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 in the treatment of COVID-19 in hospitalised patients (Version 5)

Publication date: 27 January 2022

Effective from: 10 February 2022

Commissioning position

Neutralising monoclonal antibodies (nMABs) or antivirals are recommended to be available as a treatment option for COVID-19 through routine commissioning for adults and children (aged 12 years and above) in hospital with COVID-19 infection in accordance with the criteria set out in this document.

This policy applies to hospitalised patients with COVID-19 that are symptomatic and showing no evidence of clinical recovery and covers the following populations:

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

   For treatment with casirivimab and imdevimab (an nMAB combination)[1]

   Patients admitted to hospital due to COVID-19 who are ineligible for casirivimab and imdevimab may be considered for entry into the RECOVERY trial, which is studying sotrovimab versus standard of care.

2) **Group 2. Patients with hospital-onset COVID-19**

   For treatment with one of the following:

   - First-line: PF-07321332 (may also be known as nirmatrelvir) plus ritonavir (Paxlovid, antiviral)[2]
   - Second-line: Remdesivir (antiviral)
   - Third-line: Sotrovimab (nMAB)

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

[1] Remdesivir is also a treatment option for some patients hospitalised for symptoms of COVID-19 requiring low-flow supplemental oxygen. Please refer to the UK Clinical Commissioning Policy for remdesivir.
[2] This therapy will be referred to in this document as PF-07321332 (nirmatrelvir) plus ritonavir

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

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.

Recent evidence suggests that antivirals and nMABs significantly improve clinical outcomes in 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 patients with COVID-19:

1) **Casirivimab and imdevimab**

   Evidence

   Results from the RECOVERY trial indicate that casirivimab and imdevimab, an nMAB combination, reduced the relative risk of mortality by 20% (24% in the treatment group vs 30% in those who received standard care alone) in hospitalised patients with COVID-19 who had not mounted an antibody response of their own to the virus (were seronegative[3]) at the time of treatment. Emerging evidence however indicates that the casirivimab and imdevimab combination has significantly decreased efficacy against the Omicron variant of concern (Hoffmann et al, 2021).

   Marketing authorisation

   Casirivimab and imdevimab delivered intravenously has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for use in prophylaxis and treatment of acute COVID-19 infection in adults and children (aged 12 years and above and weighing at least 40kg). Access to casirivimab and imdevimab in Northern Ireland for the above indications is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

2) **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 day 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.

3) **Remdesivir**

   Evidence

[3] Refers to patients who were negative for serum antibodies against SARS-CoV-2 spike protein (anti-S antibody negative)

Remdesivir administered intravenously over 3 days to non-hospitalised patients within 7 days of COVID-19 symptom onset and had risk factors for disease progression[4], 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.

4) **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.

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria under one of the following pathways:

1) Patients hospitalised for acute COVID-19 illness

Hospitalised patients are eligible to be considered for treatment with **casirivimab and imdevimab** if:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or where a multidisciplinary team (MDT) has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis

  AND

[4] Risk factors for progression to severe disease included the following: hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (body mass index [BMI] ≥30 kg/m2), immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, and sickle cell disease

- Hospitalised specifically for the management of acute symptoms of COVID-19[5]

  AND

- Negative for baseline serum anti-spike (anti-S) antibodies against SARS-CoV-2 (see section on 'Serum antibody status' below)

  AND

- Genotyping confirms the patient is infected with a non-Omicron variant.

> For patients hospitalised with acute COVID-19 illness there are no available routine nMAB treatment options under this policy. Please see UK Clinical Commissioning policies for dexamethasone (CAS alert), remdesivir and IL-6 inhibitors for these patients.
>
> Patients admitted to hospital due to COVID-19 who are ineligible for casirivimab and imdevimab due to confirmed infection with the Omicron variant may be considered for entry into the RECOVERY trial, which is studying sotrovimab versus standard of care.

Samples for genotyping from patients being considered for treatment with casirivimab and imdevimab should be marked clearly as **"urgent – treatment is variant-dependent".**

Patients in Group 2 (see below) with a confirmed non-Omicron infection may be eligible for a 2.4g dose of casirivimab and imdevimab if they continue to deteriorate such that their acute COVID-19 illness requires hospital-based care, providing they fulfil the eligibility criteria for Group 1 above. The serostatus result taken prior to initial treatment (if treated with an nMAB) will inform eligibility for additional treatment[6].

2) Patients with hospital-onset COVID-19

Patients are eligible to be considered for treatment if the initial criteria below are met:

- Hospitalised for indications other than for the management of acute symptoms of COVID-19[7];

  AND

- SARS-CoV-2 infection is confirmed by either:
  - Polymerase chain reaction (PCR) testing OR
  - Lateral flow test[8]

  AND

- Symptomatic with COVID-19[9] and showing no signs of clinical recovery

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[5] Eligible patients will be acutely ill and admitted specifically to manage symptoms of COVID-19 infection or if COVID-19 infection has been contracted during the hospital stay, symptoms are such that they would have otherwise prompted a hospital admission, independent of the other reasons for the patient's current admission.

[6] As those previously treated with an nMAB will be seropositive for anti-S antibodies against SARS-CoV-2, repeat serology need not be performed upon clinical deterioration. Patients who are seronegative on baseline testing will be eligible for treatment.

[7] This includes patients admitted to community and mental health hospitals. Where possible patients being considered for intravenous treatment should be transferred to a suitable facility for treatment delivery.

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

[9] 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

AND

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

  OR

  COVID-19 infection presents a material risk of destabilising a pre-existing condition or illness or compromising recovery from surgery or other hospital procedure (as determined by multidisciplinary team [MDT] assessment).

Children aged 12-17 years in Group 2 may only be considered for treatment with remdesivir (off-label) or sotrovimab. 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.

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

- First-line: PF-07321332 (nirmatrelvir) plus ritonavir (antiviral)
- Second-line: Remdesivir (antiviral)
- Third-line: Sotrovimab (nMAB)

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.

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

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **PF-07321332 (nirmatrelvir) plus ritonavir** if:

- Treatment is commenced within 5 days of symptom onset[10]

  AND

- The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease[11] [12]

  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.

Second-line: Remdesivir

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **remdesivir** if:

- Treatment with PF-07321332 (nirmatrelvir) plus ritonavir is contraindicated or not possible

  AND

- Treatment is commenced within 7 days of symptom onset

[10] 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)
[11] If PF-07321332 (nirmatrelvir) plus ritonavir is being considered for the treatment of patients with severe renal or liver disease, the treatment decision will need to be discussed with the responsible specialist clinical team
[12] Dose modification in stage 3 chronic kidney disease may be considered in hospitalised patients. See the Summary of Product Characteristics for more information.

Third-line: Sotrovimab

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **sotrovimab** if:

- Clinical judgement deems that an nMAB should be the preferred treatment

  OR

- Treatment with remdesivir and PF-07321332 (nirmatrelvir) plus ritonavir are both contraindicated or not possible

  AND

- Treatment is delivered within 5 days of symptom onset[10]

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 a sotrovimab, if this is deemed the most appropriate treatment option.

Exclusion criteria

The following patients are NOT eligible for treatment in **Group 1**:

- Children aged less than 12 years
- Children weighing less than 40kg
- Known hypersensitivity reaction to the active substances or to any of the excipients of casirivimab and imdevimab as listed in the respective Summary of Product Characteristics

The following patients are not eligible for treatment in **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
- Children aged less than 12 years
- Adolescents (aged 12-17 years) weighing less than 40kg
- 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 following additional exclusion criteria applies to patients in Group 2 being considered for 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 further advice)

Serum antibody status

Patients may be tested for anti-S1 or anti-S2 antibodies using any validated quantitative or qualitative anti-S assay that measures either IgG or total antibody levels. Serostatus should be established in line with the pre-determined thresholds relevant to the assay being used by the testing laboratory. Quantitative assays with pre-specified thresholds for seropositivity should return clear binary (i.e. either 'negative' or 'positive') results based on these thresholds. For quantitative assays without a formal threshold for serostatus, clinical decision-making should guide treatment decisions.

In immunocompromised groups, very low 'positive' levels of anti-S antibody on a quantitative assay (within the bottom 10% of the assay's positive range) should be interpreted in the context of clinical decision-making and laboratory advice, and a decision to treat may still be made by the MDT on a case-by-case basis. Providers will be required to report anti-S antibody levels in treated patients, and the corresponding reference range of the local assay, for central monitoring.

In immunodeficient patients on replacement immunoglobulin (intravenous or subcutaneous), the positive detection of anti-S antibodies should be regarded as a 'positive result of unknown significance'. Patients on replacement immunoglobulin testing positive only for anti-S (and negative for anti-N) antibodies should therefore be considered to be seronegative for SARS-CoV-2, and MDT assessment should judge their eligibility for nMAB treatment. Should evidence for passive transmission of anti-N antibodies through replacement immunoglobulin emerge in the future, the detection of anti-N antibodies should also be regarded as a 'positive of unknown significance'.

If there are concerns or questions around laboratory sensitivity or cut-offs these should be discussed in the first instance with local laboratory leads who will have access to comparative and performance data from the External Quality Assessment (EQA) scheme participation.

Dose

1) <u>Patients hospitalised for acute COVID-19 illness</u>

   The recommended dose of casirivimab and imdevimab is 2.4g[13] (1.2g each of casirivimab and imdevimab) to be administered as a combined single intravenous infusion[14]. Patients may only receive one 2.4g dose (1.2g each of casirivimab and imdevimab) during a course of infection.

   Please note that the use of casirivimab and imdevimab in patients hospitalised with COVID-19 at the 2.4g dose is off-label.

2) <u>Patients with hospital-onset COVID-19</u>

   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.

   The recommended dose of remdesivir for this cohort is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3.

   The recommended dose of sotrovimab is 500mg to be administered as a single intravenous infusion[15].

[13] This dose for hospitalised patients was recommended by consensus of an expert group, based on available research and other pharmacokinetic data.
[14] No dose adjustment is recommended in patients with renal impairment. The pharmacokinetics of casirivimab and imdevimab have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment.
[15] No dose adjustment is recommended in patients with renal or hepatic impairment.

Administration

Casirivimab and imdevimab

1.2g (10ml of 120mg/ml) of casirivimab and 1.2g (10ml of 120mg/ml) of imdevimab should be diluted in a 250mL bag of 0.9% sodium chloride and given over a minimum of 30 minutes.

Casirivimab and imdevimab should not be infused concomitantly in the same intravenous line with other medication.

Preparation and administration of casirivimab and imdevimab 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.

PF-07321332 (nirmatrelvir) plus ritonavir

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[10]. 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 hospital-based care 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.

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. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days of symptom onset.

Renal and liver function should be monitored carefully during treatment with remdesivir as clinically appropriate.

Sotrovimab

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. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset[10].

Sotrovimab should not be infused concomitantly in the same intravenous line with other medication.

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.

Cautions

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

Casirivimab and imdevimab

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions (IRRs) have been observed with IV administration of casirivimab and imdevimab. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion. The commonly reported signs and symptoms for these reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, IRRs may present as severe or life-threatening events and may include other signs and symptoms. If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.

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) plus ritonavir, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of 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.

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.

Sotrovimab

Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. Hypersensitivity reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing. If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated.

If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered.

COVID-19 vaccines

Casirivimab and imdevimab or sotrovimab are not intended to be used as a substitute for vaccination against COVID-19.

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

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

- Liverpool COVID-19 Interactions (covid19-druginteractions.org)
- 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 remdesivir for more information on use during pregnancy or lactation.

Casirivimab and imdevimab

The RECOVERY trial included women who were pregnant or breastfeeding, and no serious adverse events were reported. The SmPC for casirivimab and imdevimab states that it should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus considering all associated health factors.

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.

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).

Sotrovimab

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

Co-administration

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

There is no interaction expected between nMABs or remdesivir 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[16]. 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 Policy for the use of IL-6 inhibitors (tocilizumab or sarilumab) in hospitalised patients with COVID-19 who require supplemental oxygen can be found here.

Safety reporting

Any suspected adverse reactions from treatment with the drugs in this policy should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

Governance

Off-label use of medication

Any provider organisation treating patients with off-label products will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee, or equivalent.

Data collection requirement

All patients being considered for treatment with nMABs for COVID-19 during their hospital stay should have their baseline serum antibody (anti-S) status measured prior to treatment to enable further evidence generation around the differential impact of treatment based on serology status.

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.

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

Clinicians are also required to ensure that any data collection requirements are met for the purpose of ongoing surveillance, audit and relevant evaluation, including of clinical effectiveness, around the use of nMABs (see 'Surveillance and service evaluation' section below).

Clinical outcome reporting

It is vital to be able to monitor the clinical progression of patients treated with nMABs. 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/). In addition, completion of the Blueteq forms (in England) will provide further essential data. Intermittent blood sampling (sparse sampling) may be required to collect serum concentration data. There will be a standard operating procedure circulated on sparse sampling to monitor serum concentration levels with nMAB treatment.

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 casirivimab and imdevimab, sotrovimab or remdesivir for COVID-19 would supersede this policy when completed.

Surveillance and service evaluation

There is an urgent need to generate more evidence and greater understanding around the use of 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 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
Anti-S antibody	Antibodies directed against the spike protein of the SARS-CoV-2 virus

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Appendix 1: Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs

The following patient cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC)[17].

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 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 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.

[17] 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[18]

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

[18] The information in this appendix is based on Specialist Pharmacy Service (SPS) guidance (version: 20 January 2022) and is correct at the time of publication. Please refer to the SPS guidance and the University of Liverpool COVID-19 Drug Interaction checker 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 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	