Discharge Planning and Follow-up

Patients with Suspected, Probable or Confirmed COVID-19 who are being considered for discharge need to have specific decisions made about the following aspects of post-discharge care:

FURTHER INVESTIGATIONS	• Follow-up investigations are not universally required after COVID-19 • A repeat chest x-ray in 6-12 weeks to confirm resolution of pulmonary opacities should be arranged for individuals with significant radiographic abnormalities and / or risk factors for lung cancer	
DISCHARGE DESTINATION	• Anyone with COVID symptoms or suspected infection being discharged before PCR results are available should be tested using a RAT. If the RAT (or a PCR) is negative, the person should be advised to stay home until symptoms resolve and seek a further test if symptoms worsen. • Anyone who tests positive (on RAT or PCR) should be able to be discharged home but should be linked in through the Care in the Community Model if needed for follow-up, and household members should be advised to self-isolate as per standard advice for positive cases. Note that positive RAT results need to be recorded in My COVID Record. • The local Medical Officer of Health does not need to be notified of discharge of a positive case.	
CLEARANCE FROM ISOLATION	• The decision to end isolation should be consistent with Public Health policies and local hospital infection prevention and control policies which may be different. • **Local hospital isolation policy should be followed until point of discharge** • Release from isolation after discharge should align with the current Public Health Policy for community isolation: this is now taken as **7 days from date of onset of symptoms or date of positive test** (whichever is earlier, starting from day zero). • **'Rebound' COVID-19** is characte ised by recurrence of symptoms and/or a new positive viral test after having tested negative, irrespective of prior antiviral therapy. It occurs within a week of symptom improvement or completion of antiviral treatment. Data informing the approach to 'rebound' COVID 19 is limited, although 'rebound' does not appear to be associated with increased risk of severe COVID-19. It is important that 'rebound' be differentiated from both re-infection (rare within the first 4 weeks of COVID-19 recovery) and persistent SARS-CoV-2 infection (very rare and affects only **severely immunocompromised** hosts). We suggest clinicians discuss possible 'rebound' COVID-19, and **all COVID-19 in severely immunocompromised patients** with an infectious disease specialist or clinical microbiologist. • Exceptions to this duration may include severe immunocompromise and severe/critical COVID-19. It is advisable to seek the advice of an infectious disease specialist or microbiologist for severely immunocompromised individuals. Additional testing may be useful, such as serial NAAT/PCR testing suggestive of low viral load (i.e. negative or with high cycle threshold), high or increasing antibody levels or repeatedly negative RAT tests.	
	All patients	**Encourage vaccination if not completed eligible vaccination course (including booster dose[s]).** • If not completed primary vaccination series before infection, vaccination is recommended from 4 weeks after clinical recovery, even if treated with anti-SARS-CoV-2 antibody therapy (convalescent plasma or monoclonal antibody such as Ronapreve) • If completed primary vaccination series before infection, booster vaccination is recommended from 12 weeks after clinical recovery Educate about anticipated gradual recovery from COVID-19, and potential for persistent symptoms.

		• Encourage those with persistent symptoms after 6 weeks to arrange assessment by their GP.
	Severely immunocompromised	Suggest discuss all patients with infectious diseases or clinical microbiology to clarify duration of isolation (if inpatient) and consider screening for persistent SARS-CoV-2 infection. If eligible for Evusheld and not treated in the past 6 months, suggest discuss timing of administration during discharge process. Further guidance available here.
	Patients with significant respiratory failure (and/or persistent dyspnoea), or other persistent organ dysfunction	Specialist clinic follow-up, investigations and support following discharge (as advised by local specialty services)
	Pregnancy (or recently post-partum)	• VTE prophylaxis - refer to specific guidelines above • Recommend follow up growth scan within 2 weeks • If possible, delay follow-up CXR until post-partum

Links to other guidelines

- Australian COVID-19 living guidelines: https://covid19evidence.net.au/
- NICE (UK) living guideline: https://www.nice.org.uk/guidance/ng191
- National Institute of Health (USA): https://www.covid19treatmentguidelines.nih.gov/
- WHO COVID-19 living guideline: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1
- **Ontario COVID-19 Science Advisory Group guideline (Canada)**: https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19-version-11-0/

Antiviral Options for COVID-19 Infection in Chronic Kidney Disease – Therapeutics TAG position statement

Date: 05 October 2022
Updated: 20 March 2023

The Manatū Hauora COVID-19 Therapeutics Technical Advisory Group (Therapeutics TAG) was established by the Ministry of Health in August 2021 to provide expert advice on existing and emerging medicines for use in the management of COVID-19.

Update relating to change in clinical guidance for molnupiravir

- Paxlovid remains the first-line treatment in patients without contraindications, while remdesivir is the recommended second-line treatment.
- Clinical evidence to date suggests that molnupiravir likely has no clinical benefit in highly vaccinated populations against the current Omicron variants. This aligns with the current situation in Aotearoa New Zealand.
- On 24 February 2023 the Manatū Hauora COVID-19 Therapeutics TAG removed its recommendation to use molnupiravir in Aotearoa New Zealand. The rationale supporting this change can be found in a position statement (link)

Contents

Context of COVID-19 in Aotearoa New Zealand

SARS-CoV-2 Omicron variants have spread widely in the Aotearoa New Zealand community during 2022, peaking in the winter. As of March 2023, a several immune-evasive Omicron variants, with no single dominant lineage, are in circulation in Aotearoa New Zealand. [1] Risk factors for hospitalisation and mortality have included increasing age, vaccination status, comorbidities (particularly when multiple), and Māori or Pacific ethnicity. The risk of hospitalisation overall has been less with Omicron than for earlier variants, particularly in those who are fully vaccinated. [2] A

bivalent COVID-19 vaccine booster dose is currently being rolled out ahead of the 2023 winter. COVID-19 vaccination booster doses are very effective in reducing the rate of hospitalisation and should be prioritised for all eligible people and especially for those with higher risk conditions.

COVID-19 Antivirals Available in Aotearoa New Zealand

The antivirals Paxlovid (oral), remdesivir (IV) and molnupiravir (oral) remain available for the treatment of COVID-19 in Aotearoa New Zealand for people who meet the Pharmac clinical risk criteria.

Paxlovid remains the recommended first line treatment. Evidence has indicated that Paxlovid is effective against the Omicron variants in reducing the development of serious illness and hospitalisation in those who are most at risk.

In patients with contraindications to Paxlovid, remdesivir is the recommended second line treatment, where available, and the clinical risk is assessed to be very high.

Early clinical trial evidence in an unvaccinated population pre-Omicron indicated that molnupiravir had a lesser benefit in preventing (~30%) hospitalisation in high-risk (but not standard-risk) cases, and as such it was recommended as an option after Paxlovid and remdesivir. However, a recent very large UK trial of people with Omicron infection found no significant reduction in hospitalisation or death. On the balance of evidence to date, the use of molnupiravir is no longer recommended (link).

Chronic Kidney Disease and Risk of Adverse Outcomes from COVID-19

Chronic kidney disease (CKD) is associated with an increased risk of hospitalisation, mortality, and other adverse outcomes from COVID-19 infection. Fo example, one systematic review showed an increased risk of hospitalisation in patients with CKD and COVID–19 (RR = 1.63, 95% CI 1.03–2.58). [3]

Vaccination substantially reduces the risk of hospitalisation associated with COVID-19 in the general population and most people with CKD appear to respond to the vaccination, with the development of protective antibodies. Haemodialysis and kidney transplant patients have reduced humoral and cellular immune responses when compared to healthy controls. However, the immune response from haemodialysis patients improves greatly, reaching near healthy-control levels, when patients are fully up-to-date with vaccination (e.g., two primary and one booster dose). The lower immune response among kidney transplant patients also improved but remained significantly lower than healthy controls.

The response to vaccination appears to be reduced in people with renal transplants on some anti-rejection medications (e.g., mycophenolate). [4] Some renal transplant patients have developed persistent COVID-19 infection and have difficulty with clearing the virus. Overall, post-COVID syndrome (generally known as ‘long COVID’) is relatively common following infection, but it is currently unknown whether it is more common in patients with CKD or whether antiviral therapies reduce the occurrence.

Effectiveness at Preventing Hospitalisation

Phase 3 clinical trials of the agents available in Aotearoa New Zealand were conducted in the pre-Omicron era and mostly in unvaccinated and COVID-19-naïve patients. Patients with stage 4 CKD and a GFR<30 mL/min were excluded from these trials. The trials showed a significant reduction in hospitalisation when given to patients at increased risk early after the onset of COVID-19 symptoms. [5-7] In general these medicines are well tolerated with a good safety profile.

In general, Paxlovid and remdesivir were considerably more effective at preventing hospitalisation (>85%) than molnupiravir (~30%). The antiviral activity of these agents is thought to be retained in patients with Omicron variant infections.

Options for Treatment in Renal Failure

Medications must be looked at very carefully, as patients with CKD are likely to be on multiple regular medications.

Nirmatrelvir and ritonavir (Paxlovid™)

Patients with moderate to severe renal impairment were excluded from the main clinical phase 3 EPIC-HR study of Paxlovid™ use in non-hospitalised patients. [5] However, some data and experience of dose-adjusted use of Paxlovid™ has recently been published from Ontario and has been included in the Ontario treatment guidelines. [8, 9]

We note the reduced dosing regimen is pragmatic, and appears duly cautious, noting the effectiveness could differ from the EPIC-HR study results. Some limited early data suggests a reduced dose Paxlovid™ in renal failure (eGFR < 30) may not be associated with significant harm. We recommend consideration of Paxlovid™ in this population after careful risk-benefit assessment.

The Aotearoa New Zealand Paxlovid™ datasheet wording uses 'contraindicated', which differs subtly from 'not recommended' in the FDA EUA Fact Sheet. [10, 11] The reason given in the datasheet was a lack of data in renal failure, and that appropriate dosage for patients with severe renal impairment had not yet been determined.

From data available to date, there does not appear to be evidence of harm from dose-reduced use of Paxlovid™ in renal failure (eGFR < 30). A phase 1 dosing study among health volunteers reported Paxlovid™ was safe and well-tolerated in single-ascending dose, multiple-ascending dose, and supratherapeutic cohorts. [12] Ritonavir has a long track history of use in HIV infection, similarly with a 100mg dose to 'boost' the level of another protease inhibitor. In that setting ritonavir has been found safe when taken by patients often over years. The relatively short standard treatment course of 5 days should also reduce any risk of major drug accumulation. Both common (diarrhoea, vomiting, dysgeusia, headache) and uncommon (myalgia, hypertension) reported side-effects of Paxlovid™ are usually relatively easy to clinically manage.

Considerations of the significant Paxlovid™ drug interactions are as applicable to patients with CKD as for those without any renal dysfunction. Risks of causing unintended harm due to changes to a patient's other regular medications, such as leading to subsequent medication omission, should be carefully considered, and mitigated against if Paxlovid™ is used. A summary of the use of Paxlovid™ in CKD can be seen in Table 1 below

Table 1 Nirmatrelvir and ritonavir (Paxlovid™) in CKD

Kidney failure	eGFR (mL/min)	Dosage (NB: 150mg nirmatrelvir tablets)
Nil	≥90	(nirmatrelvir 300mg + ritonavir 100mg) po q12h for 5 days
Mild	60 - 89	As above, no dose reduction
Moderate	30-59	(nirmatrelvir 150mg + ritonavir 100mg) po q12h for 5 days
Severe	<30	*Consider* (nirmatrelvir 300mg + ritonavir 100mg po) daily on day 1, then (nirmatrelvir 150mg + ritonavir 100mg po) daily for 4 days
PD or HD		*Consider*, with dose as for eGFR <30 ml/min, but dose after dialysis. Strongly recommend decision on use to be made in conjunction with the renal dialysis team
Renal transplants		Avoid, unless on advice from patient's transplant specialist[1].

Abbreviations: po = per oral, PD = peritoneal dialysis, HD = haemodialysis, q12h = every 12 hours, eGFR = estimated glomerular filtration rate

- Suggested dosing for weight <40kg here.
- Use barrier contraception for 7 days after last dose
- Do not prescribe Paxlovid™ for **'rebound' COVID-19**

Remdesivir (Veklury™).

While the PINETREE study showed that 3 days of intravenous remdesivir was effective in reducing hospitalisation, [7] use of remdesivir in Aotearoa New Zealand is largely constrained to being hospital-based. The WHO Solidarity trial showed a modest benefit in non-ventilated hospital inpatients against death or progression to ventilation (or both). [13] Remdesivir has an advantage of few drug-drug interactions. With remdesivir, the excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with reduced renal function. Caution is advised if eGFR is less than 30 mL/min/1.73m^2, with several international regulators advising against use due to a lack of information. In a case series of people with CKD on haemodialysis, remdesivir was well tolerated. [14, 15] Pharmacokinetic analysis suggest that in patients with reduced renal function 2 days of treatment is expected to provide equivalent concentrations to the 3-day regimen in patients with normal renal function.[16, 17]

Molnupiravir (Lagevrio™)

Although molnupiravir is a relatively well tolerated and safe option, and presently remains funded by Pharmac, it is no longer recommended for treatment of COVID-19 by the Manatū Hauora Therapeutics TAG.

Specialist Advice

Specialist advice may be helpful to discuss the risk/benefit of COVID-19 antiviral therapeutics for individual patients with CKD. Relevant specialists include infectious diseases physicians, clinical microbiologists, renal physicians, and renal transplantation specialists. Such advice should usually be sought for patients on renal dialysis or with transplants.

[1] Due to significant interactions with anti-rejection medications.

Abbreviations:

CKD: Chronic Kidney Disease

eGFR: estimated Glomerular Filtration Rate

HD: Haemodialysis

PD: Peritoneal Dialysis

po: per oral

q12h: every 12 hours

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MINISTRY OF HEALTH
MANATŪ HAUORA

REMDESIVIR: Clinical Criteria and Distribution

Contents

Background:

Remdesivir has been used for the treatment of individuals with respiratory compromise from SARS-CoV-2. PHARMAC has been in discussion with Gilead Sciences, Australia & New Zealand (Gilead) and Medsafe to secure a supply of **Remdesivir** for New Zealand. Initially, supply was not considered possible until later this year due to manufacturing constraints and high demand overseas. However, with the re-emergence of community transmission in New Zealand, PHARMAC has been in urgent discussions with the supplier to secure an emergency supply.

s 9(2)(b)(ii) [redacted]

s 9(2)(b)(i) [redacted]

In Australia, the current criteria for access for **Remdesivir** can be found on the Australian Department of Health webpage[1]. These note that 6 - 12 100 mg doses can be used per patient, depending on the severity of the disease – however, the current average usage in Australia is said to be approximately 600 mg in total per patient. They have also commented that better clinical outcomes are being observed with less severe patients (i.e. hospitalised but not requiring mechanical ventilation), and these patients generally require shorter treatment courses.

In Australia, although given provisional approval, the supply is enabled through Emergency Exemption Use under Section 18A of the Therapeutic Goods Act. Similarly, in New Zealand the initial stock will be distributed under Section 29 of the Medicines Act. The bulk of the drug would be held at an institution with a pharmaceutical wholesale license., with distribution to DHBs around the country as discussed below. Unlike in Australia, there would not be any requirement for New Zealand to provide any patient data to Gilead.

Literature Review: Remdesivir

Currently, there are four published randomised controlled trials examining use of Remdesivir in hospitalised patients [1-4]. The earliest (Lancet) Chinese study did not show a significant benefit, although this study was unable to enroll sufficient participants [1].

Interim results from the largest study National Institutes of Health–sponsored Adaptive COVID-19 Treatment Trial (ACTT-1) (NEJM), were reported when the data safety monitoring board noted improved outcomes with time to recovery of 11 days vs 15 days in controls, and a trend (but not significant) towards improvement in mortality [2]. The ATT-1 study was largely limited to in-patients with severe pneumonia on medical wards or in ICU.

The GS-US-540-5773 study (NEJM) reported a comparison of 5 vs 10 days of Remdesivir in severe COVID-19 infection in non-ICU inpatients, showing no difference in outcome between the two treatment durations [3].

The JAMA study of inpatients with COVID-19 infection of moderate severity without hypoxia, mostly enrolled within 2 days of hospital admission, comparing 5 or 10 days of remdesivir with controls. This did not show benefit of 10 days of Remdesivir, and clinical improvement with the 5-day course which was statistically significant but of uncertain clinical significance [4].

Overall, Remdesivir had some clinical benefit but relatively modest and there was no evidence of significant reductions in ICU utilisation or mortality. Remdesivir was mostly well tolerated. Side effects included nausea, elevations in liver function tests (e.g. ALT). Renal impairment was observed in animal studies at doses of 5-20 mg/kg, but has not been seen in adults or children treated for Ebola [5]. Side effects more common in ICU inpatients. The predominant drug-attributable adverse effect was nausea [6].

[1] https://www.health.gov.au/sites/default/files/documents/2020/07/criteria-for-access-to-remdesivir-from-the-national-medical-stockpile_0.pdf

Summary of current situation

Important questions remain regarding the efficacy of Remdesivir [7].

- The optimal patient population is unclear.
- The optimal time of initiation and duration of therapy is unclear
- The randomised studies are underpowered to quantify the effect on discrete clinical outcomes, but it was modest rather than substantial in these studies.
- The additional benefit effect of the drug (if any) in patients treated with dexamethasone, or other corticosteroids, is unclear.

A systematic review in the BMJ following the ATT-1 trial recommended use of Remdesivir in severe COVID-19 infection based on what it assessed to be relatively weak evidence of benefit [8].

Some patient groups were excluded from these studies, including children, pregnant women, and those with significant renal or liver disease. Administration of Remdesivir for 5 days was assessed likely to be safe in renal disease [9], but the Gilead data sheet describes risks of accumulation of an excipient. Remdesivir is a 'repurposed' anti-viral, and its pharmacology has recently been reviewed [10].

The novelty of the SARS-CoV-2 pandemic in association, the relative lack of information regarding the efficacy and most appropriate clinical use of Remdesivir and small number of doses available require recognition of several important issues as follows:

1. The criteria for use may change at short notice

It is recommended that approval for Remdesivir is not linked to a set of clinical indicators, as the clinical indications for the most efficient use of Remdesivir could change at short notice.

The ability to vary the indications for use at short notice would ensure the maximal benefit is obtained from a limited supply. In addition, due to the relatively unique situation in New Zealand with very low rates of infection outside of managed isolation, guidelines for use within New Zealand may vary from those in countries with widespread community transmission.

2. Initiation and prolongation of remdesivir therapy will be obtained by consultation between Infectious Disease (ID) Physicians

Remdesivir will be available on the advice of ID physicians. Supply will need to be managed nationally which requires co-ordination and co-operation between physicians across DHBs.

It is recommended that the initiation of treatment and the prolongation of treatment beyond 5 days would require discussion between two ID physicians, preferably from different clinical centres (DHB) or the clinical (non-MOH) team of the technical advisory group.

1. Estimate of the number of patients receiving treatment

- The anticipated initial allocation of s 9(2)(b)
- For average of 6 vials per patient = s 9(2)(b)
- For average of 10 vials per patient = s 9(2)(b)

Total cases	157	
Hospitalisation	19	12% of total cases
Intensive care admission	5	3% of total cases. 25% of admissions

If all patients admitted received **Remdesivir**, s 9(2)(b) would be sufficient for an outbreak of between 100 – 160 cases. If one half of patients admitted received **Remdesivir,** s 9(2)(b) would be sufficient for an outbreak of 200-300 cases.

Outbreak demographics and hospitalization.

When COVID-19 is limited to returned travellers in MIQ facilities, the affected population is mostly healthier and under 60 years of age. If community outbreaks occur but do not affect aged residential care (ARC) facilities, the hospitalization rate may also remain relatively low (5%). If community spread becomes more extensive, affecting more people with comorbidities or enter ARC facilities again, the expected hospitalization rate could be higher (20%). Of those hospitalised, around 50% would be expected to develop hypoxia to meet the inclusion criteria

2. How/where will remdesivir be held and distributed

Importation

The drug will be imported into New Zealand under Section 29 of the Medicines Act by the nominated wholesaling pharmacy. Under Section 29, distribution of the medicine to medical practitioners requires notification of the distribution or sale to Medsafe. The Section 29 notification form is attached (Appendix 2)

Storage

The national stock would be based in Auckland to make it most accessible to those most likely to need it. The stock should be managed through institutions with a pharmaceutical wholesale license, with distribution to DHBs around the country with isolation facilities.

To date, most COVID-19 cases requiring hospitalisation have been located in Auckland region, followed by Southern, Waikato and Canterbury.

Until / Unless a further outbreak of SARS-C0V-2 in the community occurs, the majority of individuals requiring hospitalisation will be identified through managed isolation.

Distribution

Guidelines for the management and distribution of the drug should be developed by the group of infectious disease specialists responsible for authorising the drug. The outline provided above reflects the current prevalence of Covid-19 in NZ. It is anticipated that manging the stock will vary on the need for treatment around the country at any given time.

To ensure minimal delay in starting therapy, it would be logical to have a supply of enough drug for an initial loading dose at each of the DHB's which oversee a quarantine facility (Auckland Region: Manukau, Waitemata, and Auckland, Central Region: Waikato and Lakes, Wellington Region: Capital and Coast. Southern Region: Canterbury.)

3. Additional comments

Many in the New Zealand and Australian infectious diseases community have called for a culture supportive of high-quality evidence based clinical trials, which could best answer important clinical questions about the optimal use of emerging therapeutic agents for COVID-19 infection. In this context, it would be important that any requirements for use of Remdesivir do not directly or indirectly act to impede inpatients participating in other clinical research studies.

- Concern has been expressed by some ID physicians, whether use of Remdesivir through the proposed programme could have significant requirements for additional documentation. This could serve as a barrier to other clinical research participation. It has been questioned whether this Remdesivir programme might require detailed documentation for enrolment and/or for logging adverse events. As the proposed programme is in our understanding not a compassionate access programme or research study, reporting of clinical information would not be required to Gilead, and that adverse events would be reported to CARM in the first instance.
- Sub-groups who were excluded from clinical trials should not be excluded from clinical access. This should be in conjunction with careful specialist input: for example, children, pregnant women, renal or liver disease. In the NZ context these are likely to be very rare cases.

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Appendix 1.

Current clinical indicators for the use of Remdesivir

The clinical indicators are based on the Australian guideline for use of Remdesivir, modified by expert advice within New Zealand

1. Population indications for use of remdesivir

Inclusions:

- All Adults
- Children over the age of 12 years and 40 kg.

Cautions

- Pregnancy
    - Category (B2)
    - Animal reproduction studies have failed to demonstrate a risk to the fetus
    - There are insufficient human data to evaluate risk in humans
- Renal impairment
    - In animal studies severe renal toxicity has been observed. The mechanism of this renal toxicity is not fully understood. Some evidence for use of remdesivir in acute or chronic renal disease has been reviewed [8].
    - With an eGFR less than 30 mL per minute the excipient sulfobutylether-β-cyclodextrin (SBECD) could accumulate as it is renally cleared. The clinical significance of this would need clarification, for example with a 5-day course the exposure is unlikely to cause substantive issues, but this is not yet known.
- Liver disease.
    - The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. Significant liver synthetic impairment is seen in people with cirrhosis.
    - remdesivir may not uncommonly cause a rise in liver transaminases e.g. ALT. Patients with a pre-existing hepatitis due to varying causes may therefore be a relative contraindication e.g. if ALT > 5 times the upper limit of normal. Gilead also recommend discontinuation if “ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.”
- Children
    - Children have so far not been included in clinical trials of Remdesivir. Most children with COVID-19 infection have a mild illness. Whether there is a subgroup who have the potential to benefit is unknown.
    - The ASID Paediatric Special Interest Group would be a suitable source of expertise in guiding any exceptional use of Remdesivir in children. If compassionate access for use in children is not available or unduly difficult, access through the national stocks could be a reasonable mechanism.

2. Dosing regimen for remdesivir

Use confined to healthcare facilities in which patients can be monitored closely.

Recommended Dose & Duration

- Day 1: loading dose of 200 mg (2 vials) given by intravenous infusion.
- Day 2 onwards: 100 mg (1 vial) given once-daily by intravenous infusion.
- Duration:
    - (i) Treatment course is limited to 5 days for the large majority of eligible patients, in the absence of an exceptional circumstance.
    - (ii) Treatment duration could be extended to 10 days in exceptional circumstances.
    - (iii) Patients clinically sufficiently well to be discharged could have their remdesivir course stopped, whatever the duration, rather than remain in hospital for further doses.

Comments

- The Australian Government 'Criteria for access to Remdesivir from the National Medical Stockpile' states that 'Treatment course is limited to 5 days for eligible patients' but mentions courses longer than 5 days under (unspecified) 'Special circumstances'. The Australian criteria also list ECMO or >48 hours of mechanical ventilation as exclusion criteria.
- The optimal time to initiate Remdesivir and duration of treatment are not definitively known, as described in a JAMA editorial [6].
- Available evidence suggests that the optimal time to start treatment is early in those with a poor trajectory. This would be before patients require ICU, such as with COVID-19 pneumonia when first developing hypoxia (requiring oxygen therapy). This could make sense in terms of pathophysiology and in general an anti-infective agent is more effective before infection becomes overwhelming
- The Goldman study of Remdesivir for 5 or 10 days in patients with severe Covid-19, started on wards, did not show a benefit of the longer treatment [3]. Nor was any benefit for longer treatment seen in those with moderate COVID-19 [4]. This limited information suggests limited benefit in extending Remdesivir use beyond 5 days. However, the study information are insufficient to definitively limit treatment to 5 days. Exceptional circumstances may be a reasonable basis for extending the course to 10 days.

3. Clinical indications for the use of Remdesivir

Recommended clinical indications:

Inclusion Criteria:

- Informed consent provided by the patient or the patient's legal representative, according to local practices.
- Approval by a named (local or regional) Infectious Diseases physician
- Hospitalised with confirmed COVID-19 (e.g. positive PCR test on nasopharyngeal swab) or known contact of a confirmed case with a syndrome consistent with coronavirus disease (COVID 19) awaiting confirmation by diagnostic testing.
- Oxygen saturation (SpO2) < 92% on room air, associated with COVID-19 lower respiratory tract infection.

Exclusion Criteria:

- Renal failure (eGFR < 30 mL/min or dialysis or continuous venovenous haemofiltration)
- Alanine aminotransferase (ALT) $\geq$ 5 x upper limit of normal (ULN) by local laboratory measure, or evidence of significant liver synthetic impairment e.g. known cirrhosis.
- Pregnancy (unless Remdesivir is recommended on balance following specialist obstetric and ID consultation).
- Mechanical ventilation for longer than 48 hours at time of application
- Receiving ECMO
- Evidence of multi-organ failure including but not limited to coagulopathy (significant thrombocytopenia), hepatic failure (elevated bilirubin) or renal failure (low urine output or estimated glomerular filtration rate (eGFR) < 30 mL/min), or significant cardiomyopathy (low cardiac output)
- Known hypersensitivity to the study drug, the metabolites, or formulation excipient

Considerations in Elderly or Advanced Comorbidity:

- Clinicians should give strong consideration to whether remdesivir is likely to benefit the patient in the following scenarios
- Premorbid frailty such as the patient has a poor prognosis and is unlikely to gain long term benefit from treatment.

Concomitant Therapies:

- Can be used concurrently with other treatments including corticosteroids.
- Use does not preclude patient participation in treatment studies with other agents.

Comments

- Have used the Australian criteria as a base.
- Informed consent should be sought in a manner consistent with normal NZ practice. We advise against requiring additional documentation for consent, which are not usual NZ practice.

- Requiring Infectious Diseases specialist as a co-applicant ensures there has been a full consideration of differential diagnoses and treatment options. Most COVID-19 inpatients are already known to local ID services, who typically provide clinical consultation to general medical or other teams who care for COVID-19 inpatients, which is to be encouraged. The numbers of inpatients meeting criteria for Remdesivir is likely to be within the capacity of ID services to meet this requirement. The ID physician community has a strong track record in antimicrobial stewardship and being seen as mostly giving good advice on antimicrobial use. This will help expedite clinical experience and 'institutional knowledge' on the use of Remdesivir until its place in therapy is better understood.
- Consideration of discussion with an ID specialist at another DHB would both develop decision making experience in NZ and harmonise decision making to give consistency across the country. This is particularly important if resource is limited as the goal posts may need to change if the incidence of disease changed, given the limited resource.
- Onset of hypoxia has been used as the primary marker of disease severity. Most trials used a threshold of O2 saturation < 94%. "Requiring supplemental oxygen', as in the Australian criteria, is a mechanism to avoid having to stop oxygen to get a reading. Some patients with chronic lung disease such as COPD have pre-existing chronic hypoxia, which limits the utility of hypoxia as a disease marker and could bias in favour of treating some patients who may only have mild disease.
- Requiring CXR evidence of pneumonia is problematic, as CXR changes are often delayed. International reports have shown that CT scans can detect pneumonia before CXR, but routine CT is discouraged.
- In the case of Remdesivir renal and liver disease are co-morbidities rather than drug specific issues and should be considered in a similar context to other organ impairment e.g. heart failure.
- Pregnancy has been an exclusion in the published clinical trials. Currently there is no available evidence of harm in pregnancy. Current evidence is that COVID-19 generally does not cause more severe illness in pregnancy, such as was seen with H1N1 influenza. Maternal condition may be improved if delivery can be safely undertaken for mother and child. Usual clinical processes apply.
- The limited evidence available suggest futility in severe illness such that initiation is unlikely to confer benefit. If treatment had been initiated prior to ventilation, it does not need to be ceased.
- Specific mention of those with comorbidities warrants specific mention, as these are groups more likely to develop severe COVID-19 disease and have been associated with an increased incidence of mortality. In elderly frail people, clinical judgement and discussion with patient/family is likely to be a sufficient means to guide appropriate use in most circumstances. General, ID, geriatric and respiratory physicians in NZ are overall very experienced in this.
- Specific mention of concomitant corticosteroids is warranted. Recent clinical trials have reported evidence that corticosteroids e.g. dexamethasone can reduce mortality when given to in-patients with severe COVID-19 infection. The interaction with Remdesivir is unknown but it is currently thought that there is no deleterious interaction between Remdesivir and corticosteroids.
- Specific mention of concomitant clinical trials and other research studies is warranted. It is important that use of remdesivir or not should not directly or indirectly be a barrier to offering patients to participate in research studies which are well-designed to answer valuable clinical questions. Of note there may be trials requiring the use of Remdesivir as standard care in both arms. Participation in research would not be an indication to use publicly funded remdesivir.

4. Subgroup analysis: Risk / Benefit

Recommendations

- Hospitalised ward (non-ICU) inpatients with confirmed COVID-19 infection causing respiratory infection with hypoxia (e.g. O2 saturation < 92% on room air), on current evidence are the group most likely to benefit.
- Inclusion of specific advice for the elderly and those with advanced comorbidities in the criteria as recommended above.

Comments

- Requiring ID approval as discussed above would likely be a constructive and non-onerous means to ensure adherence with the criteria for use, avoiding inappropriate broader use.
- Inclusion of specific consideration of comorbidities, as discussed above, could support appropriate non-use in those patients with a poor prognosis. The frail elderly are particularly vulnerable to severe COVID-19, which limits the utility of specific criteria.

MINISTRY OF HEALTH
MANATŪ HAUORA

Appendix 2 Section 29 Notification Form

Medsafe Declaration/Notification Form for medicines supplied **pursuant to Section 29 of the Medicines Act 1981**

This form is to be completed by the supplier in New Zealand that imported or manufactured the medicine.

INN / generic name of medicine:
Trade name of medicine:
Dose form:
Strength:
Pack size:
Month and year of supply:
Number of packs supplied:

I declare that:

- the above named and described medicine was supplied under the provisions of section 29 of the Medicines Act 1981 during the month stated above
- the name of the medicine as stated above is correct
- the following records have been kept:
  - the name(s) of the medical practitioner(s) who requested the supply of the medicine
  - the name(s) of the patient(s) the medicine was required for
  - the INN / generic name and trade name of the medicine
  - the dose form(s), pack size(s) and strength(s) of the medicine
  - the quantity supplied
  - the date(s) of the month and year the medicine was supplied
  - the name(s) of the place(s) the medicine was supplied to
- the complete and accurate records are available for audit by the Ministry of Health
- this organisation has a licence, issued under the Medicines Act 1981, which allows the supply of the medicine **or** is exempt from this requirement under section 26 (because the supplier is a pharmacy).

Signature: ..... **Date:** .....

Name of person making the declaration:.....

Designation of person making the declaration:.....

Name and address of Supplier, being the New Zealand importer or manufacturer:

.....

.....

.....

.....

Forward completed forms to Compliance Management Branch, Medsafe, Ministry of Health, PO Box 5013, Wellington 6140.

Lucy Lindsay-Shepherd

From: Susan Morpeth (CMDHB) <Susan.Morpeth@middlemore.co.nz>
Sent: Friday, 20 August 2021 2:33 pm
To: Anne Buckley
Cc: Dan Bernal; Jeremy Tuohy; Mark Ayson; COVID-19 Science Technical; Christian Marchello; Christopher Hopkins (CMDHB)
Subject: RE: 'Middlemore guidelines' Clinical Guidelines (therapeutics) - for patients with COVID-19 - Copy required today if possible
Attachments: Infection_Service-Management_of_COVID-19_in_adults.pdf

Hi Anne,
Sure - please find attached the current version. Please note that these are a dynamic guideline and subject to revision. They were drafted for Middlemore by Dr Chris Hopkins who has already supplied them to NZ ASID and the MOH by request, and have had input from the Middlemore Infectious Diseases, Respiratory and ICU services. Please note that they do not cover Paediatrics.
Ngaa mihi,
Susan

Dr Susan Morpeth, MBChB, FRACP, FRCPA, DTM&H, PhD
Clinical Microbiologist I Infectious Diseases Physician I Chair NZ Microbiology Network

T: +64 9 276 0044 I Ext: 59853 I M: s 9(2)(a) (internal: 51360)

susan.morpeth@middlemore.co.nz
Laboratory I Level 1, Harley Gray Building
Middlemore Hospital, 100 Hospital Road, Otahuhu
Private Bag 93311, Auckland 1640

From: Anne Buckley [mailto:Anne.Buckley@health.govt.nz]
Sent: Friday, 20 August 2021 2:11 p.m.
To: Susan Morpeth (CMDHB)
Cc: Dan Bernal; Jeremy Tuohy; Mark Ayson; COVID-19 Science Technical; Christian Marchello
Subject: 'Middlemore guidelines' Clinical Guidelines (therapeutics) - for patients with COVID-19 - Copy required today if possible
Importance: High

Kia ora Susan

Re**. 'Middlemore guidelines' Clinical Guidelines (therapeutics) - for patients with COVID-19 - Copy required today if possible**

I was on the meeting with you a short while ago as part of the Ministry's team, to discuss therapeutics needed in NZ for patients with COVID-19.

Could you please provide a copy of the 'Middlemore guidelines' to me for circulation to the team. It was supported in the meeting that the 'Middlemore guidelines' be progressed as an interim guideline for NZ. Our STA team in the Ministry are beginning the work to support this process.

Look forward to working with you further.
Regards
Anne

Anne Buckley
Senior Advisor
Science and Technical Advisory | Rōpū tohutohu i te pūtaiao me te hangarau
COVID-19 Science and Insights
COVID-19 Health System Response | Ministry of Health - Manatū Hauora | New Zealand
http://www.health.govt.nz
Email: Anne.Buckley@health.govt.nz