Record of the COVID-19 Treatments Advisory Group Meeting held via video conference on 1 February 2022

COVID-19 Treatments Advisory Group records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the COVID-19 Treatments Advisory Group meeting held on 1 February 2022; only the relevant portions of the meeting record relating to COVID-19 Therapeutics Advisory Group discussions about an Application or Pharmac staff proposal that contain a recommendation are generally published.

The COVID-19 Treatments Advisory Group may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac is not bound to follow the recommendations made below.

Attendance

Present:
Jane Thomas (Chair)
Brian Anderson
Tim Cutfield
Eamon Duffy
Jessica Keepa
Stephen Munn
Marius Rademaker
Nigel Raymond

Apologies:
Graham Mills
Justin Travers
Kerry Benson-Cooper

Remdesivir for the treatment of COVID-19

Application

1.1. The Advisory Group reviewed material provided by Pharmac staff regarding the use of remdesivir for the treatment of COVID-19.

1.2. The Advisory Group took into account, where applicable, Pharmac's relevant decision-making criteria when considering this item.

Recommendation

1.3. The Advisory Group recommended that remdesivir be funded in the community for the treatment of mild to moderate symptomatic COVID-19, subject to the following access criteria:

Initial Application – (Acute COVID-19 disease). Approvals valid for all applications meeting the following criteria:

All of the following:

1. Patient has confirmed (or highly suspected) COVID-19; and
2. Patient's symptoms started within the last seven days; and
3. Patient has not received any dose of COVID-19 vaccine; and
4. Patient has at least three of the following risk factors for severe disease (Adapted from the Ministry of Health): Māori or Pacific ethnicity, severely immunocompromised*, severe cardiac disease, uncontrolled hypertension, uncontrolled diabetes, chronic lung disease, chronic kidney disease, chronic liver disease, active malignancy, age 60 years or more, history of smoking, BMI 40 or higher.
5. Patient does not require supplemental oxygen for established pneumonitis (oxygen saturation >93%**); and
6. Not to be used in conjunction with other COVID-19 antiviral treatments; and
7. Treatment not to exceed three days.

Notes:

*Conditions and treatments which weaken the immune system include: having chemotherapy or radiotherapy, bone marrow or organ transplantation, some blood cancers, immune deficiencies including HIV infection, immunity weakening medications such as high-dose corticosteroids and any disease modifying drug with an immunomodulatory effect, to treat systemic inflammatory disorders. Adapted from the Ministry of Health.

**or saturations no lower than baseline for patients with chronic resting hypoxia

1.4. The Advisory Group recommended the remdesivir criteria in DHB hospitals should be amended to the following access criteria:

Restricted

Initiation – (Acute COVID-19 disease) - hospitalised patients. Approvals valid for all applications meeting the following criteria:

All of the following:

1. Patient has confirmed (or highly suspected) COVID-19; and
2. Patient's symptoms started within the last seven days; and
3. Patient has not received any dose of COVID-19 vaccine; and
4. Patient has at least three of the following risk factors for severe disease (Adapted from the Ministry of Health): Māori or Pacific ethnicity, severely immunocompromised*, severe cardiac disease, uncontrolled hypertension, uncontrolled diabetes, chronic lung disease, chronic kidney disease, chronic liver disease, active malignancy, age 60 years or more, history of smoking, BMI 40 or higher.
5. Patient does not require supplemental oxygen for established pneumonitis (oxygen saturation >93%**); and

6. Not to be used in conjunction with other COVID-19 antiviral treatments; and
7. Treatment not to exceed five days.

*Conditions and treatments which weaken the immune system include: having chemotherapy or radiotherapy, bone marrow or organ transplantation, some blood cancers, immune deficiencies including HIV infection, immunity weakening medications such as high-dose corticosteroids and any disease modifying drug with an immunomodulatory effect, to treat systemic inflammatory disorders. Adapted from the Ministry of Health.
**or saturations no lower than baseline for patients with chronic resting hypoxia

1.5. In making this recommendation, the Group considered that the current evidence shows that remdesivir use in the community can prevent high risk, unvaccinated individuals with early COVID-19 infection from being admitted to hospital. The Group also noted that remdesivir stock is currently limited and therefore considered that available stock should be directed to those with the greatest potential to benefit from treatment.

1.6. The Advisory Group noted that no priority ranking (within the context of treatments for COVID-19) was sought by Pharmac, reflecting the rapidly evolving evidence for treatments in COVID-19 and separate funding outside the Combined Pharmaceutical Budget.

1.7. The Group reiterated this was an area of rapidly evolving evidence and knowledge and specified that its recommendation may need to be re-considered in the future as more evidence becomes available. The Group also noted that the eligibility criteria may need to be reviewed if further stock is made available and/or oral antiviral medicines become available.

Discussion

1.8. The Group noted that currently remdesivir is only available in the hospital setting and not in the community. The Group noted that the current funding criteria were recommended in September 2020 and focus on the treatment of moderate to severe COVID-19 in the hospital setting (Remdesivir COVID-19 Advisory Group record. 2020). The Group noted that at its December 2021 meeting it considered that more recent evidence shows that remdesivir is unlikely to provide substantial benefit in the moderate to severe, hospitalised patient group.

1.9. The Group noted a meta-analysis by Kaka et al. which concluded that remdesivir probably results in little to no mortality difference in hospitalised adults, however that it probably does improve the percentage recovered and reduces serious harms (Kaka et al. Ann Int Med. 2021;174:663-72).

1.10. The Group noted that real world data for remdesivir has recently been published:

1.10.1. A large cohort study which reported that remdesivir was associated with improved survival among patient with COVID-19 when administered on hospital admission compared to matched patients (Mozaffari et al. Clin Infect Dis. 2021; https://doi.org/10.1093/cid/ciab875). Members noted that this study was financially supported by the pharmaceutical supplier.

1.10.2. A smaller cohort study which concluded that use of remdesivir may be associated with increased hospital stays while not being associated with improvements in survival when used in hospitalised COVID-19 cases (Ohl et al. JAMA. 2021;4:doi:10.1001/jamanetworkopen.2021.14741).

1.11. The Group considered that the randomised controlled trials of remdesivir in hospitalised patients, either taken individually or in aggregate, do not provide compelling evidence of reduced mortality. The Group considered that the cohort studies using propensity matching techniques, provide conflicting evidence of benefit. Members considered that if hospitalisations reached the numbers modelled for the omicron outbreak in New Zealand, using the current criteria would likely result in all of the currently available remdesivir being used on hospitalised patients with marginal benefits.

1.12. The Group considered that the availability of remdesivir only in hospitals (and level 1 hospitals such as rural clinics) creates substantial access equity barriers. Members noted that individuals in rural areas may be less likely to be admitted to hospital and therefore less likely to receive treatment. Members considered that appropriate levers to assist in equitable access to remdesivir include further community access (eg. primary care), communication to primary providers that it is available, and further work on the implementation of medicine delivery. The Group noted that the Ministry of Health is managing the implementation of COVID-19 medicines and considered it was important that these equity issues be addressed. Members noted it was important that any facility administering remdesivir should be appropriately resourced to manage any acute adverse events that may occur.

Evidence

1.13. The Group noted it discussed remdesivir at its December 2021 meeting, however that new evidence has since emerged, namely the published results from the PINETREE trial (Gottleib et al. N Engl J Med. 2022;386:305-15). The Group noted:

1.13.1. that the PINETREE trial was a randomised, double-blind, placebo-controlled trial involving non-hospitalised patients with COVID-19 who had symptom onset within the previous 7 days and who had at least one risk factor for disease progression.

1.13.2. patients were treated over a three-day period with remdesivir or placebo, the median age of participants was 50 years and the most common coexisting conditions were diabetes mellitus (61.6%), obesity (55.2%), and hypertension (47.7%). The Group noted that the trial and supplementary material of the PINETREE trial did not detail the number of participants who had more than one risk factor. However, the group considered, based on the available information, that it was likely that a large proportion of trial participants had number of relevant risk factors.

1.13.3. the inclusion and exclusion criteria of the study, specifically the exclusion of participants who had received any SARS-CoV-2 (or COVID-19) vaccine.

1.13.4. that recruitment occurred mainly in the United States prior to delta and omicron becoming the dominant strains.

1.13.5. COVID-19–related hospitalisation or death from any cause occurred in two patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.03 to 0.59; P = 0.008).

1.13.6. a total of 4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group had a Covid-19–related medically attended visit by day 28 (hazard ratio, 0.19; 95% CI, 0.07 to 0.56).

1.13.7. no patients in either group had died by day 28. Members considered that therefore it was not possible to make any conclusions regarding the effectiveness of remdesivir at preventing death in this patient population, as neither the treatment nor placebo group experienced this outcome in the trial.

1.14. The Group noted that in the PINETREE study (supplementary material), the number of viral copies from patient nasal samples did not differ between those treated with remdesivir or placebo. Members noted the following:

1.14.1. That the Gottleib et al. 2021 paper discusses that animal model evidence suggests that the viral load in the pharynx and lung is not comparable and that the viral load in the lung determines case fatality risk.

1.14.2. The Group considered that while the evidence regarding viral load is not necessarily of concern in regard to patient outcomes (ie. community use of the treatment has been shown to reduce hospitalisation risk), it does indicate that it is unlikely that remdesivir would reduce the transmission of COVID-19 between the patient treated and any close contacts.

Access criteria

1.15. The Group recommended that the current access criteria be updated, and that access be widened to community use (as detailed above). The Group developed the criteria predominantly based on the patient population of the PINETREE trial. Specifically, the Group noted that in the PINETREE trial:

1.15.1. Patients were treated within seven days of symptom onset; and

1.15.2. Patients were likely to have more than one risk factor; and

1.15.3. Participants were excluded if they had received any COVID-19 vaccine dose.

1.16. The Group considered that while there was no biological reason that remdesivir would not exert an antiviral effect in individuals who had been vaccinated against COVID-19, the current evidence of benefit is only proven in those who have not been vaccinated. The Group considered that in order to direct limited stock to those with the most certainty of benefit, only unvaccinated individuals should be eligible for treatment with remdesivir. Members considered if criteria were widened to include vaccinated individuals, stock would be used in a short space of time on vaccinated people with less overall benefit likely be gained, compared with limiting treatment to unvaccinated patients at increased risk of severe disease. The Group considered that the wider the treated patient population becomes, proportionally more people that would need to be treated to prevent hospitalisations (ie. the 'number needed to treat' (NNT) increases). The Group considered that currently stock is limited, it is important to direct treatment to those with the highest health need, who would benefit the most from treatment.

1.17. The Group noted that exclusion of people who had received at least one vaccination dose against COVID-19 would exclude a number of patients who might benefit from treatment with remdesivir, including people who have not completed their full primary course of vaccination (including booster dose), people who are immunocompromised and may have not developed maximal immunity to their vaccination, or fully vaccinated people whose immunity is waning because of the time since last vaccine dose. Members acknowledged that these patients may

benefit from treatment with remdesivir; however, members noted that current evidence only shows benefit in those who have not received any dose of COVID-19 vaccine. The Group noted that this would be reconsidered if evidence for the use of remdesivir for the treatment of COVID-19 in vaccinated people becomes available and the available supply of remdesivir allow widening of access. Members considered that if further stock should be available, funding criteria similar to that of the oral antiviral treatments would be appropriate.

Variants of concern

1.18. The Group noted that while the PINETREE trial did not evaluate the effectiveness of remdesivir against the Delta and Omicron variants of COVID-19, two studies had explored the in vitro efficacy of remdesivir against different variants on interest. The Group noted Vangeel et al. 2022 reported that remdesivir was effective in similar concentrations across COVID-19 variants, including Alpha, Delta and Omicron (Vangeel et al. Antiviral Res. 2022;198: doi.org/10.1016/j.antiviral.2022.105252). The Group also noted a correspondence piece published in the New England Journal of Medicine which similarly reported that remdesivir efficacy was similar between variants, including Alpha, Delta and Omicron (Takashita et al. NEJM. 2022. DOI:10.1056/NEJMc2119407). As such, the Group considered that with the currently available evidence it was reasonable to conclude that remdesivir was likely to have similar efficacy against delta and omicron variants of COVID-19 as that observed in the PINETREE study.