

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

## Initiation of remdesivir treatment for COVID-19

### Rapid review question

What is the evidence on timing of initiation of remdesivir treatment for COVID-19?

### In brief

- Remdesivir is an antiviral drug that has been authorised for emergency use to treat COVID-19 in several countries.<sup>1</sup>
- In November 2020, the World Health Organization published a conditional recommendation against the use of remdesivir in hospitalised patients with COVID-19 noting insufficient evidence to support its use.<sup>2</sup>
- Many studies show that in patients with mild-to-moderate COVID-19 cases with no requirement for respiratory support, remdesivir does not offer significant clinical benefits. However, for patients with severe COVID-19, at risk of hyperinflammation and requiring supplemental oxygen, remdesivir shortens time to recovery and reduces risk of progression when diagnosed early ( $\leq 10$  days).<sup>3, 4</sup>

### Initiation of treatment

- Randomised controlled trials have reported on timing of initiation of remdesivir treatment for moderate-to-severe COVID-19, with most reporting some benefit of earlier treatment:
  - higher rate of recovery for patients randomised  $\leq 10$  days after symptom onset compared to  $> 10$  days after symptom onset<sup>5</sup>
  - higher discharge rates for patients with symptoms less than 5 days before receiving treatment<sup>6</sup>
  - non-significant faster time (median reduction 5 days) to clinical improvement for remdesivir compared to placebo in patients with symptoms  $< 10$  days<sup>7</sup>
  - treatment beyond 5 days for patients receiving non-invasive positive-pressure ventilation or high-flow oxygen, low-flow oxygen, or breathing ambient air did not appear to improve outcomes<sup>8</sup>
  - use of remdesivir not supported in hospitalised patients with COVID-19 with symptoms for more than 7 days and requiring oxygen support.<sup>9</sup>
- Observational studies have also shown benefits of early remdesivir treatment in moderate-to-severe COVID-19 including:
  - significantly shorter hospitalisation and number of days to negative swab if administered within 48 hours of admission<sup>10</sup>

- significantly lower mortality in patients with a symptom onset to treatment time of  $\leq 9$  days compared to  $>9$  days<sup>11</sup>
- improved length of stay and reduced odds of requiring mechanical ventilation if administered  $\leq 3$  days from positive test compared with  $>3$  days.<sup>12</sup>

### Treatment course

- Randomised controlled trials have compared a 5-day or 10-day course of remdesivir with standard care or placebo using different outcome measures. Overall, both courses were found to be effective, with greater improvements reported in the 5-day group:
  - A systematic review and two separate network meta-analyses found both 5-day and 10-day courses of remdesivir are effective for patients with severe COVID-19 not requiring mechanical ventilation.<sup>4, 13, 14</sup> The meta-analyses also reported that a 5-day course provided greater clinical improvement than a 10-day course.<sup>13, 14</sup>
  - Four separate systematic reviews found no significant difference in efficacy between 5-day and 10-day courses, with similar outcomes including clinical improvement, length of hospitalisation, mortality and adverse events.<sup>8, 15-17</sup> Another systematic review found no difference in mortality between 5-day, 10-day and control groups.<sup>18</sup>
  - One systematic review found 5-day and 10-day courses of remdesivir decreased the rate of adverse events compared with standard care.<sup>19</sup> Five other systematic reviews reported a 5-day course decreased serious adverse events compared with a 10-day course.<sup>16-18, 20, 21</sup> Adverse events were similar between the two groups.<sup>17, 18</sup>
  - Two systematic reviews found the 5-day course group showed greater clinical improvement than both the 10-day course and control groups.<sup>22, 23</sup> One also found that the 5-day group was also superior to the 10-day group in mortality, recovery, discharge, time to clinical improvement, time to mortality, and time to recovery.<sup>22</sup>
  - Generally, a 10-day course is not more effective than a 5-day course. However, patients with worsening symptoms and/or who require ventilation may benefit from extending treatment to 10 days.<sup>5</sup>

## Limitations

There are limited studies on timing of remdesivir initiation for treatment of COVID-19. Existing studies have small sample sizes and some variability in results. There is heterogeneity in study design and definition of clinical outcomes. Studies do not always specify the time between symptom onset and remdesivir treatment initiation.

## Background

Remdesivir is an antiviral drug that has been reported to significantly reduce the time to recovery, the recovery rate, and mortality in moderate-to-severe COVID-19 patients.<sup>24</sup> In non-COVID-19 viral infections, early use (within 48 hours of onset) of an effective antiviral drug is associated with improved outcomes.<sup>25</sup> The World Health Organization recommends against the use of remdesivir in hospitalised patients with COVID-19. However, the US National Institute of Health COVID-19 treatment guidelines recommend remdesivir for mild-moderate COVID-19 patients requiring supplemental oxygen but not high-flow oxygen, during the early phase of the disease.<sup>26</sup>

## Methods (Appendix)

PubMed and grey literature were searched on 20 September 2021.

**Table 1: Systematic reviews or randomised controlled trials**

Source	Summary
<b>Peer reviewed sources</b>	
<p><a href="#">Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial</a></p> <p>Ader, et al. September 2021<sup>9</sup></p>	<ul style="list-style-type: none"> <li>• Randomised controlled trial (n=857) comparing remdesivir plus standard of care versus standard of care alone</li> <li>• Remdesivir (200mg intravenous infusion) administered on day 1 followed by once daily 1-hour infusions of 100mg up to 9 days. Stopped after 5 days if patient was discharged.</li> <li>• Results:             <ul style="list-style-type: none"> <li>○ No significant differences between remdesivir group and standard of care alone group at day 15</li> <li>○ No significant difference in adverse events between groups</li> </ul> </li> <li>• Conclusion: Use of remdesivir not supported in hospitalised patients with COVID-19 with symptoms for more than 7 days and requiring oxygen support</li> </ul>
<p><a href="#">Efficacy and safety of remdesivir in hospitalised COVID-19 patients: a systematic review and meta-analysis</a></p> <p>Angamo, et al. July 2021<sup>27</sup></p>	<ul style="list-style-type: none"> <li>• Systematic review and meta-analysis on the effectiveness and safety of remdesivir in the treatment of moderate to severe COVID-19</li> <li>• Recovery rate with remdesivir decreased from 29% on day 14 to 9% on day 28 suggesting early treatment may be more effective</li> <li>• 5-day and 10-day courses of remdesivir are associated with higher clinical improvement compared with placebo or standard care</li> <li>• Early initiation of remdesivir associated with mortality benefit on day 14; treatment should be appropriately timed in moderate-to-severe COVID-19</li> </ul>
<p><a href="#">Remdesivir for the Treatment of Covid-19 - Final Report</a></p> <p>Beigel, et al. October 2020<sup>5</sup></p>	<ul style="list-style-type: none"> <li>• Randomised controlled trial (n=1062) of intravenous remdesivir in adults who were hospitalised with COVID-19</li> <li>• Median number of days between symptom onset and randomisation 9</li> <li>• Benefit of remdesivir was larger when given earlier in illness</li> </ul>
<p><a href="#">Efficacy and safety of remdesivir in hospitalized Covid-19 patients: Systematic review and meta-analysis including network meta-analysis</a></p> <p>Elsawah, et al. July 2021<sup>4</sup></p>	<ul style="list-style-type: none"> <li>• Systematic review on efficacy of remdesivir in COVID-19 treatment</li> <li>• Remdesivir may be more effective among early severe cases</li> <li>• Patients who did not need mechanical ventilation had higher recovery and lower mortality rates; remdesivir treatment may be more effective in severe COVID-19 patients not on mechanical ventilation</li> <li>• 5-day and 10-day course of remdesivir is effective for patients with severe COVID-19 who do not require mechanical ventilation</li> </ul>
<p><a href="#">Remdesivir for 5 or 10 Days in Patients with Severe Covid-19</a></p> <p>Goldman, et al. November 2020<sup>8</sup></p>	<ul style="list-style-type: none"> <li>• Randomised controlled trial (n=397) comparing 5-day and 10-day course (median length of treatment 9 days) of remdesivir</li> <li>• Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg per day</li> <li>• Results:             <ul style="list-style-type: none"> <li>○ At day 14, clinical improvement of at least 2 points on the 7-point ordinal scale in 65% of 5-day group compared with 54% of 10-day group</li> </ul> </li> </ul>

Source	Summary
<b>Peer reviewed sources</b>	
	<ul style="list-style-type: none"> <li>○ After adjustment for baseline clinical status, groups had similar outcomes for clinical improvement as well as median duration of hospitalisation and mortality</li> <li>○ Treatment beyond 5 days for patients receiving non-invasive, positive-pressure ventilation or high-flow oxygen, low-flow oxygen, or breathing ambient air did not appear to improve outcomes</li> <li>○ Adverse events were similar in both groups</li> <li>● Conclusion: No significant difference in efficacy between 5-day and 10-day course of remdesivir for patients with severe COVID-19</li> </ul>
<p><a href="#">Effectiveness of remdesivir for the treatment of hospitalized COVID-19 persons: A network meta-analysis</a></p> <p>Jiang, et al. February 2021<sup>13</sup></p>	<ul style="list-style-type: none"> <li>● Network meta-analysis on effectiveness of remdesivir for treatment of hospitalised patients with COVID-19</li> <li>● 10-day and 5-day course had positive effects on clinical improvement and clinical recovery</li> <li>● 5-day course may be superior to 10-day course in clinical improvement and recommended in severe hospitalised COVID-19</li> </ul>
<p><a href="#">Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis</a></p> <p>Kim, et al. December 2020<sup>19</sup></p>	<ul style="list-style-type: none"> <li>● Systematic review and meta-analysis on efficacy and safety of COVID-19 treatments</li> <li>● Decreased rate of adverse events with both short-term (5-day) and long-term (10-day course) course of remdesivir compared with standard care</li> </ul>
<p><a href="#">Clinical efficacy and safety of remdesivir in patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials</a></p> <p>Lai, et al. July 2021<sup>22</sup></p>	<ul style="list-style-type: none"> <li>● Systematic review and meta-analysis on efficacy and safety of remdesivir in the treatment of hospitalised patients with COVID-19</li> <li>● 5-day course group showed greater clinical improvement than 10-day course and control</li> <li>● 5-day and 10-day groups associated with higher discharge compared to control</li> <li>● Shorter time to clinical improvement and recovery in both remdesivir groups compared to control</li> <li>● Rank probability results 5-day group superior to 10-days in clinical improvement, mortality, recovery, discharge, time to clinical improvement, time to mortality, and time to recovery</li> <li>● 5-day course may be sufficient to treat moderate-to-severe COVID-19</li> </ul>
<p><a href="#">Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study</a></p>	<ul style="list-style-type: none"> <li>● Randomised controlled trial comparing 5-day course of remdesivir to standard care alone</li> <li>● Discharge rates higher for patients with symptoms less than 5 days before receiving treatment (remdesivir or standard care)</li> <li>● No significant difference in efficacy between 5-day course of remdesivir and standard care in moderate-to-severe COVID-19</li> </ul>

Source	Summary
<b>Peer reviewed sources</b>	
Mahajan, et al. March 2021 <sup>6</sup>	
<a href="#">Remdesivir for coronavirus disease 2019 (COVID-19): a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials</a> Okoli, et al. September 2021 <sup>15</sup>	<ul style="list-style-type: none"> <li>• Systematic review and meta-analysis of randomised controlled trials of remdesivir for COVID-19</li> <li>• No significant difference between remdesivir and no treatment or placebo</li> <li>• No difference between 10-day and 5-day course of remdesivir in clinical progression</li> </ul>
<a href="#">Efficacy and harms of remdesivir for the treatment of COVID-19: A systematic review and meta-analysis</a> Piscocya, et al. December 2020 <sup>18</sup>	<ul style="list-style-type: none"> <li>• Systematic review and meta-analysis on efficacy and safety of remdesivir for treatment of COVID-19</li> <li>• 5-day course of remdesivir decreased need for invasive ventilation and serious adverse events compared with 10-days but did not decrease mortality</li> <li>• Adverse events similar for 5-days compared to 10-days</li> </ul>
<a href="#">Remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis</a> Rezagholizadeh, et al. April 2021 <sup>16</sup>	<ul style="list-style-type: none"> <li>• Systematic review and meta-analysis on safety and efficacy of remdesivir administration in hospitalised COVID-19 patients</li> <li>• No significant differences between 5-day and 10-day course of remdesivir in any evaluated clinical outputs</li> <li>• 5-day course may provide similar benefits and have less serious adverse events than 10-day course</li> </ul>
<a href="#">The efficacy of remdesivir in coronavirus disease 2019 (COVID-19): a systematic review</a> Roshanshad, et al. October 2020 <sup>20</sup>	<ul style="list-style-type: none"> <li>• Systematic review on efficacy and safety of remdesivir in hospitalised patients with COVID-19</li> <li>• Severe adverse event rates are lower in 5-day group compared with 10-day group</li> <li>• 5-day course of remdesivir is probably efficacious and safe; treatment can be extended to 10 days if no satisfactory improvement by day 5</li> </ul>
<a href="#">Remdesivir: A potential game-changer or just a myth? A systematic review and meta-analysis</a> Shrestha, et al. January 2021 <sup>17</sup>	<ul style="list-style-type: none"> <li>• Systematic review and meta-analysis on remdesivir use for COVID-19</li> <li>• Higher discharge rate at day 14 for 10-day course compared with 5-day course</li> <li>• 10-day course of remdesivir resulted in significantly more serious adverse outcomes and drug discontinuation than 5-day course with no significant benefits</li> <li>• No significant differences for 14 days mortality rate, clinical improvement, clinical recovery or overall adverse effects</li> </ul>
<a href="#">Effect of Remdesivir vs Standard Care on Clinical</a>	<ul style="list-style-type: none"> <li>• Randomised controlled trial (n=584) comparing 5-day and 10-day course of remdesivir with standard care on clinical status</li> </ul>

Source	Summary
<b>Peer reviewed sources</b>	
<p><a href="#">Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial</a></p> <p>Spinner, et al. September 2020<sup>23</sup></p>	<ul style="list-style-type: none"> <li>• Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg per day</li> <li>• Results:                             <ul style="list-style-type: none"> <li>○ 5-day course was significantly better compared with standard care</li> <li>○ No significant difference between 10-day course (median length of treatment 6 days) and standard care</li> <li>○ Adverse events not significantly different between 5-day group (51%) and standard care (47%) but was statistically significant between 10-day group (59%) and standard care</li> </ul> </li> <li>• Conclusion: 5-day course of remdesivir resulted in significantly better clinical status compared with standard care</li> </ul>
<p><a href="#">Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial</a></p> <p>Wang, et al. May 2020<sup>7</sup></p>	<ul style="list-style-type: none"> <li>• Randomised controlled trial (n=237) of remdesivir in adult patients admitted to hospital for severe COVID-19</li> <li>• Remdesivir not associated with statistically significant clinical benefits compared with placebo</li> <li>• There was a non-significant faster time (median reduction 5 days) to clinical improvement for remdesivir compared with placebo in patients with symptoms &lt;10 days</li> </ul>
<p><a href="#">Remdesivir for Adults With COVID-19: A Living Systematic Review for American College of Physicians Practice Points</a></p> <p>Wilt, et al. February 2021<sup>21</sup></p>	<ul style="list-style-type: none"> <li>• Living systematic review – 4 randomised controlled trials (RCTs) – on effectiveness and harms of remdesivir for COVID-19 treatment</li> <li>• 5-day course may reduce mortality by a small amount, increase recovery by a moderate amount, and reduce adverse events by a large amount compared with 10-day course in hospitalised patients with severe COVID-19 not requiring mechanical ventilation</li> <li>• Patients with worsening symptoms and who require ventilation may benefit from extending treatment to 10 days</li> <li>• 5-day course may decrease mortality and serious adverse events and increase clinical improvement compared with standard care in moderate COVID-19 patients</li> <li>• 10-day course not more effective than 5-days or standard of care in moderate COVID-19 patients</li> </ul>
<p><a href="#">Effect of remdesivir on patients with COVID-19: A network meta-analysis of randomized control trials</a></p> <p>Yokoyama, et al. October 2020<sup>14</sup></p>	<ul style="list-style-type: none"> <li>• Network meta-analysis (4 RCTs) comparing clinical improvement among COVID-19 patients receiving a 5-day course of remdesivir, 10-day course of remdesivir or standard care alone</li> <li>• Clinical improvement was significantly higher in 5-day and 10-day groups compared with standard care</li> <li>• Clinical improvement was significantly higher in 5-day group compared with 10-day group</li> </ul>

**Table 2: Grey literature**

Source	Summary
<b>Grey literature</b>	
<p><a href="#">Coronavirus Disease 2019 (COVID-19) Treatment Guidelines</a></p> <p>National Institutes of Health USA, September 2021<sup>26</sup></p>	<ul style="list-style-type: none"> <li>• Recommend remdesivir for hospitalised COVID-19 patients requiring supplemental oxygen but not high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO, and during the early phase of the disease</li> <li>• Treatment may be extended for up to 10 days if there is no substantial clinical improvement after 5 days</li> </ul>
<p><a href="#">IDSA Guidelines on the treatment and management of patients with COVID-19</a></p> <p>Infectious Diseases Society of America, updated 14 September 2021</p>	<ul style="list-style-type: none"> <li>• Remdesivir recommended over no antiviral treatment for hospitalised patients with severe COVID-19 with SpO2 ≤94%</li> <li>• 5-day course suggested over 10-day course in patients on supplemental oxygen but not mechanical ventilation or ECMO</li> </ul>

## Appendix

### PubMed search terms

((("remdesivir"[Title/Abstract] OR "remdesivir triphosphate"[Title/Abstract]) AND ("SARS-CoV-2"[Title/Abstract] OR "COVID-19"[Title/Abstract]) AND ("efficac\*" [Title/Abstract] OR "effectiveness"[Title/Abstract] OR "standard of care"[Title/Abstract] OR "standard care"[Title/Abstract]) AND (day[Title/Abstract] OR days[Title/Abstract] OR course[Title/Abstract] OR week\*[Title/Abstract]) AND ((randomizedcontrolledtrial[Filter] OR systematicreview[Filter] OR "random\*" [Title] OR "systematic"[Title] OR ((randomised[Title/Abstract] OR randomized[Title/Abstract]) AND trial[Title/Abstract])) AND (english[Filter])))

### Google search terms

remdesivir AND COVID-19 AND early initiation AND course

### Inclusion and exclusion criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>Published in English</li> <li>Systematic reviews or randomised controlled trials</li> </ul>	<ul style="list-style-type: none"> <li>Not in English</li> <li>Not systematic reviews or randomised controlled trials</li> <li>Abstract only</li> </ul>

While the search was limited to systematic reviews and randomised controlled trials, observational studies directly answering the question on interval to drug initiation were included in the in brief.

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