Remdesivir for Patients with COVID-19 (Adults and Paediatric Patients) Guidelines for NHS GGC

Background and Evidence

Remdesivir is an adenosine nucleotide prodrug that is metabolised intracellularly to form the pharmacologically active substrate remdesivir triphosphate. Remdesivir triphosphate inhibits SARS-CoV-2 RNA polymerase which perturbs viral replication.

Current evidence shows that remdesivir improves clinical outcomes in both hospitalised and non-hospitalised patients with COVID-19. The World Health Organization (WHO) updated its 'Therapeutics and COVID-19: Living guideline' on 16 September 2022 and the recommendations have been considered in the development of this policy (WHO, September 2022).

- **Hospitalised patients**: evidence from the ACTT-1 trial showed that remdesivir improved time to recovery in patients hospitalised with COVID-19 by 5 days compared to placebo. All-cause mortality was 11.4% with remdesivir and 15.2% with placebo (hazard ratio, 0.73; 95% CI, 0.52 to 1.03) (Beigel et al, 2020). The World Health Organization (WHO) SOLIDARITY trial indicated that remdesivir did not improve overall mortality, initiation of ventilation or duration of hospitalisation (Pan et al, 2020).
- **Non-hospitalised patients**: evidence from the PINETREE trial, which studied the use of remdesivir in non-hospitalised patients within 7 days of COVID-19 symptom onset and had risk factors for disease progression indicated that a 3-day course of remdesivir resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 compared with placebo (Gottlieb et al, 2020).

Remdesivir delivered intravenously has conditional marketing authorisations for the following indications:

- treatment of COVID-19 in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) 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 and paediatric patients (weighing at least 40kg) 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.**

Eligibility criteria

For a short summary, please see the remdesivir flowcharts in Appendix 1 for clinical indications in patients hospitalised due to symptomatic COVID-19 and brief dosing and monitoring information.

Please remember that dexamethasone and the IL-6 inhibitors have demonstrated a mortality benefit in patients admitted unwell with COVID-19. Please refer to this summary for an overview of COVID-19 treatments in Group 1 patients.

The eligibility is split into 3 groups according to stage of infection and whether the patient is hospitalised or in the community:

Group 1: Patients Hospitalised Due to Symptoms of COVID-19
Patients are eligible for treatment if they fulfil the following eligibility criteria:

•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
•Hospitalised specifically for the management of COVID-19 symptoms

AND
•Requiring supplemental oxygen (see later section on 'Immunocompromised patients' for how this criterion applies to this group)

AND
•Presented to hospital not more than 10 days since symptom onset

AND
•Estimated glomerular filtration rate (eGFR) at least 30 ml/minute

AND
•Alanine aminotransferase (ALT) below 5 times the upper limit of normal at baseline.

Exemptions to the above eligibility criteria apply to the following patient groups:
- Patients with end-stage renal disease on haemodialysis are exempt from the eGFR treatment threshold above
- Significantly immunocompromised patients (see later section on 'Immunocompromised patients' for exemptions in this cohort).

Group 2: Patients with Hospital-Onset COVID-19
Please see the Group 2 Guidelines for eligibility and exclusion criteria and dosing in this patient group. Please note the guidance is for a total of 3 days of Remdesivir in this circumstance.

Group 3: Non-Hospitalised Patients with COVID-19
Due to logistical reasons NHS GGC does not offer remdesivir routinely for out-patients, but it may be considered in pregnant women in discussion with the patient's obstetrician. Other complex cases may be able to be accommodated if their local specialist is able to facilitate this within their unit- please see the Group 3 guidelines for eligibility and exclusion criteria and dosing in this patient group. Please note the guidance is for a total of 3 days of Remdesivir in this circumstance.

Exclusion criteria and cautions

Patients who meet any of the following exclusion criteria are NOT eligible for treatment in any of the above groups with remdesivir:
- Children aged less than 4 weeks of age and/or weighing less than 3 kg
- Known hypersensitivity reaction to the active substances or to any of the excipients of remdesivir as listed in the Summary of Product Characteristics for Great Britain and Northern Ireland.
- Estimated glomerular filtration rate (eGFR)<30ml/min (except in patients with end-stage renal disease on haemodialysis)
- Alanine transaminase (ALT) ≥ 5 times the upper limit of normal

An individual clinical decision should be made as to whether pre-treatment urea and electrolytes and liver function tests are required, based upon whether recent bloods are available or the patient is considered at risk of undiagnosed liver or kidney disease.

The decision to initiate remdesivir must be made by a Consultant and be within the defined criteria. If a patient does not meet the eligibility criteria and remdesivir therapy is still felt to be a therapeutic consideration, the Consultant in charge of the patient's care must discuss the case with at least one other Consultant who has expertise in the management of COVID, for example the on call Infectious Diseases or Respiratory Consultant. It may be that a broader MDT discussion is required in complex cases. The summary and outcome of this discussion, along with the names of the clinicians involved in the discussion, must be clearly documented in a clinical note on Portal.

Severely Immunocompromised Patients

These patients are most likely to benefit from treatment with Remdesivir. For significantly immunocompromised patients** hospitalised for COVID-19 symptoms, e.g. B cell deficiencies, bone marrow transplant:

- 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 criterion on the need for supplemental oxygen requirement does not apply.
- Consider discussing these patients with the Infectious Diseases team.

**Refers to patients with a significant impairment of humoral immune response (antibody production) and/or cellular immune competence.

Remdesivir Supply, Dosing, Duration and Administration

Please note the detailed dosing and duration advice below apply to Group 1 patients only, ie patients hospitalised due to symptoms of COVID-19.

For Group 2 and Group 3 patients the recommended dose is remdesivir 200mg intravenously on day 1, followed by remdesivir 100mg once a day on days 2 and 3. Please see corresponding NHS GGC Guidelines for these groups –links on page 2 above.

Supply

Supplies can be obtained from departments of pharmacy during opening hours via an indent for a named patient supply. Please do not call an on-call pharmacist out for supply. Some supplies of loading doses are available in emergency drug cupboards.

Dose

The recommended dosage for patients hospitalised due to symptoms of COVID-19 is a single loading dose of remdesivir intravenously on day 1, followed by a once daily maintenance dose of remdesivir for the remainder of the treatment course, which should not exceed 5 days (see exemption in immunocompromised patients in section above). Please see table below for detail

	Given by intravenous infusion		
	Adults	**Paediatric patients (weighing at least 40 kg)**	**Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Day 1 (single loading dose)	200 mg	200 mg	5 mg/kg
Day 2 and onwards (once daily)	100 mg	100 mg	2.5 mg/kg
	Treatment Duration		
Group 1 Patients with pneumonia and requiring supplemental oxygen	Daily for at least 5 days and not more than 10 days.		

Duration of treatment

- All patients treated must receive a maximum of 5 days of remdesivir in total (comprising a loading dose plus 4 further days of maintenance doses).
- 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.
- Patients re-admitted for symptoms of COVID-19 (and meeting the eligibility criteria, 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 are eligible for an extended course of remdesivir (up to 10 days), if agreed following multidisciplinary team assessment.

Administration

200mg of remdesivir (day 1 loading dose) and 100mg of remdesivir (days 2-5 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. In Group 1 patients, treatment should be initiated as soon as possible after admission to hospital and within 10 days of symptom onset.

For paediatric patients at least 4 weeks old (weighing at least 3kg but less than 40kg), the single loading dose of remdesivir (5mg/kg intravenously on day 1) and the once daily maintenance dose (2.5mg/kg on days 2-5) should be diluted in either a 25ml, 50ml 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 admission to hospital and within 10 days of symptom onset.

Side effects and monitoring

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

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)

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
Please refer to the SmPC for Remdesivir for a fuller list of side effects and precautions for use.

Genotyping and sequencing of samples
Sequencing is an important part of surveillance activities to monitor for the development of new variants and drug resistance. Therefore, in patients being considered for treatment with remdesivir, samples pre-treatment and where part of the clinical pathway, post-treatment, should be prioritised for sequencing. Genotype results do not form part of the eligibility criteria for treatment with remdesivir and treatment should not be delayed pending these results.

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of remdesivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures of the major metabolite of remdesivir that were around human therapeutic exposures (see section 5.3 remdesivir SmPC). Remdesivir should not be used during pregnancy unless the clinical condition of the women requires treatment with it. Women of child-bearing potential have to use effective contraception during treatment.

RCOG Guidance (updated 15/12/2022) https://app.magicapp.org/#/guideline/LqgJ3E

- Remdesivir, an antiviral, may be considered in pregnant women with COVID-19 in community and hospital settings.
- Clinicians should be aware that the fetal risk profile of remdesivir is largely unknown. See SmPC for further information.

Co-administration
There is no interaction expected between remdesivir and other commissioned treatments for COVID-19. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Safety reporting
Any suspected adverse drug reactions (ADRs) for patients receiving remdesivir 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

Clinical outcome reporting

Hospitals managing COVID-19 patients are 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/).

Surveillance and service evaluation

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

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.

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764
2. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2022;386(4):305-315. doi:10.1056/NEJMoa2116846
3. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021;384(6):497-511. doi:10.1056/NEJMoa2023184
4. Therapeutics and COVID-19: living guideline, 16 September 2022. Geneva: World Health Organization; 2022 (WHO/2019-nCoV/therapeutics/2022.5). Licence: CC BY-NC-SA 3.0 IGO.

Appendix 1

Remdesivir Treatment Guide – **Group 1 Adult & Paediatric** patients

Remember Dexamethasone and IL-6 inhibitors save lives! Click here for summary of treatment options

Positive COVID PCR (inc POC tests) and/or radiological Changes related to COVID pneumonia **AND**
illness onset<10 days **AND** supplemental O2 required
AND 4 weeks or older, >3kg, eGFR >30ml/min, and ALT<5x ULN

Don't initiate treatment if
- Presentation >10 days after **illness onset****
- Patient considered to be at end of life/ Unlikely to survive/treatment assessed as futile
- On ECMO or IMV

Adults (all weights) & Paed >40kg:
Start Remdesivir 200mg IV day 1. Maintenance 100mg IV daily Days 2-5

Paed >4 weeks **AND** >3kg, <40kg
Start Remdesivir 5mg/kg IV day 1. Maintenance 2.5mg/kg IV daily Days 2-5

MAX TOTAL DURATION 5 DAYS**

Do not start Remdesivir out of hours or call pharmacy out of hours to obtain this.

Review daily
- Clinical response
- U&Es
- LFTs

Stop
- If improves and no O2 requirement after 72 hours.
- If deteriorates after 48 hours ventilation
- If Patient assessed to be at end of life
- If 5 days completed
- Discharged even if <5 days treatment course
- eGFR<30ml/min or ALT>5x ULN

** **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 criterion on the need for supplemental oxygen requirement does not apply.
- Consider discussing patient with Infectious Diseases

Remdesivir Treatment Guide – **Group 2&3** patients

Consider if
- Adult (all weights), Paediatric >40kg
- Positive COVID test within 7 days (PCR or registered LFT result)
- Symptoms within 7 days and showing no evidence of clinical recovery
- Identified as High Risk (see GGC guideline in Therapeutics Handbook for details)

Exclusion Criteria
- New supplemental oxygen requirement specifically for the management of COVID-19 symptoms (go to Group 1 treatment guide)
- Children/adolescents weighing <40kg
- eGFR <30ml/min *
- ALT>5x ULN *

*In Group 3 patients, do baseline U&E and LFTs if these not checked in the last 6 months

Start Remdesivir 200mg IV day 1, then 100mg IV daily Days 2 & 3

Review daily
- Clinical response
- Consider U&E and LFT monitoring if abnormal at baseline

Stop
- If eGFR<30ml/min or ALT>5x ULN

Please note Remdesivir is second line in these patients with Paxlovid as first line treatment

Document History

Version	Date	Description
First release not versioned	June 2021	First release approved after MHRA CAS Alert 14/06/2021 as EAMS process in therapeutic handbook
2.0	08/04/2022	Review after MHRA CAS Alert 24/02/2022
3.0	29/12/2022	Review after MHRA CAS Alert 28/11/2022
4.0	12/01/2024	Routine review; minor typo corrected; add document history

COVID-19
CLINICAL GUIDELINE

Note: This guideline has been fast-tracked for approval for use within NHSGGC

Covid 19 Remdesivir for Patients with COVID-19 (Adults and Paediatric Patients)

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Does this version include changes to clinical advice:	Yes
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Approval Group:	Covid 19 Tactical Group (Acute)

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.