Remdesivir for the treatment of Covid-19

Background
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. 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.

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 is indicated for the treatment of adults and adolescent patients aged ≥ 12 years and weighing at least 40kg who are hospitalised with SARS-CoV-2 infection with pneumonia requiring low-flow oxygen (facemask or nasal cannula at a flow rate usually up to 15L/min). The criterion on the need for supplemental oxygen does not apply to those with significant immunosuppression.

Current evidence suggests lack of benefit for those on ventilation, including non-invasive ventilation such as CPAP. At the time of decision to treat with remdesivir, patients should NOT be receiving on-going mechanical ventilation or ECMO. Patients who present with an initial rapid deterioration can, however, be considered for treatment with remdesivir. See Appendix 1 - Flow diagram for use of remdesivir during times of limited supply to support decision making.

Additionally, the following criteria should be met before starting treatment:

1. SARS-CoV-2 infection confirmed by PCR or in the absence of a confirmed virological diagnosis only when a multidisciplinary team have a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis.
2. No more than 10 days since the onset of symptoms (except for those with significant immunosuppression).
3. eGFR ≥ 30mL/min excluding patients on haemodialysis
4. ALT < 5 times upper limit of normal and no history of chronic liver disease (defined as Childs Pugh C).

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].

<table>
<thead>
<tr>
<th>4C Mortality Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 3</td>
<td>Low risk. Highly likely to recover without treatment with remdesivir</td>
</tr>
<tr>
<td>4 - 8</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>9 - 14</td>
<td>High risk</td>
</tr>
</tbody>
</table>


Approved by: Medicines Governance Group – June 19th 2020. Review: 3 months from latest approval or sooner if clinical information changes
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Very high risk

The decision to treat with remdesivir is not an emergency and should be made judiciously after assessment and in a timely manner.

A second course of remdesivir is permitted should a patient be re-admitted and meets all eligibility criteria other than duration from symptom onset.

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

Approval & Governance

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

1. The clinical team (SpR or above) who has responsibility for the patients’ care
2. Infectious Diseases Consultant – ext. 65207 (or microbiologist on-call via switchboard if out-of-hours)
3. Infection Specialist Pharmacist (ID Consultant to contact)

A BlueTeq form must be completed for all requests. This will be done by an infection specialist pharmacist.

Dosage

Loading dose of 200mg on day 1 then 100mg once daily for a further 4 days.

Maximum treatment duration of 5 days (this may be extended to a maximum of 10 days in significantly immunocompromised patients following discussion with the MDT).

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

Remdesivir should be prescribed on the Intravenous Infusion Prescription Sheet (pages 14 & 15 of adult drug-chart or pages 12 & 13 of paediatric drug-chart) or Metavision.
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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.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Infusion fluid</th>
<th>Infusion time</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentrate for Solution for Infusion</td>
<td>250mL sodium chloride 0.9%</td>
<td>30 – 120 minutes</td>
<td>Fridge (2 - 8 ºc)</td>
</tr>
<tr>
<td>100mg in 20mL vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powder for Concentrate for Solution for</td>
<td>100 - 250mL sodium chloride 0.9%</td>
<td>30 – 120 minutes</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Infusion 100mg vial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Side-effects and Drug Interactions
Side-effects reported in the clinical trials include:-

- Infusion-related reactions (fever, chills, hypotension, tachycardia, dyspnoea, angioedema, rash, vomiting). Slower infusion rates may prevent these signs and symptoms but if clinically significant hypersensitivity occurs immediately discontinue remdesivir and manage the reaction appropriately.
- Increases in transaminases.

There are limited clinical data available for remdesivir and adverse events may occur during treatments that have not been previously reported. Adverse effects experienced by patients receiving remdesivir should be reported as below.
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.

There is no interaction expected between remdesivir and dexamethasone

Co-administration of remdesivir and hydroxychloroquine is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.

Further information of potential drug interactions may be found via the University of Liverpool COVID-19 drug interactions website\(^3\).

Contact Medicines Information for patient specific advice if needed ext. 8153 or email bsuh.medicines.information@nhs.net Monday to Friday 9am – 5pm

Data Reporting

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/

Paediatric use

Remdesivir is available to treat children < 12 years or < 40kg via the remdesivir compassionate use programme https://rdvcu.gilead.com/

Pregnancy & Breastfeeding

Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks. Breastfeeding is not recommended with remdesivir.

Clinical Trials

Patients are still eligible to be randomised to the RECOVERY and REMAP-CAP clinical trials if receiving remdesivir.
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References