University Hospitals Sussex
NHS Foundation Trust

Guideline for the use of Remdesivir for the treatment of COVID-19 in hospitalised patients

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

Scope:
This document provides guidance for healthcare professionals considering remdesivir for patients hospitalised due to COVID-19 or with hospital onset COVID-19. It follows recommendations from the CMO alert CEM/CMO/2021/013 dated 14th June 2021 and the CMO alert CEM/CMO/2021/023 dated 24th December 2021.

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

The evidence that it improves outcome in acute COVID-19 is limited and sits early in the course of disease. Its place in treatment at the current time is for a subset of acute COVID-19 patients who do not meet eligibility criteria for IL6-blockers or monoclonal antibodies.

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

Evidence summary:
Remdesivir has demonstrated superiority to placebo in a double-blind, randomised, placebo-controlled study in shortening the time to recovery in adults hospitalised with Covid-19 and evidence of lower respiratory tract infection (Biegel JH, 2020). This conflicts with the conclusion of the WHO Solidarity trial in which remdesivir appeared to have little or no effect on hospitalised Covid-19, as indicated by mortality, initiation of ventilation and duration of hospital stay (WHO Solidarity Trial Consortium, 2020).

Remdesivir administered intravenously for 3 days to non-hospitalised patients within 7 days of COVID-19 symptom onset who had risk factors for disease progression, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (Gottlieb RL, 2021).

It is now licensed in the UK and is available for the treatment of SARS-CoV-2 infection in adults and children 12 years and older.

Indication:
Remdesivir should be considered as an adjuvant treatment to standard care in eligible hospitalised patients with COVID-19 if they meet the eligibility criteria defined below.

Eligibility criteria:

Patients hospitalised with acute COVID-19 (Group 1)

When a patient is admitted to hospital for the treatment of COVID-19 infection they may be eligible for treatment with remdesivir if they meet **all** of the following **inclusion criteria** and none of the exclusion criteria**:**

- SARS-CoV-2 infection confirmed by PCR ***OR*** in the absence of a confirmed virological diagnosis, when the multi-disciplinary team (MDT) (see below) have a high level of confidence that COVID-19 is the most likely diagnosis based on clinical and radiological features.
- Hospitalised specifically for the management of acute symptoms of COVID-19
- Not eligible for treatment with IL6 blockers – see separate guidance
- With pneumonia requiring low-flow supplemental oxygen (facemask or nasal cannula at a flow rate usually up to 15L/min). ***This criterion does not apply to those with significant immunosuppression.***[1]
- No more than 10 days since the onset of symptoms ***This criterion does not apply to those with significant immunosuppression***[1]

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

When a patient in hospital acquires COVID-19 infection or is admitted with COVID-19 but is not unwell enough to need hospital treatment for COVID-19 disease, they may be eligible for treatment with remdesivir if they meet **all** of the following **inclusion criteria** and none of the exclusion criteria**:**

- SARS-CoV-2 infection confirmed by PCR **within the preceding 5 days.** Note that Group 2 patients must have a virologically confirmed diagnosis of COVID to be eligible for remdesivir.
- No more than 7 days since the onset of symptom
- Not eligible for nMAB treatment for any reasons – link to separate guidance
- The patient must be
    - Member of the highest risk group (appendix 1)
      OR
    - COVID-19 infection presents a material risk of destabilising a pre-existing condition or illness or compromising recovery from surgery or other hospital procedure, determined by MDT assessment (see below for members).

[1]Significant immunosuppression is defined as a significant impairment of humoral immune response (antibody production) and/or cellular immune competence.

Exclusion criteria

Patients must meet NONE of the following **exclusion criteria:**

- Weighing less than 40 kg.
- Children aged under 12.
- eGFR less than 30mL/min excluding patients on haemodialysis
- ALT > 5 times upper limit of normal and no history of chronic liver disease (defined as Childs Pugh C)
- Known hypersensitivity reaction to the active substances or to any of the excipients
- Remdesivir should not be initiated in patients who are unlikely to survive (determined by clinical judgement). The 4C mortality score can help support clinical judgement. The calculator can be accessed here [advise using in Firefox or Google Chrome browser].

Further Exclusion criteria for Group 2

- The pattern of clinical presentation indicates that there is recovery rather than risk of deterioration from infection
- Require hospitalisation specifically for the management of acute COVID-19 illness
- New supplemental oxygen requirement specifically for the management of COVID-19 symptoms (treat as per group 1)

Drug Interactions:

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

For up to date information check the University of Liverpool COVID-19 drug interactions website.

Pregnancy & Breastfeeding:

There are limited data from the use of remdesivir in pregnant women. Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (please see SmPC for further information).

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

Approval & Governance:

A decision to prescribe remdesivir must always be made by a **multi-disciplinary team (MDT)** consisting of:

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

For patients hospitalised with acute Covid-19 (Group 1) and on general wards Remdesivir will be available to be administered between 8.00am and 8.00pm. Last supply orders for Remdesivir should be received in pharmacy by 6.00pm in order to deliver to wards and allow nursing staff to administer.

For patients in ITU, remdesivir is available at all times.

For patients who have hospital onset Covid-19 or who are incidentally PCR positive on admission (Group 2) Remdesivir will be available during normal working hours of 9.00am to 6.00pm.

Completion of a Blueteq form is mandatory for approval and supply of remdesivir.

RSCH/PRH

The Blueteq form must be completed by the specialist pharmacist for all requests. The pharmacist supplying the medication should inform the infection specialist pharmacist via email or on bleep 8033.

Worthing/SRH

The Blueteq form must be completed by the prescribing clinician and processed by the ward pharmacist. This is available on the intranet. Blueteq forms must be emailed to uhsussex.COVIDdrugforms@nhs.net and uhsussex.research@nhs.net by the ward pharmacist to be reviewed by the antimicrobial pharmacists.

Continuing care:

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals) must explicitly mention that Remdesivir has been given and the date(s) of administration.

The GP should be informed on the discharge summary that Remdesivir has been prescribed specifying the date(s) of administration.

Dosage

	Loading Dose	Maintenance Dose	Number of days Treatment	Other
Group 1	200mg (D1)	100mg (D2-D5)	5 days	May be extended to a maximum of 10 days in significantly immunocompromised[1] patients following discussion with the MDT
Group 2	200mg (D1)	100mg (D2-D3)	3 days	Please note that a 3-day course of remdesivir at the dose specified is off-label.

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 remdesivir; or
- The patient continues to deteriorate despite 48 hours of sustained mechanical ventilation.

Prescribing & Administration

Two formulations are available for use. **Information on preparation and administration** can be found on the **Injectable Medicines Guide** accessed via the Pharmacy homepage on the Trust intranet.

Formulation	Infusion fluid	Infusion time	Storage
Concentrate for Solution for Infusion 100mg in 20mL vial	250mL sodium chloride 0.9%	30 – 120 minutes	Fridge (2 - 8°c)
Powder for Concentrate for Solution for Infusion 100mg vial	100 - 250mL sodium chloride 0.9%	30 – 120 minutes	Room temperature (<30°c)

All unused vials should be returned without delay to Pharmacy.

Monitoring

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

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

Monitoring during administration

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

Monitor for signs of hypersensitivity and blood pressure.

Safety Reporting

Remdesivir delivered intravenously has conditional marketing authorisation in the UK for treatment of COVID-19 in adults and adolescents (aged 12 years and over and weighing at least 40kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), for a treatment duration of 5-10 days.

Marketing authorisation variation for Great Britain is currently being considered by the Medicines and Healthcare products Regulatory Authority (MHRA) under the 'reliance route'. **Ahead of MHRA's determination, use or remdesivir under this policy for Group 2 patients in Great Britain would be considered off-label.**

There is limited clinical data available for remdesivir and adverse events may occur during treatments that have not been previously reported. Any suspected adverse drug reactions for patients receiving remdesivir must be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/

Appendix 1

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

Cohort	Description
Down's syndrome	All patients with Down's syndrome
Patients with a solid cancer	• Active metastatic cancer and active solid cancers (at any stage) • All patients receiving chemotherapy within the last 3 months • Patients receiving group B or C chemotherapy 3-12 months prior (see below) • Patients receiving radiotherapy within the last 6 months

Patients with a haematological diseases and stem cell transplant recipients	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases)
	• Autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases)
	• Individuals with haematological malignancies who have
	  ○ received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months, or
	  ○ radiotherapy in the last 6 months
	• Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months except patients with chronic phase chronic myeloid leukaemia (CML) in molecular response or first or second line tyrosine kinase inhibitors (TKI).
	• All patients with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma) or myelodysplastic syndrome (MDS) who do not fit the criteria above.
	• All patients with sickle cell disease.
	• Individuals with non-malignant haematological disorder (e.g. aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (e.g. anti-CD20, anti-thymocyte globulin [ATG] and alemtzumab) within the last 12 months.

Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly

	those who: ○ Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin) ○ Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals ○ Not been vaccinated prior to transplantation • Non-transplant patients who have received a comparable level of immunosuppression • Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression
Patients with liver disease	• Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease). • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) • Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders (IMID)	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable disease on corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID with stable disease on either corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Primary immune deficiencies	• Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • Severe Combined Immunodeficiency (SCID) • Autoimmune polyglandular syndromes/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Primary immunodeficiency associated with impaired type I interferon signalling

	• X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)
HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 <350 cells/mm^3 and stable on HIV treatment or CD4>350 cells/mm^3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	• Multiple sclerosis • Motor neurone disease • Myasthenia gravis • Huntington's disease

Group B	**Group C**
10-50% risk of grade 3/4 febrile neutropenia or lymphopenia	**>50% risk of grade 3/4 febrile neutropenia or lymphopenia**
Etoposide based regimens CMF Irinotecan and Oxaliplatin based regimens Cabazitaxel Gemcitabine Chlorambucil Temozolomide Daratumumab Rituximab Obinutuzumab Pentostatin Proteosome inhibitors IMIDs PI3Kinase inhibitors BTK inhibitors JAK inhibitors Venetoclax Trastuzumab-emtansine Anthracycline-based regimens Fluorouracil, epirubicin and cyclophosphamide (FEC) Methotrexate, vinblastine, adriamycin/doxorubicin, cisplatin (MVAC) Adriamycin/doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) Cyclophosphamide, doxorubicin, vincristine,	All acute myeloid leukaemia/acute lymphocytic regimens Bleomycin, etoposide and platinum Highly immunosuppressive chemotherapy (e.g. FluDAP, high dose Methotrexate & Cytarabine) Trifluradine/ Tipiracil KTE-X19 Gilteritinib

prednisolone (CHOP) Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOPP) Liposomal doxorubicin Taxane – 3-weekly Nab-paclitaxel Carboplatin-based regimens Ifosphamide-based regimens Bendamustine Cladrabine Topotecan Cyclophosphamide/Fludarabine combinations Ifosphamide, carboplatin, etoposide (ICE) Gemcitabine, dexamethasone, cisplatin (GDP) Isatuximab Polatuzumab Acalabrutinib Dexamethasone, cytarabine, cisplatin (DHAP) Etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP) Cyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD) Dacarbazine-based regimens Lomustine Magalizumab Brentuximab vedotin Asparaginase-based regimens	