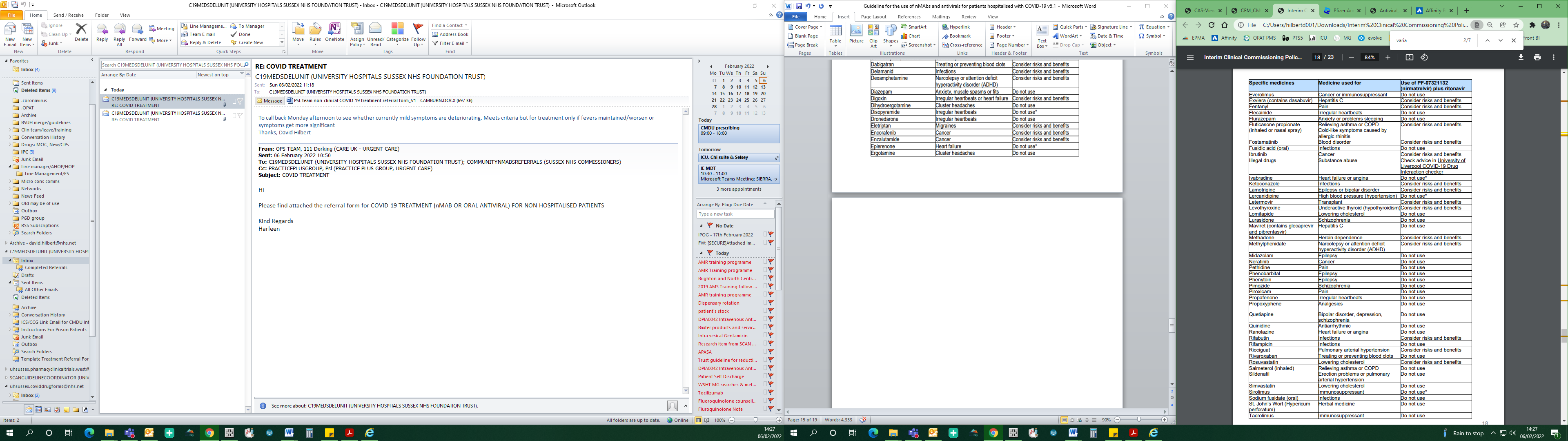
The following patient cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC) at highest risk from COVID-19 and to be prioritised for treatment with nMABs.

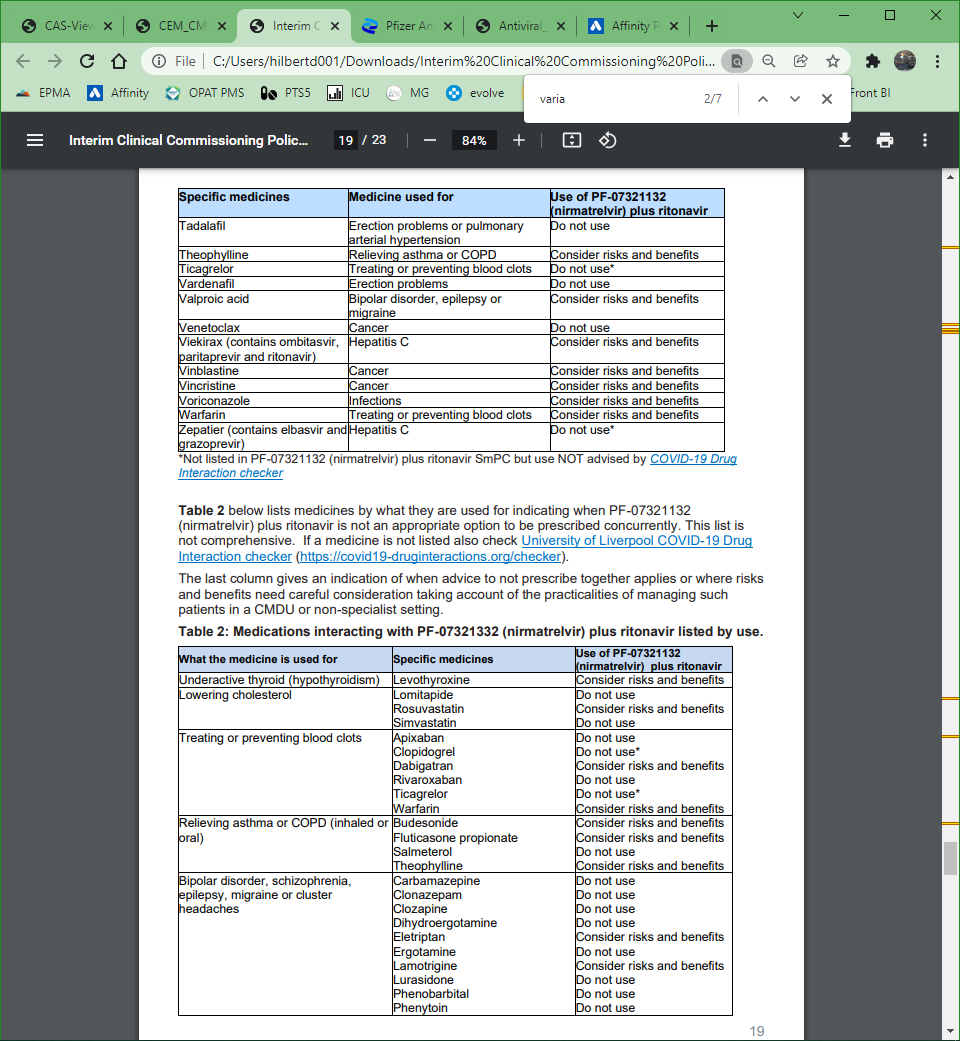
|  |  |
| --- | --- |
| **Cohort** | **Description** |
| Down’s syndrome | All individuals with Down’s syndrome or other chromosomal disorders known to affect immune competence (decision to treat to be at the discretion of the treating clinician). |
| Patients with a solid cancer | * metastatic or locally advanced inoperable cancer * lung cancer (at any stage) * people receiving any chemotherapy (including antibody-drug conjugates), PI3K inhibitors or radiotherapy within the last 12 months * people who have had cancer resected within 3 monthsand who received no adjuvant chemotherapy or radiotherapy * people who have had cancer resected within 3 to 12 months and receiving no adjuvant chemotherapy or radiotherapy are expected to be at less risk (and thus less priority) but still at increased risk compared with the non-cancer populations |
| Patients with a 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 12 months * Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months * all people who do not fit the criteria above, and are diagnosed with:   + myeloma (excluding monoclonal gammopathy of undetermined significance (MGUS))   + AL amyloidosis   + chronic B-cell lymphoproliferative disorders (chronic lymphocytic leukaemia, follicular lymphoma)   + myelodysplastic syndrome (MDS)   + chronic myelomonocytic leukaemia (CMML)   + myelofibrosis * All patients with sickle cell disease. * people with thalassaemia or rare inherited anaemia with any of the following (the decision to treat these patients will need to be at the individual patient level with input from the haematology consultant responsible for the management of the patient’s haematological condition):   + severe cardiac iron overload (T2 \* less than 10ms on magnetic resonance imaging)   + severe to moderate iron overload (T2 \* greater than or equal to 10ms on magnetic resonance imaging) plus an additional co-morbidity of concern (for example, diabetes, chronic liver disease or severe hepatic iron load on MRI) * 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. |
| 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. Please refer to the section on ‘Immune-mediated inflammatory diseases’ below for a list of qualifying immunosuppressive therapies * 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 A, B and C, whether receiving immune suppressive therapy or not. Those with decompensated liver disease (Child-Pugh B and C) are at greatest risk * Patients with a liver transplant * Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis). Please refer to the section on ‘Immune-mediated inflammatory diseases’ below for a list of qualifying immunosuppressive therapies |
| Patients with immune-mediated inflammatory disorders (IMID) | * people who have received a B-cell depleting therapy (anti-CD20 drug for example rituximab, ocrelizumab, ofatumab, obinutuzumab) in the last 12 months * people who have been treated with cyclophosphamide (IV or oral) in the 6 months prior to positive PCR * people who are on biologics or small molecule JAK-inhibitors (except anti-CD20 depleting monoclonal antibodies) or who have received these therapies within the last 6 months * people who are on corticosteroids (equivalent to greater than 10mg per day of prednisolone) for at least the 28 days prior to positive PCR * people who are on current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine/mercaptopurine (for major organ involvement such as kidney, liver and/or interstitial lung disease), methotrexate (for interstitial lung disease) and/or ciclosporin * people who exhibit at least one of: (a) uncontrolled or clinically active disease (that is required recent increase in dose or initiation of new immunosuppressive drug or IM steroid injection or course of oral steroids within the 3 months prior to positive PCR); and/or (b) major organ involvement such as significant kidney, liver or lung inflammation or significantly impaired renal, liver and/or lung function) |
| Primary 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 |

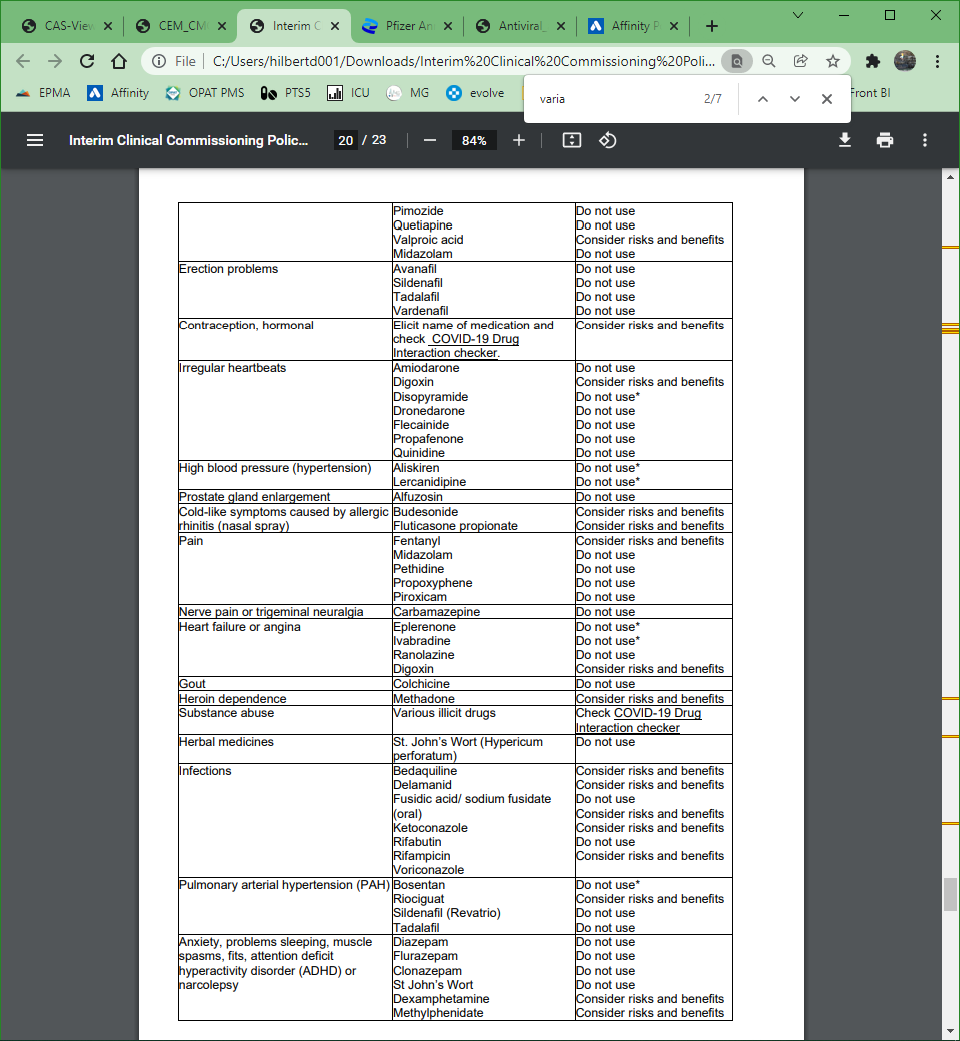
**Appendix 2**

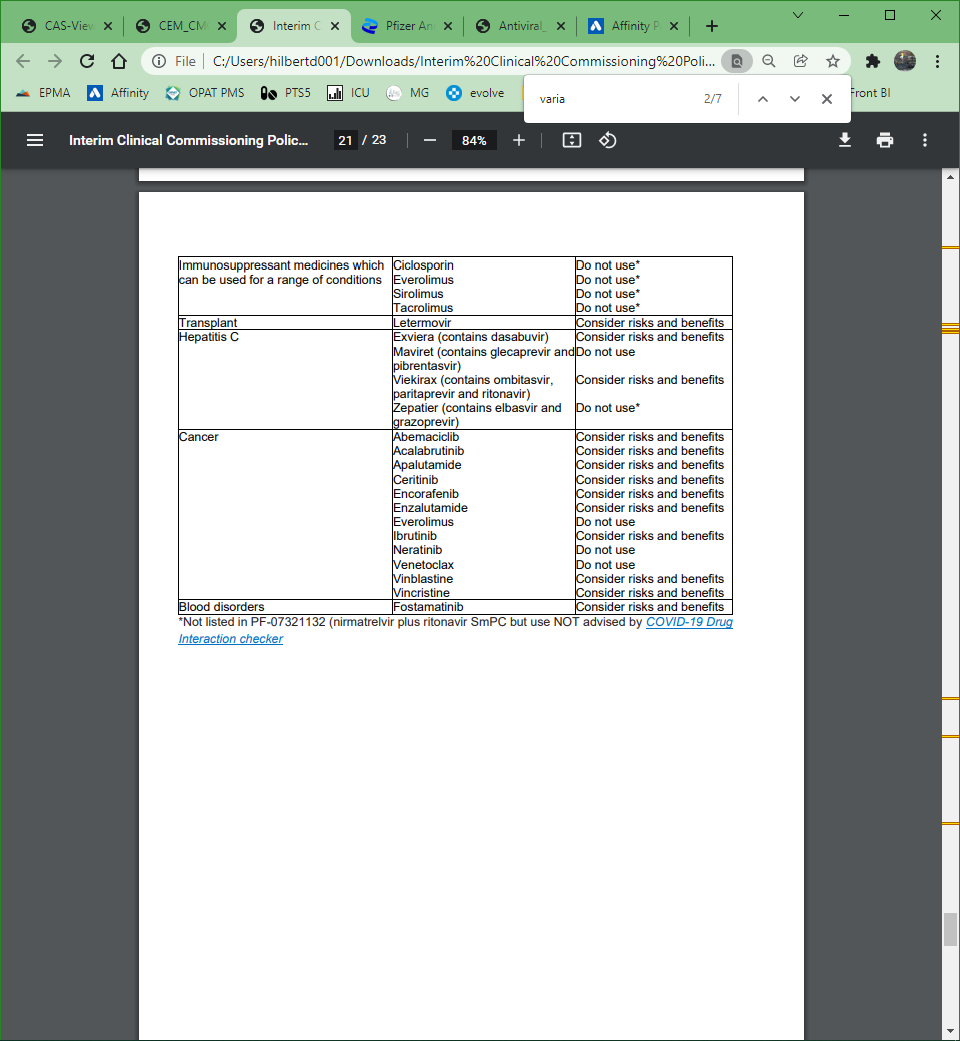
Drug-drug interactions involving PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid®) based on the Specialist Pharmacy Service (SPS) guidance v20/1/22. Please refer to the [SPS guidance](https://www.sps.nhs.uk/home/guidance/covid-19-treatments/oral-antivirals/) and the [University of Liverpool COVID-19 Drug Interaction checker](https://covid19-druginteractions.org/) for the most up to date information:











1. Symptoms include; feverish, chills, sore throat, cough, SOB or difficulty breathing, nausea, vomiting, diarrhoea, headache, body aches, loss of taste or smell, fatigue, loss of appetite, pressure or tight chest, chest pain, runny nose [↑](#footnote-ref-1)
2. University of Liverpool, Liverpool Drug Interactions Group: [Crushing nirmatrelvir and ritonavir tablets](https://liverpool-covid19.s3.eu-west-2.amazonaws.com/23f1r1d370m1163mi33609uololl?response-content-disposition=inline%3B%20filename%3D%22Covid_PaxlovidCrushing_Nov28.pdf%22%3B%20filename%2A%3DUTF-8%27%27Covid_PaxlovidCrushing_Nov28.pdf&response-content-type=application%2Fpdf&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Credential=AKIAI7XER5GUPWKQNOYA%2F20221205%2Feu-west-2%2Fs3%2Faws4_request&X-Amz-Date=20221205T114048Z&X-Amz-Expires=300&X-Amz-SignedHeaders=host&X-Amz-Signature=48c2ef019f25a59552e247bd7e7a8ab738d011cf60f6cc99fc28cdffe559d467)  2/12/22 [↑](#footnote-ref-2)