DRUG TREATMENTS OF COVID-19 IN HOSPITALISED ADULT PATIENTS

UNCONTROLLED IF PRINTED.

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BACKGROUND

There are currently several drug treatments with evidence of benefit in hospitalised patients with COVID-19 disease.

REMDESIVIR

Final results from the WHO led SOLIDARITY trial have shown that remdesivir has no significant effect on patients with COVID-19 who are already being ventilated. Among other hospitalised patients, it has a small effect against death or progression to ventilation (or both) [1].

Gottlieb et al [15] showed if remdesivir is administered intravenously over 3 days to non-hospitalised unvaccinated patients (who had risk factors for disease progression) within 7 days of COVID-19 symptom onset, then this resulted in a relative risk reduction of 87% in hospitalisation or death at day 28. Therefore, remdesivir may have a role in early disease.

CORTICOSTEROIDS

In June 2020 the RECOVERY trial showed that in adult patients hospitalised with COVID-19 dexamethasone 6mg per day for up to 10 days reduces 28- day mortality in those receiving invasive mechanical ventilation by one third, and by one fifth in patients receiving oxygen without invasive mechanical ventilation [2]. Since then, the REMAP-CAP trial for hydrocortisone [3] and a meta-analysis of corticosteroids [4] confirmed those results. The World Health Organization (WHO) has issued guidance recommending the use of systemic corticosteroids in severe and critical COVID-19 disease [5].

In RECOVERY only the group receiving respiratory support benefitted from dexamethasone. Possible harm was identified in the group not requiring oxygen.

Similarly, benefit was clearer in patients treated more than 7 days after symptom onset, when inflammatory lung damage is likely to have been more common.

INTERLEUKIN-6 INHIBITORS

Tocilizumab is a recombinant humanised monoclonal antibody of the IgG1 class, which is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor. Tocilizumab is used for the treatment of severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and life-threatening cytokine release syndrome induced by chimeric antigen receptor T cell therapy.

On 7th January 2021the REMAP-CAP trial investigators reported efficacy of tocilizumab and sarilumab (another monoclonal antibody medication against the interleukin-6 receptor) when given to critically ill patients with COVID-19 within 24 hours of commencing organ support in an intensive care unit [10]. Relative to control, median adjusted odds ratios were 1.64 (95% credible intervals [CrI] 1.25, 2.14) for tocilizumab and 1.76 (95%CrI 1.17, 2.91) for sarilumab, yielding >99.9% and 99.5% posterior probabilities of superiority compared

with control. Hospital mortality was 28.0% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control.

On 11th February 2021 the RECOVERY trial (https://www.recoverytrial.net/) announced their results for tocilizumab in patients hospitalised with COVID-19 [12]. Treatment with tocilizumab improved survival and the chances of discharge from hospital alive by 28 days and reduced the chances of progressing to require invasive mechanical ventilation. Most patients recruited also received dexamethsone, suggesting an effect in addition to steroids. Overall, 596 (29%) of the 2022 patients allocated tocilizumab and 694 (33%) of the 2094 patients allocated to usual care died within 28 days (rate ratio 0·86; 95% confidence interval [CI] 0·77-0·96; p=0·007). Patients allocated to tocilizumab were more likely to be discharged from hospital alive within 28 days (54% vs. 47%; rate ratio 1·22; 95% CI 1·12-1·34; p<0·0001). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (33% vs. 38%; risk ratio 0·85; 95% CI 0·78-0·93; p=0·0005).

Patients randomised in the tocilizumab vs usual care arm of the RECOVERY trial had clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L). Patients with known hypersensitivity to tocilizumab, evidence of active tuberculosis infection or clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19) were not eligible for randomisation to tocilizumab.

BARICITINIB

Baricitinib is an anti-inflammatory treatment licensed for use in moderate to severe rheumatoid arthritis and moderate to severe atopic dermatitis and has been studied in patients who are hospitalised due to COVID-19. It is a selective and reversible Janus kinase (JAK) 1 and 2 inhibitor. JAK-inhibitors are thought to control high levels of cytokines and inflammation, seen in patients with severe SARS-CoV-2 infection. Results from the RECOVERY trial demonstrate that baricitinib reduces the risk of death when given to hospitalised patients with severe COVID-19 [6].

NEUTRALISING MONOCLONAL ANTIBODIES (NMAB)

The RECOVERY trial has demonstrated [13] that the casirivimab and imdevimab combination reduced the relative risk of mortality by 20%, and the absolute risk of mortality by 6%, in hospitalised patients with COVID-19 who had not mounted an antibody response of their own to the virus (i.e. were seronegative) at the time of treatment. However, **importantly, casirivimab /imdevimab is not active against the Omicron variant of SARS-CoV2.** It has therefore been removed from these guidelines.

Sotrovimab (Xevudy®) is an nMAB that both blocks viral entry into healthy cells and clears cells infected with SARS-CoV-2. Sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression resulted in a relative risk reduction in hospitalisation or death[14]. However, data on sotrovimab in patients hospitalised due to COVID-19 is not available yet, and at present it is only available to this patient group via clinical trials.

There is growing concern over in vitro data demonstrating that sotrovimab does not neutralise the currently circulating variants of SARS-CoV-2 and their subvariants.

The reduction of in vitro neutralisation activity suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab. Therefore, in September 2022, the WHO made a strong recommendation against the use of sotrovimab patients with COVID-19.

The UK interim clinical commissioning policy (Treatments for hospital-onset COVID-19) from 28 November 2022 therefore states that sotrovimab may be considered by exception where the available antiviral treatments (Paxlovid or remdesivir) are contraindicated or determined to be unsuitable following multi-disciplinary team (MDT) assessment.

OTHER ANTIVIRALS: PF-07321332 (NIRMATRELVIR) PLUS RITONAVIR

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. At present, PF-07321332 (nirmatrelvir) plus ritonavir is used for non-hospitalised patients with COVID-19 or for patients with hospital-onset COVID-19 (page 26).

Note:

All of the above therapies for COVID-19 should generally not be started without confirmatory evidence of the diagnosis (SARS-CoV-2 PCR or strongly suggestive chest imaging).

Updates in v4.7

- Addition of baricitinib as per CAS alert from 5th May 2022 [8]

Updates in v4.8

- Changes to definition of high-risk groups eligible for treatment of hospital-onset COVID-19
- Removal of requirement for ID approval for a number of agents
- Dose adjustment for Paxlovid use in patients with CKD 3

Updates in 4.9

- Changes in line with CAS alerts from 28 November 2022 [16, 17, 18, 19]
- Casirivimab and imdevimab treatment removed
- Advice on monitoring QTc with remdesivir use
- Advice to discuss with pharmacist when using Paxlovid where patient has swallowing difficulties or NG/PEG tube in situ.

TREATMENT OVERVIEW

This document aims to be a comprehensive guide of the available drug treatments for adult patients hospitalised with COVID-19. It does currently not cover supportive treatments, e.g. oxygen, thromboprophylaxis, pain relief, anxiolytics, etc.

Each section contains details regarding indications, contraindications, cautions, dosing & administration, and advice relating to the pregnant patient. Below figure gives a quick overview of the available therapeutic management based on disease severity. Please note that the graphic does not contain exact indications and contraindication and hence should not be used as a standalone guide, but rather as an overview of which treatments to consider in which scenario. For more details see the specific chapters for each drug.

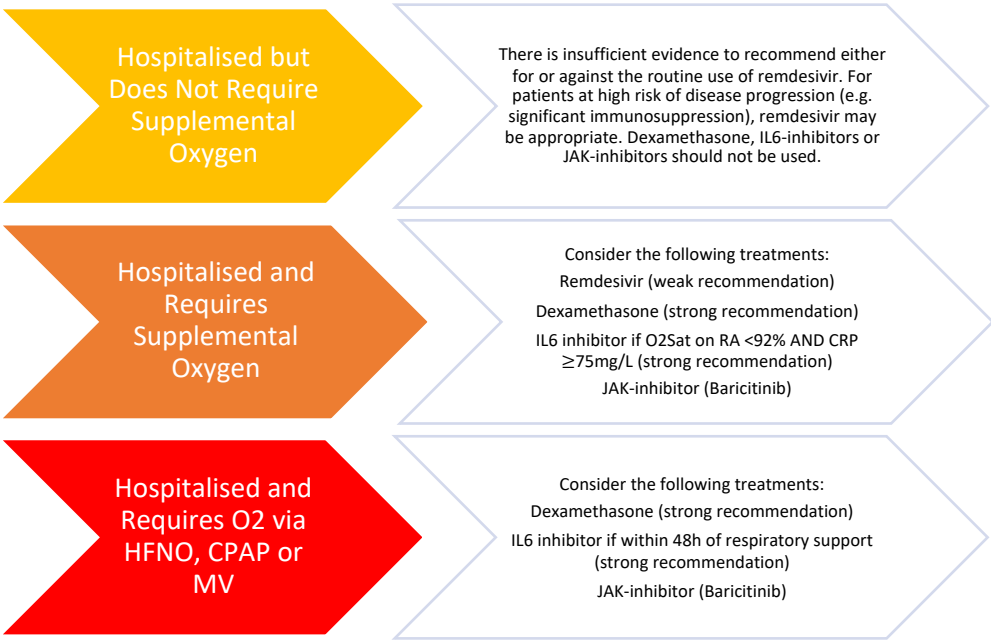

Figure 1: Overview of the therapeutic drug management of adult patients hospitalised with COVID-19 based on disease severity. For more details please see the chapters for each drug.

For patients in certain high-risk groups who are admitted for medical reasons other than COVID-19 but who develop mild COVID-19, certain additional treatment options may be available. Please see 'hospital-onset' COVID section (page 26) and Figure 2 for further information on this guidance.

Please continue to consider enrolling patients into ongoing COVID-19 trials, e.g. RECOVERY or HEAL-COVID.

REMDESIVIR

INDICATIONS

Most of this chapter deals with the use of remdesivir in patients hospitalised for acute COVID-19 illness. Patients who have been hospitalised for reasons other than for the management of acute symptoms of COVID-19 who test positive for SARS-CoV2 may also be considered for remdesivir. Please see full details and eligibility criteria at the end of this chapter and in the nMAB section (page 29).

PATIENT HOSPITALISED FOR ACUTE COVID-19 ILLNESS

Remdesivir is indicated for the treatment of patients with COVID19 who meet the following criteria [7]:

- Hospitalised with COVID-19 disease
- With pneumonia requiring low-flow supplemental oxygen*(see later section on 'immunocompromised patients' for how this criterion applies to this group)
- Adults and adolescents ≥12 years of age and ≥40kg
- eGFR≥30ml/min
- Alanine aminotransferase (ALT) below 5 times the upper limit of normal at baseline

Exemptions:

- Patients with end-stage renal disease on haemodialysis are exempt from the eGFR treatment threshold above.
- See later section on 'Immunocompromised patients' for exemptions in this cohort.

INITIATION OF TREATMENT

- The decision to initiate treatment with remdesivir should be made by the admitting care consultant. The decision to treat with remdesivir is not an emergency and should be made judiciously after assessment and in a timely manner.
- Remdesivir should **not be initiated** in patients who present to hospital **more than 10 days after symptom onset** (see later section on 'Immunocompromised patients' for how this criterion applies to this group).

*Low-flow oxygen supplementation: oxygen delivered by a simple face mask or nasal cannula at a flow rate usually up to 15 litres/min.

RISK ASSESSMENT

Clinical judgement around treatment with remdesivir can be informed by a risk score. Those with a low 4C Mortality Score[†] (0 to 3) are highly likely to recover without treatment with remdesivir.

Remdesivir should not be initiated in patients who present to hospital and are unlikely to survive (determined by clinical judgement). The 4C Mortality Score might be helpful in this assessment.

Remdesivir may prolong the QT interval, and a patient risk-assessment should be undertaken prior to initiation of treatment. A baseline ECG should be performed, with monitoring of QTc interval from days 1 to 3 in patients at increased risk, eg who are prescribed additional QT prolonging medication. Seek advice from cardiology as necessary.

DURATION

All patients should receive a **maximum of 5 days of remdesivir** in total (comprising a loading dose plus 4 further days of maintenance doses).

Patients re-admitted with COVID-19 (and meeting the eligibility criteria above, with the exception of the requirement on the timing from symptom onset) are permitted a second course of up to 5 days upon readmission.

Significantly immunocompromised patients (see below) are eligible for an extended course of remdesivir (up to 10 days), if agreed following multidisciplinary team assessment (for NHS Lothian: discuss with ID consultant on-call).

REASSESSMENT AND REVIEW

The use of remdesivir should be reassessed daily. Consider stopping remdesivir if:

- The patient clinically improves and no longer requires supplemental oxygen 72 hours after commencement of treatment; or
- The patient continues to deteriorate despite 48 hours of sustained mechanical ventilation.

IMMUNOCOMPROMISED PATIENTS

For significantly immunocompromised patients:

- a course of remdesivir can be extended to a maximum of 10 days
- the criterion on time between symptom onset and treatment initiation does not apply

[†]The 4C Mortality Score (available at https://isaric4c.net/risk/) is a validated risk stratification score, which can help inform clinical decision making for patients admitted to hospital with COVID-19 [9]. Other clinical risk scores are available.

- the criterion on the need for supplemental oxygen requirement does not apply.

Immunocompromise is defined as significant impairment of humoral immune response (antibody production) and/or cellular immune competence.

DOSING AND ADMINISTRATION

DOSE & DURATION

- The recommended dosage is a single loading dose of remdesivir 200mg intravenously on day 1, followed by a once daily maintenance dose of remdesivir 100 mg for the remainder of the treatment course. The total duration of treatment is 5 days (see exemption in immunocompromised patients above).

ADMINISTRATION

- Given via IV infusion over 30 – 120 minutes
- Flush with at least 30mL 0.9% sodium chloride after infusion complete

TWO FORMS OF REMDESIVIR ARE AVAILABLE

- **100mg concentrate for solution for infusion (each mL contains 5mg) – KEPT IN FRIDGE**
    - For full guidance on preparation and administration see SmPC (https://www.medicines.org.uk/emc/product/11596/smpc) or use Medusa Injectable Medicine Guide on the NHS Lothian intranet homepage links.
    - Equilibrate to room temperature
    - For 200mg dose - from 250mL bag of 0.9% sodium chloride, withdraw 40mL and discard - add 2 x 20mL of remdesivir (5mg/mL) to bag
    - For 100mg dose - from 250mL bag of 0.9% sodium chloride, withdraw 20mL and discard – add 20mL of remdesivir (5mg/mL) to bag
    - Gently invert bag 20 times to mix (do not shake)
- **100mg powder for concentrate for infusion (after reconstitution each mL contains 5mg) – DOES NOT NEED TO BE KEPT IN FRIDGE**
    - For full guidance on preparation and administration see SmPC (https://www.medicines.org.uk/emc/product/11596/smpc) or use Medusa Injectable Medicine Guide on the NHS Lothian intranet homepage links.
    - As above but reconstitute each vial with 19mL water for injection, shake for 30 seconds then allow to settle for 2-3 minutes

MONITORING

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

DOCUMENTATION

- The consultant / team in charge of the patient should:
    - Check the patient meets the remdesivir eligibility criteria as detailed above.
    - Gain the agreement of the patient to use this medicine. Patient information leaflet available here (https://www.medicines.org.uk/emc/product/11596/pil).
    - Document remdesivir prescription in the patient's TRAK notes using the short code **\remd** .
    - Report any adverse drug reactions on the COVID-19 yellow card reporting site. https://coronavirus-yellowcard.mhra.gov.uk/
- Nursing staff should order the remdesivir on a pharmacy order form from pharmacy; include the patient name and CHI number on the order.
- When ordering supply, the full course of remdesivir should be requested and transferred with the patient.
- Pharmacy will supply remdesivir Monday–Sunday 9am - 4pm. Requests out with these times will be supplied the next day.

STOPPING CRITERIA

Remdesivir should be discontinued in patients who develop any of the following:

- ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR)
- eGFR <30 mL/min(except in patients with end-stage renal disease on haemodialysis).

All adverse drug reactions for patients receiving remdesivir for COVID-19 must be reported to the using MHRA using COVID-19 Yellow Card reporting site: https://coronavirus-yellowcard.mhra.gov.uk/

PREGNANCY AND BREASTFEEDING

Remdesivir should be avoided in pregnancy unless the clinician believes the benefits of treatment outweigh the risks to the individual (see SmPC for further information: https://www.medicines.org.uk/emc/product/11596/smpc). The care and treatment of pregnant women with COVID-19 should be discussed with a senior obstetrician.

INTERACTIONS

Please refer to the BNF or Summary of product characteristics for a list of potential drug interactions.

Coadministration with dexamethasone has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.

For drug interactions please also see the COVID-19 drug interaction checker: https://www.covid19-druginteractions.org/

PATIENTS WITH HOSPITAL-ONSET COVID-19‡

Patients who have been hospitalised for reasons other than for the management of acute symptoms of COVID-19 who test positive for SARS-CoV2 may be considered of for a 3-day treatment course with remdesivir. Further details can also be found in the nMAB/antiviral section (page 29).

The recommended dose of remdesivir for this cohort is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3. Please note that a 3-day course of remdesivir at the dose specified is off-label. If the patient is discharged prior to day 3 then remdesivir should be stopped. If the patient deteriorates then a 5-day course (10 days in immunocompromised) can be considered (see above).

As for patients hospitalised due to COVID-19 the use of remdesivir should be documented using the \remd shortcode (see Documentation section on page 11).

‡Patients hospitalised for indications other than for the management of acute symptoms of COVID-19. Infection may have been acquired in hospital or in the community.

CORTICOSTEROIDS

INDICATIONS

Corticosteroids are indicated for the treatment of adult patients hospitalised with COVID-19 who:

- have a diagnosis of COVID-19 based on confirmatory PCR or strong suspicion on the basis of chest imaging and clinical history **AND**
- need supplemental oxygen (due to COVID-19) to meet their prescribed oxygen saturation levels **OR**
- need non-invasive ventilation or invasive mechanical ventilation **OR**
- have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

Do not routinely use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen, unless there is another medical indication to do so.

DOSING AND ADMINISTRATION

For **dexamethasone** the recommended adult dose schedule is:

Route of administration	Formulation	Dose
Oral	2mg tablet	6mg once daily for 7-10 days[§]
Oral or NG	2mg soluble tablet	6mg once daily for 7-10 days
	2mg/5ml oral solution	6mg (15ml) once daily for 7-10 days
IV	3.3mg (**base**) / ml intravenous 1ml ampoules	5.94 mg **base** (1.8ml) once daily for 7-10 days

Oral administration should be used first line where possible. IV administration should be limited to patients with no alternative route of administration. Treatment should stop if discharged from hospital within the 10 days.

For **hydrocortisone** the recommended adult dose schedule is:

- 50mg hydrocortisone administered intravenously three times per day for 7-10 days
- A longer low dose duration can be considered for patients with septic shock

[§]Course generally 10 days but this can be shortened if the patient has made a full recovery prior to that, or if the risk of side effects by that point significantly outweighs benefit.

Please note that the majority of evidence in the published meta-analysis emanates from the assessment of dexamethasone in the RECOVERY trial.

PREGNANCY AND BREASTFEEDING

For information on use in pregnant or breastfeeding women, please refer to the Summary of Product Characteristics (SPC) for dexamethasone(https://www.medicines.org.uk/emc/product/5411/smpc#gref) and hydrocortisone (https://www.medicines.org.uk/emc/product/9377/smpc#gref).The care and treatment of pregnant women with COVID-19 should be discussed with a senior obstetrician.

Dexamethasone crosses the placenta and repeated courses of maternal dexamethasone have been linked with developmental delay in children. Guidance by the Royal College of Obstetricians and Gynaecologists [11] suggests 40mg oral prednisolone (instead of dexamethasone). Where the oral route is not available intravenous hydrocortisone 80 mg twice daily can be used. Where the mother has had two doses IM dexamethasone for foetal lung maturation start prednisolone after completion of dexamethasone if still appropriate.

ADVERSE EFFECTS AND ADDITIONAL PRESCRIBING CONSIDERATIONS

Adverse effects include gastrointestinal discomfort, dyspepsia, peptic ulceration, sleep disturbances, nausea and anxiety. Please refer to the BNF for further details.

Gastrointestinal: Advise patients to take oral dexamethasone with or after food. When prescribing dexamethasone, consider the patient's risk factors for gastrointestinal ulceration. A proton pump inhibitor should be strongly considered for high-risk patients for the duration of the course but should be discontinued once dexamethasone has stopped.

***Diabetes*:** High Blood Glucose levels with COVID-19 infection have been shown to result in worse patient outcomes. All patients who have diabetes or who are persistently hyperglycaemic should be discussed with the diabetes team.

- **Glucose monitoring frequency** (Target glucose 6.0 -10.0 mmol/L; up to 12.0 mmol/L is acceptable)
    - **People not known to have diabetes**
        - Check the glucose 4 times daily (before meals and at bedtime). If after 48 hours all glucose results are <10.0 mmol/L reduce frequency to once daily at 17.00-18.00 hrs. Continue until dexamethasone is stopped.
        - If any fasting glucose is above 10.0 mmol/L continue 4 times daily monitoring and discuss with the diabetes team.
    - **People with diabetes**

    - Throughout the admission, check fasting glucose at least 6 hourly, or more frequently if the glucose is outside the 6.0 -10.0 mmol/L range. Inform the diabetes team of admission.

- National guidance is available at:*https://www.diabetes.org.uk/professionals/resources/coronavirus-clinical-guidance#inpatient-guidance*

Frailty /Elderly: Use with caution in the elderly; in addition to common side-effects consider increased risk of delirium, agitation, falls and fluid retention. If patients are already on maintenance steroids (acute/maintenance) discuss with local endocrinology team. Duration of dexamethasone may require review if side-effects in the elderly are significant.

Sleep disorders: Dexamethasone should be given in the morning to minimise sleep disruption.

All adverse drug reactions for patients receiving dexamethasone for COVID-19 must be reported to the using MHRA using COVID-19 Yellow Card reporting site: https://coronavirus-yellowcard.mhra.gov.uk/

INTERACTIONS

Please refer to the BNF or Summary of product characteristics for a list of potential drug interactions.

For drug interactions please also see the COVID-19 drug interaction checker: https://www.covid19-druginteractions.org/

INTERLEUKIN-6 INHIBITORS

TOCILIZUMAB / SARILUMAB

Tocilizumab is now licensed for use in the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation [16]. This now places tocilizumab as the first-line IL-6 inhibitor for hospitalised patients with COVID-19. Patients may continue to be considered for treatment with sarilumab where tocilizumab is unavailable for this indication or cannot be used.

Clinicians should consider prescribing intravenous IL-6 inhibitors (tocilizumab or sarilumab) following the criteria defined below.

ELIGIBILITY CRITERIA

Patients must meet all of the eligibility criteria and none of the exclusion criteria. Hospitalised patients are eligible to be considered for an IL-6 inhibitor (tocilizumab or sarilumab) if:

- COVID-19 infection is confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis;

  AND

- They have not already been treated during this episode with tocilizumab or sarilumab

  AND

- They are receiving (or have completed a course of) dexamethasone or an equivalent corticosteroid unless contraindicated.

  AND

  Either

  - Hypoxaemia with evidence of inflammation but not yet critically ill requiring respiratory support defined as:
    - C-reactive protein level of at least 75mg/L; AND
    - an oxygen saturation of <92% on room air OR requirement for supplemental oxygen;

  Or

  - In the early stages of critical illness requiring respiratory support (if an IL-6-inhibitorhas not been already administered for COVID-19) defined as:

- Within 48 hours of commencement of respiratory support (high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation), regardless of C-reactive protein level.

EXCLUSION CRITERIA

- Tocilizumab should not be administered in the following circumstances:
  - Known hypersensitivity to tocilizumab
  - Liver enzymes [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] more than ten times the upper limit of normal
  - Absolute neutrophil count of less than 1 x 10^9/L
  - Platelet count of less than 50 x 10^9/L
- Sarilumab should not be administered in the following circumstances:
  - Known hypersensitivity to sarilumab
  - Liver enzymes [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] more than 5 times the upper limit of normal
  - A baseline platelet count of less than 150 x 10^9/L

Please refer to the Summary of Product Characteristics (SmPC) for tocilizumab (https://www.medicines.org.uk/emc/product/6673/smpc#gref) and sarilumab (https://www.medicines.org.uk/emc/product/8145/smpc#gref) for special warnings and precautions for use, although some may not be relevant for use in the acute setting, as the licensed indications address long-term use.

CAUTIONS

- Co-existing infection that might be worsened by IL-6 inhibitor therapy
- A pre-existing condition or treatment resulting in ongoing immunosuppression.

Caution is also necessary when prescribing IL-6 inhibitors to patients with neutropenia or thrombocytopaenia. Please note that C-reactive protein (CRP) levels may be depressed for some time after treatment with IL-6 inhibitors.

RISK OF INFECTIONS

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including IL-6 inhibitors. While being on antibiotics per se is not a contraindication, IL-6 inhibitor treatment generally must not be initiated in patients with active, severe bacterial (including active tuberculosis), fungal, viral, or other infection (besides COVID19). Healthcare professionals should exercise caution when considering the use of IL-6 inhibitors in patients with a history of recurring or chronic infections.

Of note is that the limited trial evidence of using IL-6 inhibitors in COVID-19 has not demonstrated significant safety concerns, which may be in part due the fact that only one or two doses were given as opposed to

repeated doses over weeks or months. Although it is important to note that long-term follow up data is as yet outstanding.

The SmPC states that patients should be screened for latent tuberculosis (LTBI). However, data on a large number of tocilizumab exposed patients from clinical trials indicate a very low or absent risk of TB reactivation [Cantini, F., et al. Risk of Tuberculosis Reactivation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Receiving Non-Anti-TNF-Targeted Biologics. Mediators Inflamm. 2017; 2017: 8909834.]. It is likely not feasible to screen for LTBI prior to commencing tocilizumab for severe COVID-19.

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for rheumatoid arthritis. In clinical studies with tocilizumab, patients who screened positive for hepatitis were excluded. However, screening for viral hepatitis was not required for RECOVERY or REMAP-CAP. Given the acuity of the presentation of patients with COVID-19 screening would not be feasible in a timely manner prior to consideration of tocilizumab. Instead, clinicians should be aware of the theoretical risk, and blood borne virus serology could be undertaken with routine bloods in due course. Patients with active hepatitis B or C infection should be discussed with the infectious diseases team.

MONITORING

No specific monitoring is required post infusion. Raised ALT/AST and neutropenia can occur, particularly with longer treatment courses.

Both tocilizumab and sarilumab cause **prolonged depression of CRP levels, making CRP a less reliable marker of active infection**. All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) must explicitly mention that an IL-6 inhibitor has been given and the date of administration. Clinicians **must ensure the GP is aware the patient has received tocilizumab or sarilumab** and provide information to the patient to such effect.

COMMON UNDESIRABLE EFFECTS

Please see SmPC for full list (see links above).

TOCILIZUMAB - DOSING & ADMINISTRATION

The following preparations are available:

- Tocilizumab 400mg/20mL vial (RoActemra / Actemra)
- Tocilizumab 200mg/10mL vial (RoActemra / Actemra)

- Tocilizumab 80mg/4mL vial (RoActemra / Actemra)

The recommended dose is 8mg/kg to be administered as an intravenous infusion. The total dose per infusion should not exceed 800mg. **A single dose is to be administered (no repeat dosing),** given the uncertainty over evidence of additional benefit as well as the need to maximise available supply.

Tocilizumab should be diluted in a 100mL bag of 0.9% sodium chloride, after removing an equivalent volume of saline (total volume 100mL) and given over 1 hour.

Estimated or measured weight	Dose	Vials
<41kg	8mg/kg, rounded to nearest 20mg	As required / available
≥41 and ≤45kg	360mg	As available
≥46 and ≤55kg	400mg	As available
≥56 and ≤65kg	480mg	As available
≥66kg and ≤80kg	600mg	As available
≥81 and ≤90kg	680mg	As available
≥91kg	800mg	As available

1. Calculate the volume (mL) required for the dose
2. Withdraw this volume from a 100mL sodium chloride 0.9% infusion bag
3. Discard the volume withdrawn from the sodium chloride 0.9% infusion bag. This will ensure that the final volume is 100mL after the drug has been added
4. Withdraw the required volume of tocilizumab solution for the patient dose
5. Add the tocilizumab solution to the 100mL sodium chloride 0.9% infusion bag. If dose is not exactly divisible by strengths of vials available, the excess should be discarded as per hospital policy.
6. Gently invert the bag to mix, do not shake
7. Inspect the bag. Only bags which are clear to opalescent, colourless to pale yellow and free of visible particles can be infused
8. Prime the line with the tocilizumab infusion then administer infusion intravenously over 60 minutes via a central or peripheral line
    a. The infusion speed must be 10mL per hour for 15 minutes and then increased to 130mL per hour for the next 45 minutes
9. Flush line at the same rate as the tocilizumab infusion with 10-20mL of sodium chloride 0.9%

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

SARILUMAB - DOSING & ADMINISTRATION

The recommended dose of sarilumab is 400mg to be delivered as a once-only intravenous infusion. Please note that the use of sarilumab intravenously in COVID-19 is off label.

Sarilumab is available as a pre-filled syringe. For a 400mg dose two 200mg pre-filled syringes should be injected into a 100mL sodium chloride 0.9% infusion bag. The bag should be inverted at least 10 times to ensure thorough mixing and given over 1 hour using an infusion pump and a **low protein-binding 0.2-5 micron filter** (or equivalent; Pall AEF1E 0.2 micron in line filters are available via PECOS. Stocks are held in all NHS Lothian ICU s and WGH ward 43, RIE ward 204 and SJH ward 25).

The following infusion rate is recommended: 10ml/hour for first 15 minutes then 130ml/hour for the remaining 45 minutes followed by a 20ml normal saline flush. **Sarilumab should not be infused concomitantly in the same IV line with other medications**.

DOCUMENTATION OF APPROVED USE

The use of IL-6 inhibitor therapy (tocilizumab or sarilumab) for the indication of COVID-19 pneumonitis in NHSL requires documentation on Trak using a specific shortcode. **It is important that the shortcode (see below) is used** as pharmacy will monitor use through a BOXI report which requires this particular shortcode. Weekly allocations to NHSL are provided based on usage.

The consultant in charge of the patient should:

- Check the patient meets the IL-6 inhibitor therapy approval criteria as detailed above.
- Where possible gain the agreement of the patient to use this medicine.
- Contact the clinical pharmacist responsible for their clinical area to advise which IL-6 inhibitor is currently in stock for use (this may change depending on supplies).
- The consultant in charge of the patient is responsible for:
    - Documenting the use of IL-6 inhibitor therapy in the patient's TRAK notes using the following short code: **\IL6COV**
    - Reporting any adverse drug reactions on the COVID-19 yellow card reporting site. https://coronavirus-yellowcard.mhra.gov.uk/
- **Important!** Pharmacy will only supply tocilizumab / sarilumab Monday–Sunday 9am - 4pm. Requests out with these times will be supplied the next day unless an urgent supply is requested by the ID consultant on call.
- Pharmacy staff will check Trak documentation by accessing the completed shortcode entry on TRAK (this will also inform stock holding).
- Supplies in NHS Scotland are being organised via Health Improvement Scotland and NSS National Procurement. Weekly allocations are based on national figures of COVID patients for each Board. Locally stock will be held at all acute sites in NHS Lothian; RIE, WGH and SJH.

SAFETY REPORTING

Any suspected adverse drug reactions (ADRs) for patients receiving tocilizumab or sarilumab should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/

PREGNANCY AND WOMEN OF CHILDBEARING POTENTIAL

The REMAP-CAP trial excluded pregnant women, whereas the RECOVERY trial has included pregnant women. Please check the relevant SmPC for either tocilizumab or sarilumab. The SmPC for sarilumab and tocilizumab currently states: "*Women of childbearing potential must use effective contraception during and up to 3 months after treatment*." In relation to use in pregnancy, the SmPC for tocilizumab states there is no adequate data for the use in pregnant women. In relation to use in pregnancy, the SmPC for sarilumab states there is limited data for the use in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose with tocilizumab. Tocilizumab or sarilumab should not be used during pregnancy unless clearly clinically necessary. The Royal College of Obstetrics & Gynaecology state that tocilizumab should be considered if the woman fulfils above eligibility criteria [11].

For women who are breast-feeding, the SmPC states "*It is unknown whether tocilizumab is excreted in human breast milk. The excretion of tocilizumab in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with RoActemra should be made taking into account the benefit of breast-feeding to the child and the benefit of RoActemra therapy to the woman.*"

For women who are breast-feeding, the SmPC for sarilumab states "*It is unknown whether sarilumab is excreted in human milk or absorbed systemically after ingestion. The excretion of sarilumab in milk has not been studied in animals. Because IgG1 are excreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue sarilumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman*."

The use of IL-6 inhibitor therapy in pregnant patients should ideally be discussed with the obstetric and/or infectious diseases team.

INTERACTIONS

There is no interaction of tocilizumab/sarilumab with either dexamethasone or hydrocortisone expected. There is no interaction of tocilizumab/sarilumab with remdesivir expected.

For drug interactions please also see the COVID-19 drug interaction checker: https://www.covid19-druginteractions.org/

JAK-INHIBITOR (BARICITINIB)

BARICITINIB

Baricitinib (Olumiant) is a selective and reversible Janus kinase (JAK) 1 and 2 inhibitor, licensed as an anti-inflammatory treatment for rheumatoid arthritis and atopic dermatitis. JAK-inhibitors are thought to control high levels of cytokines and inflammation, seen in patients with severe SARS-CoV-2 infection. Results from the RECOVERY trial demonstrate that baricitinib reduces the risk of death when given to hospitalised patients with severe COVID-19 [6].

Baricitinib can be considered in children (age 2 to 17 years inclusive) with severe COVID-19. However, this guidance only covers the use in adult patients. Any use in children should be discussed with paediatrics.

CO-ADMINISTRATION

Use of baricitinib in the treatment of COVID-19 should be considered as 'additive' to the use of an IL-6 inhibitor (tocilizumab or sarilumab), rather than an alternative. In other words, a patient may be given an IL-6 inhibitor after treatment with baricitinib has been commenced (or vice versa), according to clinical judgement.

Baricitinib may be administered in combination with IL-6 receptor blockers (as well as corticosteroids, unless contraindicated), according to clinical judgement, in patients with severe or critical COVID-19. If an IL-6 inhibitor is not deemed suitable, or eligibility criteria (for an IL-6 inhibitor) are unmet, baricitinib treatment may still be considered..

ELIGIBILITY CRITERIA

Patients must meet all the eligibility criteria and none of the exclusion criteria. Patients hospitalised due to COVID-19 are eligible to be considered for baricitinib if the following criteria are met:

- COVID-19 infection is confirmed by microbiological testing or where a multi-disciplinary team has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis;

AND

- Viral pneumonia syndrome is present;

AND

- Aged 2 years and over;

AND

- Receiving supplemental oxygen or respiratory support[**] for the treatment of COVID-19;

AND

- Receiving dexamethasone or an equivalent corticosteroid unless contraindicated.

EXCLUSION CRITERIA AND CAUTIONS

Baricitinib should not be administered in the following circumstances:

- Known hypersensitivity to baricitinib;
- eGFR <15 ml/min/1.73m^2 (adult patients)
- Receiving dialysis or haemofiltration;
- Absolute neutrophil count (ANC) less than 0.5 x 10^9 cells/L;
- Active tuberculosis;
- Pregnancy or breastfeeding.

The summary of Product Characteristics (SmPC) for baricitinib also advises caution in severe hepatic impairment.

Please refer to Summary of Product Characteristics (SmPC) for baricitinib (https://www.medicines.org.uk/emc/product/2434/smpc#gref).

PREGNANCY / WOMEN OF CHILDBEARING POTENTIAL & BREASTFEEDING

Baricitinib should not be used during pregnancy.

For women who are breast-feeding, the SmPC for baricitinib states: "*It is unknown whether baricitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of baricitinib in milk. A risk to newborns/infants cannot be excluded and Olumiant [baricitinib] should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue Olumiant [baricitinib] therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman*."

DOSE AND ADMINISTRATION

The use of baricitinib in COVID-19 is off label.

The recommended dose of baricitinib is 4mg once daily for 10 days (or until discharge if sooner). The dose should be halved to 2mg once daily in the following circumstances:

- eGFR 30 to <60 mL/min/1.73m^2

[**] Defined as: high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation.

- Co-administration of an Organic Anion Transporter 3 (OAT3) inhibitor with a strong inhibition potential, such as probenecid.

The dose should be reduced further to 2mg on alternate days in the following circumstances:

- eGFR 15 to <30 mL/min/1.73m^2

Dosing of baricitinib has not been studied for an eGFR <30 mL/min/1.73m^2 and clinical judgement should be exercised prior to prescribing.

Baricitinib should be taken with or without food and may be taken at any time. Seek advice from pharmacist if patient requires NG or PEG tube administration.

Individuals who are being considered for treatment under this policy, who are already taking baricitinib for a licenced indication at the dose of 4mg per day, should not receive additional baricitinib doses. However, if such individuals are already taking baricitinib at a dose of 2mg per day, the dose may be increased for the recommended treatment interval as described in these guidelines provided all eligibility criteria are met and provided the increased dose is deemed clinically appropriate (which includes the patient not being within the dose reduction categories described).

DOCUMENTATION OF APPROVED USE

The use of baricitinib for the indication of COVID-19 pneumonitis in NHSL requires documentation on Trak using a specific shortcode. It is important that the shortcode (see below) is used as pharmacy will monitor use through a BOXI report which requires this particular shortcode. Weekly allocations to NHSL are provided based on usage.

- The consultant in charge of the patient should:
    - Check the patient meets the JAK-inhibitor therapy approval criteria as detailed above.
    - Where possible gain the agreement of the patient to use this medicine.
- The consultant in charge of the patient is responsible for:
    - Documenting the use of baricitinib in the patient's TRAK notes using the following short code: \baricov
    - Reporting any adverse drug reactions on the COVID-19 yellow card reporting site. https://coronavirus-yellowcard.mhra.gov.uk/
- Important! Pharmacy will only supply baricitinib Monday–Sunday 9am - 4pm. Requests out with these times will be supplied the next day unless an urgent supply is requested by the ID consultant on call.
- Pharmacy staff will check Trak documentation by accessing the completed shortcode entry on TRAK (this will also inform stock holding).

SAFETY REPORTING

It is vital that any serious suspected adverse reactions are reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus- yellowcard.mhra.gov.uk/.

Treatment with baricitinib can lower the ability of the immune system to fight infections. This could increase the risk of getting a new infection or make any infection the patient contracts worse. All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) must explicitly mention that baricitinib has been given and the date of administration. **Clinicians must ensure the GP is aware the patient has received baricitinib** and should provide information to the patient to such effect.

NEUTRALISING MONOCLONAL ANTIBODIES& ANTIVIRALS

NEUTRALISING MONOCLONAL ANTIBODIES

SOTROVIMAB

Sotrovimab (Xevudy®): an nMAB that both blocks viral entry into healthy cells and clears cells infected with SARS-CoV-2. Sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression resulted in a relative risk reduction in hospitalisation or death [14]. However, sotrovimab has not been tested in patients hospitalised due to COVID-19 and at present is only available to this patient group via clinical trials.

ANTIVIRALS

PF-07321332 (NIRMATRELVIR) PLUS RITONAVIR (PAXLOVID™)

PF-07321332 is designed to block the activity of the SARS-CoV-2-3CL protease, an enzyme that the coronavirus needs to replicate. Co-administration with a low dose of ritonavir helps slow the metabolism, or breakdown, of PF-07321332 in order for it to remain active in the body for longer periods of time at higher concentrations to help combat the virus.

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.

REMDESIVIR

See remdesivir section above

ELIGIBILITY CRITERIA

PATIENTS WITH HOSPITAL-ONSET†† COVID-19

††Definition of "hospital-onset COVID-19": Patient is hospitalised for indications other than for the management of acute symptoms of COVID-19. The infection may have been acquired in the community or in hospital. This includes patients admitted to community and mental health hospitals.

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;

OR

- Hospitalised due to non-respiratory symptoms which may be attributed to COVID-19 (such as delirium or falls) but not requiring oxygen[‡‡];

AND

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or lateral flow test within the last 5 days

AND

- Onset of symptoms of COVID-19 within the last 7 days[§§] and showing no signs of clinical recovery[***]

AND

- The patient is a member of a 'highest' risk group (as defined in the Department of Health and Social Care commissioned Independent Advisory Group Report): https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report

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 in discussion with ID consultant on-call)

Children aged 12-17 years may only be considered for treatment with remdesivir (off-label) or sotrovimab by exception. Please note that this guideline document only covers adult patients. 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.

[‡‡] NHS Lothian deviation from national interim commissioning guidance.
[§§] NHS Lothian deviation from national interim commissioning guidance.
[***]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.

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

- **First-line: PF-07321332 (nirmatrelvir) plus ritonavir (antiviral)**
- **Second-line: Remdesivir (antiviral)**

There is growing concern over in vitro data demonstrating that sotrovimab does not neutralise the currently circulating variants of SARS-CoV-2 and their subvariants.

The reduction of in vitro neutralisation activity suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab. Therefore, in September 2022, the WHO made a strong recommendation against the use of sotrovimab patients with COVID-19.

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

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[†††]

AND

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

AND

- PF-07321332 (nirmatrelvir) plus ritonavir treatment has been deemed safe following carefully checking contraindication and drug-drug-interactions. Please use: https://www.covid19-druginteractions.org/checker and https://www.covid19-druginteractions.org/prescribing-resources. In doubt seek further guidance from the appropriate specialty team(s).

[†††]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).
[‡‡‡]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. Dose modification in stage 3 chronic kidney disease may be considered in hospitalised patients. See the Summary of Product Characteristics for more information and dosing section below.

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 delivered within 7 days of symptom onset

The recommended dose of remdesivir for this cohort is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3. Please note that a 3-day course of remdesivir at the dose specified is off-label. See remdesivir section for further details. If the patient is discharged prior to day 3 then remdesivir should be stopped. If the patient deteriorates then a 5-day course (10 days in immunocompromised) can be considered (see Remdesivir section).

SOTROVIMAB (BY EXCEPTION)

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

- 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[§§§]

AND

- Endorsement of treatment has been sought and approved by a relevant MDT (this should include an infectious diseases consultant)

[§§§] 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).

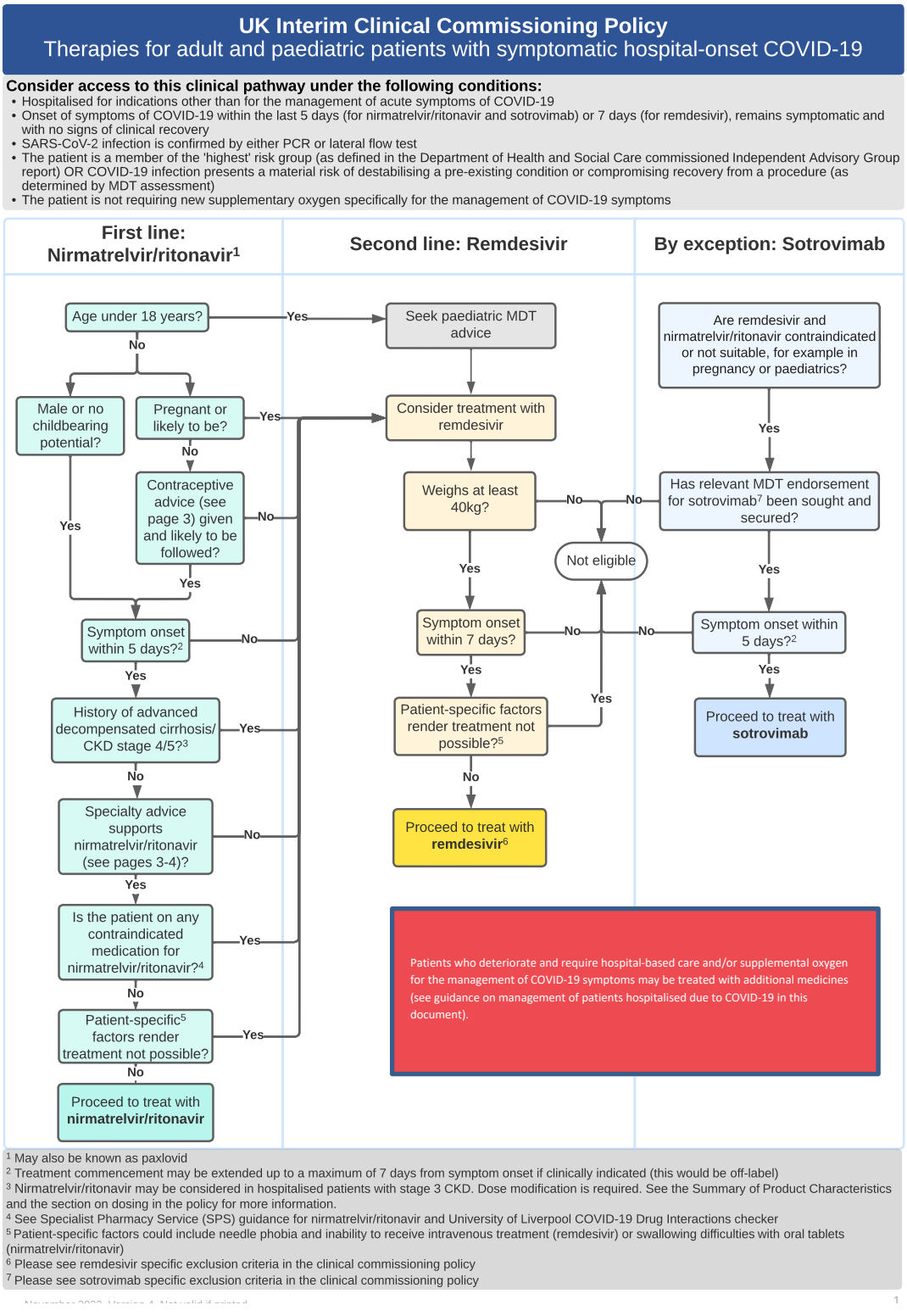

Figure 2: Therapies for patients with symptomatic hospital-onset COVID-19. Adapted from: https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103219

EXCLUSION CRITERIA

The following patients are not eligible for treatment in Group 2 (patients with hospital-onset COVID-19):

- 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 apply 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 that significantly interact with PF-07321332 (nirmatrelvir) plus ritonavir. Note that it may be possible for some medications to be temporarily stopped while the patient is receiving PF-07321332 (nirmatrelvir) plus ritonavir. Please see the following resources: https://www.covid19-druginteractions.org/prescribing-resources and https://www.covid19-druginteractions.org/checker

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

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

Remdesivir should be discontinued in patients who develop any of the following:

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

DOSE & ADMINISTRATION

PATIENTS WITH HOSPITAL-ONSET COVID-19

PF-07321332 (NIRMATRELVIR) PLUS RITONAVIR

The recommended dose of PF-07321332 (nirmatrelvir) plus ritonavir is 300mg (two 150mg tablets) PF-07321332 (may also be known as nirmatrelvir) with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days.

RENAL IMPAIRMENT

In patients with moderate renal impairment (CKD stage 3), the dose of nirmatrelvir/ritonavir should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days:

- Moderate renal impairment (eGFR 30 to 59 mL/min): Half dose: nirmatrelvir 150mg (ONE tablet instead of TWO with full dose ritonavir)
- Severe renal impairment (eGFR <30mL/min): Not recommended

REMDESIVIR

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

SOTROVIMAB

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

ADMINISTRATION

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. Clinicians should assure themselves that patients are able to swallow the oral tablets or seek advice from pharmacist where swallowing difficulties or NG/PEG administration is required.

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.

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

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.

Please note that pharmacy will only dispense PF-07321332 (nirmatrelvir) plus ritonavir Monday to Sunday 9am to 4pm.

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

500mg (8mls of 62.5mg/ml) sotrovimab should be added to a 100ml pre-filled infusion bag containing 0.9% sodium chloride and administered over 30 minutes via a 0.2micron low-protein-binding filter. Sotrovimab should not be infused concomitantly in the same intravenous line with other medication.

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.

Sotrovimab needs to be stored in the fridge at 2-8° Celsius until required.

APPROVAL OF USE

Approval to use nMAB Therapy for patients who are aged 12 to15 will need to be discussed with the paediatric infectious diseases consultant, Dr Laura Jones, or if not available, the paediatric infectious diseases team in Glasgow (9am to 5pm).

All patients aged 16 or older considered for sotrovimab by exception should a MDT assessment (including the ID consultant on-call).

DOCUMENTATION OF USE

PF-07321332 (NIRMATRELVIR) PLUS RITONAVIR

The use of PF-07321332 (nirmatrelvir) plus ritonavir should be documented using the following short code: **\PAXLOVID**

Pharmacy staff will check Trak documentation by accessing the completed shortcode entry on TRAK (this will also inform stock holding).

Please note that pharmacy will only dispense PF-07321332 (nirmatrelvir) plus ritonavir Monday to Sunday 9am to 4pm.

REMDESIVIR

The use of remdesivir should be documented using the following short code: \remd

SOTROVIMAB

The use of sotrovimab requires MDT discussion including the ID consultant on-call. Use is documented using the following short code: **\SOTROVID**

Pharmacy staff will check Trak documentation by accessing the completed shortcode entry on TRAK (this will also inform stock holding).

Please note that pharmacy will only dispense sotrovimab Monday to Sunday 9am to 4pm.

CAUTIONS

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

PF-07321332 (NIRMATRELVIR) PLUS RITONAVIR

PF-07321332 (nirmatrelvir) plus ritonavir has a risk of serious adverse reactions due to interactions with other medicinal products. Please check for interaction on this website: https://www.covid19-druginteractions.org/checker

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.

PREGNANCY AND WOMEN OF CHILDBEARING POTENTIAL

All pregnant patients eligible for treatment should be discussed with obstetrics and infectious diseases.

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.

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.

SARS-COV-2 VACCINATION

Based on currently limited evidence, no specific interval is required between receipt of nMABs and COVID-19 vaccination, or vice versa. Please see the COVID-19 - SARS-CoV-2 section of the Green Book for latest guidance: https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a

SAFETY REPORTING

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

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ABBREVIATIONS

BNF	British National Formulary
COPD	Chronic obstructive airway disease
COVID-19	Coronavirus disease 2019
IL-6	Interleukin 6
IV	intravenous
mg	milligram
MHRA	Medicines & Healthcare products Regulatory Agency
ml	millilitre
mmol/l	millimole per litre
NG	nasogastric
NHSL	National Health Service Lothian
nMAB	Neutralising Monoclonal Antibody
O2	oxygen
PCR	polymerase chain reaction
POCT	Point-of –care-test
RECOVERY (trial)	Randomised Evaluation of COVID-19 Therapy
REMAP-CAP	Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organisation

APPENDIX 1

SHORTCODES

\REMD

This is the Trak short code to be used to document the use of remdesivir. It will generate the following canned text:

```
Remdesivir approval

Complete the sections in uppercase (without all fields completed – drug will not be supplied from pharmacy).

PLANNED DURATION OF TREATMENT: 3 DAYS / 5 DAYS / 10 DAYS (delete as appropriate)

Important: for indications, duration and dose please refer to hospital guidelines on the intranet.

NAME OF CONSULTANT IN CHARGE REQUESTING REMDESIVIR:

CURRENT PATIENT WARD:

Now prescribe remdesivir course on the drug chart / HEPMA.
```

\IL6COV

This is the Trak short code to be used to document the use of IL-6 inhibitors (tocilizumab/sarilumab). It will generate the following canned text:

```
Tocilizumab approval for COVID-19 / Sarilumab approval for COVID-19

Please read the COVID-19 treatment guidelines (available on the intranet) carefully.
```

Complete all the sections in uppercase.

IS THE PATIENT CURRENTLY BEING TREATED FOR COVID-19? Yes / No (delete as appropriate)

With the exception of critical care areas, IL-6 inhibitors will only be supplied by pharmacy 9am to 5pm (7 days a week). Out of hours requests from non-critical care areas will not be processed until the following morning.

Patients must meet all the eligibility criteria and none of the exclusion criteria. Hospitalised patients are eligible to be considered for an IL-6 inhibitor (tocilizumab or sarilumab) if:

• COVID-19 infection is confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis;

AND

• They have not already been treated during this episode with tocilizumab or sarilumab;

AND

• Receiving dexamethasone or an equivalent corticosteroid unless contraindicated;

AND

Either

o Hypoxaemia with evidence of inflammation but not yet critically ill requiring respiratory support defined as:

▪ C-reactive protein level of at least 75mg/L; AND

▪ an oxygen saturation of <92% on room air OR requirement for supplemental oxygen;

Or

o In the early stages of critical illness requiring respiratory support (if an IL-6-inhibitor

has not been already administered for COVID-19) defined as:

▪ Within 48 hours of commencement of respiratory support (high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation), regardless of C-reactive protein level.

DOES THE PATIENT FULFIL THE ABOVE INCLUSION CRITERIA? Yes / No (delete as appropriate)

DOES THE PATIENT FULFIL ANY EXCLUSION CRITERIA (SEE GUIDELINES)? Yes / No (delete as appropriate)

IS THE PATIENT PREGNANT OR BREASTFEEDING? Yes / No (delete as appropriate)

If pregnant or breastfeeding the patient should be discussed with obstetrics or infectious diseases.

Patient who do not fulfil above inclusion criteria or have exclusion criteria and where an IL-6 inhibitor is still being considered should be discussed with the infectious diseases consultant on-call.

The decision to initiate treatment with tocilizumab or sarilumab should be made by the receiving consultant and with the support from multi-disciplinary colleagues in cases of uncertainty.

PLEASE CONFIRM THE NAME OF THE RESPONSIBLE CONSULTANT WHO MADE THE DECISION TO TREAT WITH AN IL-6 INHIBITOR:

CURRENT PATIENT WARD:

IL-6 INHIBITOR USED (PHARMACY WILL ADVISE ON STOCK LEVELS DURING WORKING HOURS): tocilizumab / sarilumab (delete as appropriate)

Single dose only (no additional doses recommended) - see intranet for dosing guidance.

FORM FILLED IN BY (NAME, DESIGNATION, CONTACT):

\SOTROVID

This is the Trak short code to be used to document the use of sotrovimab. It will generate the following canned text:

Sotrovimab for patients with COVID-19

Complete the sections in uppercase

Criteria:

SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) testing within the last 5 days

and

Onset of symptoms of COVID-19 within the last 5 days

and

A member of a 'highest' risk group (as defined in national policy)

SCENARIO: NOT HOSPITALISED / HOSPITAL-ONSET (delete as appropriate)

SEROLOGY SAMPLE AGAINST SARS-COV2 OBTAINED PRIOR TO TREATMENT WITH SOTROVIMAB: YES / NO (delete as appropriate)

Single dose of 500mg Sotrovimab IV in 100mls NaCl 0.9% over 30mins administered.

ANY ADVERSE REACTIONS WITHIN THE POST-ADMINISTRATION MONOTORING PERIOD: YES / NO (delete as appropriate; if answered 'yes' then describe symptoms)

GP LETTER SENT? YES / NO / NOT REGISTERED WITH GP

SIGNED BY:

\PAXLOVID

PF-07321332 (nirmatrelvir) plus ritonavir for patients with COVID-19

Complete the sections in uppercase.

For indications and criteria please see latest guidance on the intranet.

I CONFIRM THAT I CHECKED THE INDICATIONS AND CONTRAINDICATIONS FOR PF-07321332 (NIRMATRELVIR) PLUS RITONAVIR: YES / NO

I CONFIRM THAT I HAVE CHECKED FOR DRUG-DRUG-INTERACTIONS WITH PATIENT'S REGULAR MEDICINES: YES / NO

eGFR IS GREATER THAN 59ML/MIN? YES / NO

If eGFR is greater than 59ml/min then use the following dose: PF-07321332 (nirmatrelvir) plus ritonavir is 300mg (two 150mg tablets) PF-07321332 with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days.

For patients with moderate or severe renal impairment see guidance on the intranet or speak to specialist.

OUTCOME: PF-07321332 (NIRMATRELVIR) PLUS RITONAVIR PRESCRIBED: YES / NO

CURRENT PATIENT LOCATION: (please enter hospital and ward location; if outpatient write 'outpatient')

SIGNED BY:

\BARICOV

Baricitinib approval for COVID-19

Please read the COVID-19 treatment guidelines (available on the intranet) carefully.

Complete all the sections in uppercase.

IS THE PATIENT CURRENTLY BEING TREATED FOR COVID-19? Yes / No (delete as appropriate)

With the exception of critical care areas, baricitinib will only be supplied by pharmacy 9am to 4pm (7 days a week). Out of hours requests from non-critical care areas will not be processed until the following morning.

Patients must meet all the eligibility criteria and none of the exclusion criteria.

DOES THE PATIENT FULFIL THE INCLUSION CRITERIA (SEE GUIDELINES)? Yes / No (delete as appropriate)

DOES THE PATIENT FULFIL ANY EXCLUSION CRITERIA (SEE GUIDELINES)? Yes / No (delete as appropriate)

The decision to initiate treatment with baricitinib should be made by the receiving consultant and with the support from multi-disciplinary colleagues in cases of uncertainty.

CURRENT PATIENT WARD:

NAME OF CONSULTANT IN CHARGE REQUESTING BARICITINIB:

FORM FILLED IN BY (NAME, DESIGNATION, CONTACT):