Application for Inclusion of Remdesivir to the World Health Organization's Model Lists of Essential Medicines and Essential Medicines for Children

1 Summary statement of the proposal for inclusion

Cumulative cases of Covid-19 are over 642 million, with 6.6 million global deaths.[1] Vaccination is having a substantial impact on hospitalizations and death in a number of high-income countries, but limitations in global access to COVID-19 vaccines mean that many populations remain vulnerable. There remains a need for more effective treatments for COVID-19.

WHO guidance issued an initial conditional recommendation on 20 November 2020, suggesting not to use remdesivir for patients with COVID-19, regardless of illness severity. This was based on data from four RCTs which were available at the time, with 7333 participants hospitalized for COVID-19. Since the 10th iteration of the guideline, a conditional recommendation is made for the use of remdesivir for patients at highest risk with non-severe illness. This is based on a reduction in hospitalization amongst patients at highest risk (preventing 73 admissions per 1000 patient treated, moderate certainty evidence).

In this 12th iteration of the guideline, a new conditional recommendation for patients with severe COVID-19 was made, given new trial data providing sufficiently trustworthy evidence for a subgroup effect demonstrating modest benefit in patients with severe COVID-19 (reducing the number of mechanical ventilated patients by 14 per 1000 patients treated, moderate certainty evidence). There was no significant benefit in critical disease.

The evidence for benefit derives from prospective meta-analysis which is the basis of all of the WHO Therapeutics and COVID-19 Living Guidelines; these guidelines support global use of the medicine.[2]

It should be noted that while this application considers Covid-19, Gilead Sciences patent applications for the product cover indications for other RNA virus infections including hepatitis C (HCV), *Zaire ebolavirus* (EBOV), Marburg virus, SARS-CoV-1, MERS-CoV, and Zika virus (ZIKV). For these, no current international guidance is recommending the use of remdesivir.

This application will ensure that the Essential Medicines List reflects current evidence-based guidance, and supports international work through the ACT-Accelerator to make effective therapies available in an equitable and transparent manner.[3]

The application relates to both the Model List of Essential Medicines and the Essential Medicines for Children.

2 Relevant WHO technical department and focal point

Janet Diaz, Clinical Management Unit, Country Readiness Strengthening, HQ.

3 Name of organisation(s) consulted and/or supporting the application

The WHO Guideline Development Group for Covid-19 therapeutics has developed and published recommendations on the use of this medicine.[2]

4 International names for medicine within this application

4.1 International non-proprietary name (INN)

remdesivir

4.2 Anatomical Therapeutic Chemical code (ATC)

J05AB16

5 Dose

The recommended dose for remdesivir is one dose daily as intravenous infusion remdesivir is given as 200mg intravenously on day 1, followed by 100mg intravenously on subsequent days. Treatment course is total 3 days for non-severe Covid-19, and 5 days for severe Covid-19 disease.

6 Whether listing is requested as an individual medicine or as representative of a pharmacological class

This application is for listing as an individual medicine.

7 Treatment details

7.1 Requirements for diagnosis

Diagnostic possibilities include rapid diagnostic tests (RDT) and polymerase chain reaction (PCR), both of which are supplied by multiple manufacturers. There is no stated preference for diagnostic approach within the guidance, although it is noted that:

> *…availability and use of appropriate SARS-CoV-2 diagnostic tests is needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of rapid diagnostic tests such as antigen-detection assays can improve early diagnosis in the community and in primary health care settings. Health care systems must, however, gain expertise in choosing and implementing rapid tests, choosing those most applicable to their settings.*

7.2 Requirements for treatment and monitoring

Remdesivir should be administered as soon as possible after onset of symptoms, ideally within 7 days. There is no stipulated monitoring regimen.

8 Mechanism of action

Remdesivir was developed for treatment of hepatitis C virus infection, and was also studied in Ebola and Marburg virus infections before being repurposed for SARS-CoV-2. Remdesivir is a nucleoside drug. Its mechanism of action involves chain termination, which is different to lethal mutagenesis: the drug is incorporated preferentially to the endogenous adenosine nucleoside by the SARS-CoV-2 polymerase during replication of the RNA genome. Unlike many other chain-terminating nucleoside drugs used for other viruses, remdesivir elicits delayed chain termination because RNA synthesis is terminated after the addition of three more nucleotides, rather than at the point of remdesivir incorporation.[4]

9 Review of benefits (summary of evidence of comparative effectiveness)

9.1 For patients with non-severe COVID-19 at highest risk of hospitalization: conditional recommendation for use

Recommendations concerning remdesivir for patients with non-severe COVID-19 at highest risk of hospitalization were published on 22 April 2022 as the tenth version of the WHO Therapeutics and COVID-19 Living Guideline on the basis of a systematic review around a specific PICO question. The evidence summary was informed by five trials with 2709 participants, with one trial informing the outcome of hospital admission which addressed the PICO:[5,6]

Population	Patients with non-severe confirmed COVID-19 (according to WHO definitions)
Intervention	Remdesivir + usual care
Comparator	Usual care
Outcomes	See outcome prioritization
Subgroups for relative effects	Children vs adults vs. older people Time from symptom onset Disease severity
Subgroups for absolute effects	Age and chronic conditions Serological status Vaccination status
Co-intervention at baseline	monoclonal antibodies, molnupiravir, nirmatrelvir/ritonavir

For hospitalization at 28 days, from 1 study including 562 patients, treatment with remdesivir prevented hospital admission compared with placebo (OR 0.25, 95%CI 0.06-0.88), resulting in 26 fewer events per 1000 people (95%CI 4 to 33 fewer).

No subgroup effects were seen for subgroups, including age (p=0.78).

Figure 1 – Graphical evidence summary of the benefit of remdesivir for patients with non-severe Covid-19[2]

Higher risk individuals are those of older age (> 60 years), those with immunosuppression and/or chronic disease, and those unvaccinated against COVID-19. The GDG interpreted the evidence as follows:[2]

> *In patients with non-severe COVID-19, remdesivir probably reduces admission to hospital and may have little or no impact on mortality. The effect of remdesivir on mechanical ventilation and time to symptom resolution is very uncertain. Treatment probably does not increase the likelihood of adverse effects leading to drug discontinuation.*
>
> *The balance between benefits and potential harms favours treatment, but only in the highest risk group. This is because absolute benefit of remdesivir on hospital admission depends on a given patient's prognosis. The GDG defined a threshold of a 6%*

> *absolute reduction in hospital admission to represent what most patients would value as an important benefit. Remdesivir would exert such a benefit in patients at highest risk of hospitalization (above 10% baseline risk), such as older people, or those with immunodeficiencies and/or chronic diseases, further enhanced by lacking vaccination. The conditional recommendation for the use of remdesivir in those at highest risk (above 10% baseline risk) reflects this threshold: 73 fewer hospitalizations per 1000 patients.*

9.1.1 Certainty of the evidence for non-severe Covid-19

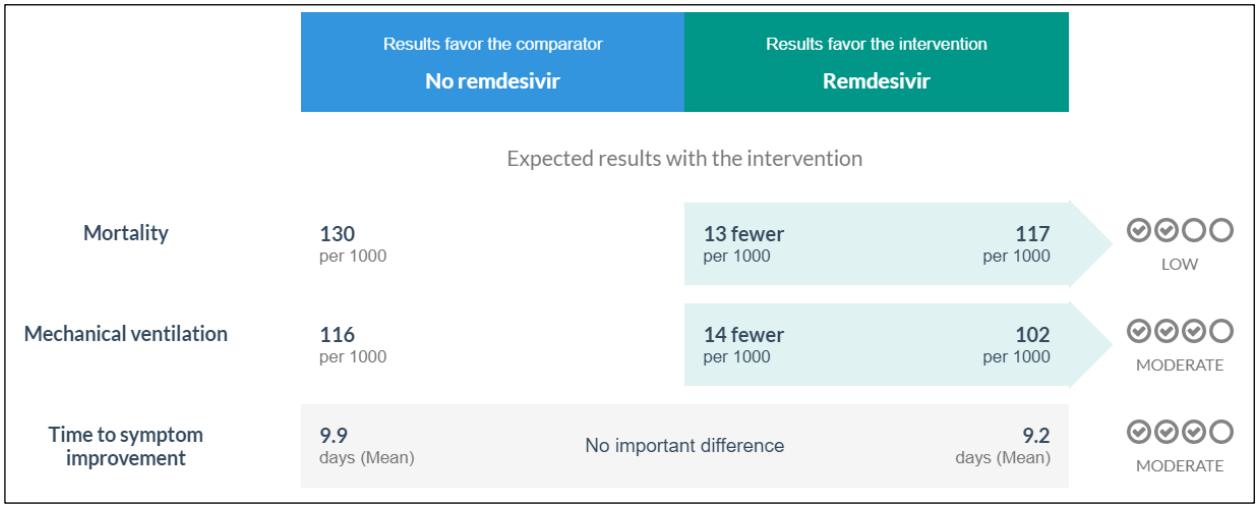
Certainty of evidence was rated as: moderate for decreased admission to hospital (due to serious imprecision); low for mortality (due to serious imprecision and indirectness); very low for mechanical ventilation (due to very serious imprecision and serious indirectness); and moderate for adverse effects leading to drug discontinuation.

Limitations in available empirically developed risk prediction tools for establishing patients' risk of hospitalization represent the major source of indirectness for which the GDG rated down the certainty of the evidence.[7,8]

9.2 For patients with severe COVID-19: conditional recommendation for use

Recommendations concerning remdesivir for patients with severe COVID-19 were published on 16 September 2022 as the twelfth version of the WHO Therapeutics and COVID-19 Living Guideline.[2] For this indication, there was evidence of reduction in mechanical ventilation in those with severe (but no critical COVID-19) treated with remdesivir compared with placebo (OR 0.87, 95%CI 0.77-0.99) based on 6620 participants in five studies. This resulted in 14 fewer events per 1000 people (95%CI 1 fewer to 24 fewer), and a conditional recommendation for its use in severe disease.

Figure 2 – Graphical evidence summary of the benefit of remdesivir for patients with severe Covid-19[2]



9.2.1 Certainty of the evidence for severe Covid-19

This is described in the WHO Therapeutics and COVID-19 Living Guideline, as follows:[2]

> *Certainty of evidence was rated as: low for no impact on mortality or invasive mechanical ventilation (rated down from high for imprecision and inconsistency given the ongoing uncertainty regarding credibility of the severity of illness subgroup effect modification); and very low for no impact on time to symptom improvement.*
>
> *Subgroup analysis based on age was not possible due to lack of trial level data. The GDG noted with concern the dearth of pediatric data and a strong call for research in this area was made. The lack of data regarding the effect in immunocompromised patients was also highlighted. While there is limited evidence in vaccinated populations, the GDG felt that the data were sufficient to conditionally recommend the use of remdesivir.*

9.3 Other evidence

A Cochrane collaboration systemic review extended the found that remdesivir probably makes little or no difference to all-cause mortality at up to day: 28 (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.81 to 1.06; risk difference (RD) 8 fewer per 1000, 95% CI 21 fewer

to 7 more; 4 studies, 7142 participants; moderate-certainty evidence.[9] There was limited evidence for a beneficial effect of remdesivir on mortality in a subset of 435 participants who received low flow oxygen at baseline in one study (RR 0.32, 95% CI 0.15 to 0.66), but no corroborative data in other studies. Remdesivir appeared to reduce the need for invasive mechanical ventilation (67 fewer participants amongst 1000 participants; RR 0.56, 95% CI 0.41 to 0.77; 2 studies, 1159 participants; low-certainty evidence).

10 Review of harms and toxicity (summary of evidence of safety)

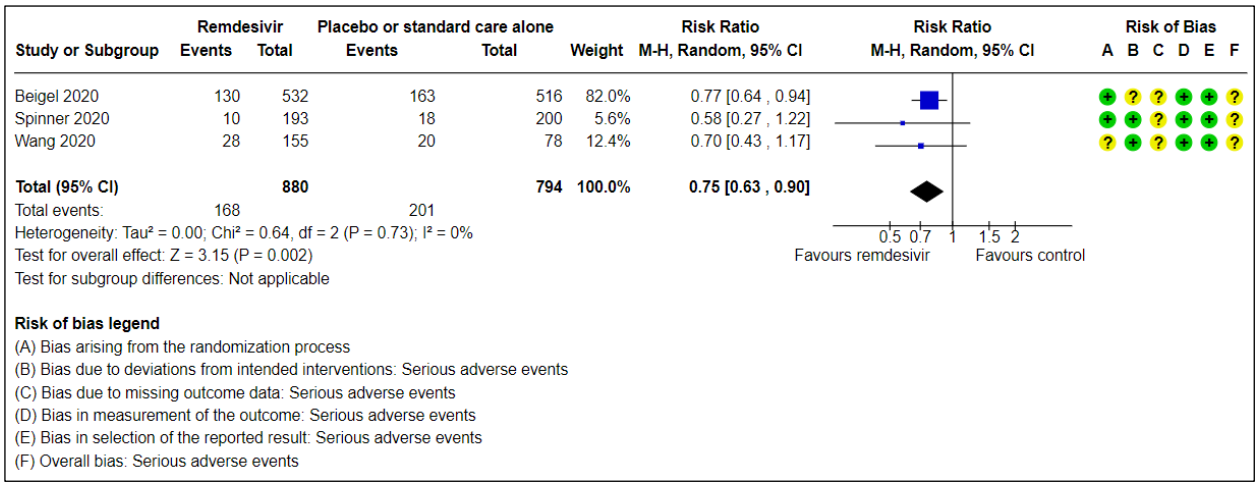
The GDG noted that: "*The drug [remdesivir] was well tolerated and adverse events were rare."* [2]

10.1 Adverse events

A systematic review which included two studies and 1281 patients with Covid-19 reported no evidence compared to placebo of acute renal kidney injury (OR 0.85, 95%CI 0.51 – 1.41), or cognitive dysfunction/delirium (OR 1.22, 95%CI 0.48-3.11).[10]

A Cochran meta-analysis reported that remdesivir decreases the serious adverse events rate at up to 28 days (RR 0.75, 95% CI 0.63 to 0.90; risk difference 63 fewer per 1000, 95% CI 94 fewer to 25 fewer; 3 studies, 1674 participants; moderate-certainty evidence).[9] The evidence for any adverse events was very uncertain (RR 1.05, 95% CI 0.86 to 1.27; RD 29 more per 1000, 95% CI 82 fewer to 158 more; 3 studies, 1674 participants; very low-certainty evidence).

Figure 3 –Systematic review of severe adverse event rates in patients receiving remdesivir for patients with severe Covid-19[9]



Adverse events listed within the SmPC are:[11]

- Very common (≥ 1/10): transaminases increased, prothrombin time increased
- Common (≥1/100 to <1/10): headache, nausea, rash
- Uncommon (≥1/1,000 to <1/100): rash, urticaria
- Rare (≥ 1/10,000 to < 1/1,000): hypersensitivity, infusion-related reaction
- Unknown: sinus bradycardia (report in post-marketing)

10.2 Safety in particular populations

The WHO Therapeutics and COVID-19 Living Guideline makes the following comment:[2]

> *None of the included RCTs enrolled children or pregnant woman, and therefore the applicability of this recommendation to children remains uncertain.*

The FDA has approved remdesivir for use in paediatric patients age ≥28 days and ≥3kg.

11 Summary of available data on comparative cost and cost-effectiveness of the medicine

There is currently no formal cost-effectiveness analysis as part of the WHO guideline. Please see below for changes in market availability which are likely to increase affordability.

12 Summary of regulatory status and market availability

Remdesivir is supplied by the patent holder, Gilead Sciences (as Veklury®), although other patent applications have been made by other entities in various regions including China.[12] Remdesivir received WHO pre-qualification on 20 July 2022.[13] The ATC-Accelerator Transition Plan,[14] is in place which promotes generic product availability, although remdesivir is not part of the Medicines Patent Pool agreement at present. Commercial costs in 2020 were US$4680 for a 10-day course,[15] and the range for cost-effectiveness in the US was estimated between $4580 and $5080.[16] However, the landscape of alternative medications has changed significantly since. The availability and cost of sublicensed product is not easily available.

13 Availability of pharmacopoeia standards

Remdesivir is listed in the British National Formulary with a specific indication for Covid-19.[17]

14 References

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