Practical guidance on the use of Ronapreve (casirivimab/imdevimab)

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The 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.

What is Ronapreve?

Ronapreve (casirivimab/imdevimab) contains two monoclonal antibodies that bind to the receptor binding domain of the SARS-CoV-2 spike protein. When people with some variants of COVID-19 are given Ronapreve early in the illness it probably reduces the chance of progression to serious or life-threatening illness.

Evidence for use

Evidence from a phase 3 trial indicates that 1200mg of casirivimab-imdevimab reduces the chance of hospitalisation from COVID-19 or death from any cause within 29 days by 70% (95% confidence interval 32-87%) (1). This study included people who had been diagnosed with COVID-19 within 3 days and had had symptoms for no longer than 7 days. The participants in the study were adults with at least 1 risk factor for severe COVID-19. Approximately 80% of participants were seronegative for COVID-19. In these people Ronapreve reduced the chance of death or hospitalisation from 3% to 1% - meaning approximately 45 doses of Ronapreve needed to be given to prevent 1 death or hospitalisation.

Evidence from RECOVERY, an open label adaptive platform trial in patients hospitalised due to COVID-19, shows that casirivimab-imdevimab reduced the chance of death from 30% to 24%, meaning 1 death could be avoided if 17 patients were given casirivimab-imdevimab (2). This result was in patients who did not have antibodies to SARS-CoV-2, and a benefit was not seen in patients who were seropositive. The mean (interquartile range) duration of symptoms of people in this trial was 7 (4 -10) days. Two thirds of participants in this study were on supplemental oxygen and 20% were being provided with non-invasive ventilatory support.

Effectiveness for SARS-CoV-2 variants

The patients were enrolled in the pivotal trial prior to the widespread distribution of the SARS-CoV-2 Delta variant, and prior to detection of the Omicron variant. In vitro and observational data indicate efficacy against the Delta variant (3, 4). Studies of viral neutralisation suggest Ronapreve will not be effective against the SARS-CoV-2 Omicron variant (5, 6).

Ronapreve is considered ineffective against the Omicron variant

Although if Ronapreve is inadvertently given to someone with the Omicron variant, it will not be harmful, clinicians should either have confirmed the patient is infected with the Delta variant, or have strong epidemiologic reasons to suspect that the COVID-19 infection is caused by the Delta variant**.** As the laboratory testing required to determine the SARS-CoV-2 variant is unlikely to be available in the required timeframe, clinicians should liaise with their local Medical Officer of Health to understand the likelihood that their patient may have a suitable COVID-19 variant.

Ronapreve use for those at most likelihood to benefit

There are limited supplies of Ronapreve, and our health system is not equipped to give Ronapreve to everyone with COVID-19. The best approach is to use the doses that we have to those who need them most – the people at highest risk of developing severe COVID-19.

From observational data we know the people most at risk are:

1. Unvaccinated people
2. People whose immune systems may not have responded adequately to vaccination due to immune suppressing conditions or medications
3. Older people
4. People with co-morbidities
5. Māori and Pacific people

There also needs to be equitable access, so that provision of Ronapreve is based on who needs it most rather than ease of access and availability of healthcare.

Who should be treated with Ronapreve?

Medsafe have approved use of Ronapreve for the indication of treatment of COVID-19 in adults and adolescents (aged 12 years and older and weighing at least 40 kg) who do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe COVID-19.

Pharmac has approved access to Ronapreve for the following groups.

Treatment of profoundly immunocompromised patients

1. Patient has confirmed (or probable) COVID-19; and
2. The patient is in the community (treated as an outpatient) with mild to moderate disease severity*; and
3. Patient is profoundly immunocompromised** and is at risk of not having mounted an adequate response to vaccination against COVID-19 **or** is unvaccinated; and
4. Patient's symptoms started within the last 10 days; and
5. Patient is not receiving high flow oxygen or assisted/mechanical ventilation; and
6. Casirivimab and imdevimab is to be administered at a maximum dose of no greater than 2,400 mg.

Treatment of mild to moderate COVID-19-hospitalised patients

All of the following:

1. Patient has confirmed (or probable) COVID-19; and
2. Patient is an in-patient in hospital with mild to moderate disease severity*; and
3. Patient's symptoms started within the last 10 days; and
4. Patient is not receiving high flow oxygen or assisted/mechanical ventilation; and
5. Any of the following:
    a. Age > 50; or
    b. BMI >30; or
    c. Patient is Māori or Pacific ethnicity; or
    d. Patient is at increased risk of severe illness from COVID-19, excluding pregnancy, as described on the Ministry of Health website***; and
6. Either:
    1. Patient is unvaccinated; or
    2. Patient is seronegative where serology testing is readily available or strongly suspected to be seronegative where serology testing is not readily available; and
7. Casirivimab and imdevimab is to be administered at a maximum dose of no greater than 2,400 mg.

Note:* Mild to moderate disease severity as described on the Ministry of Health Website

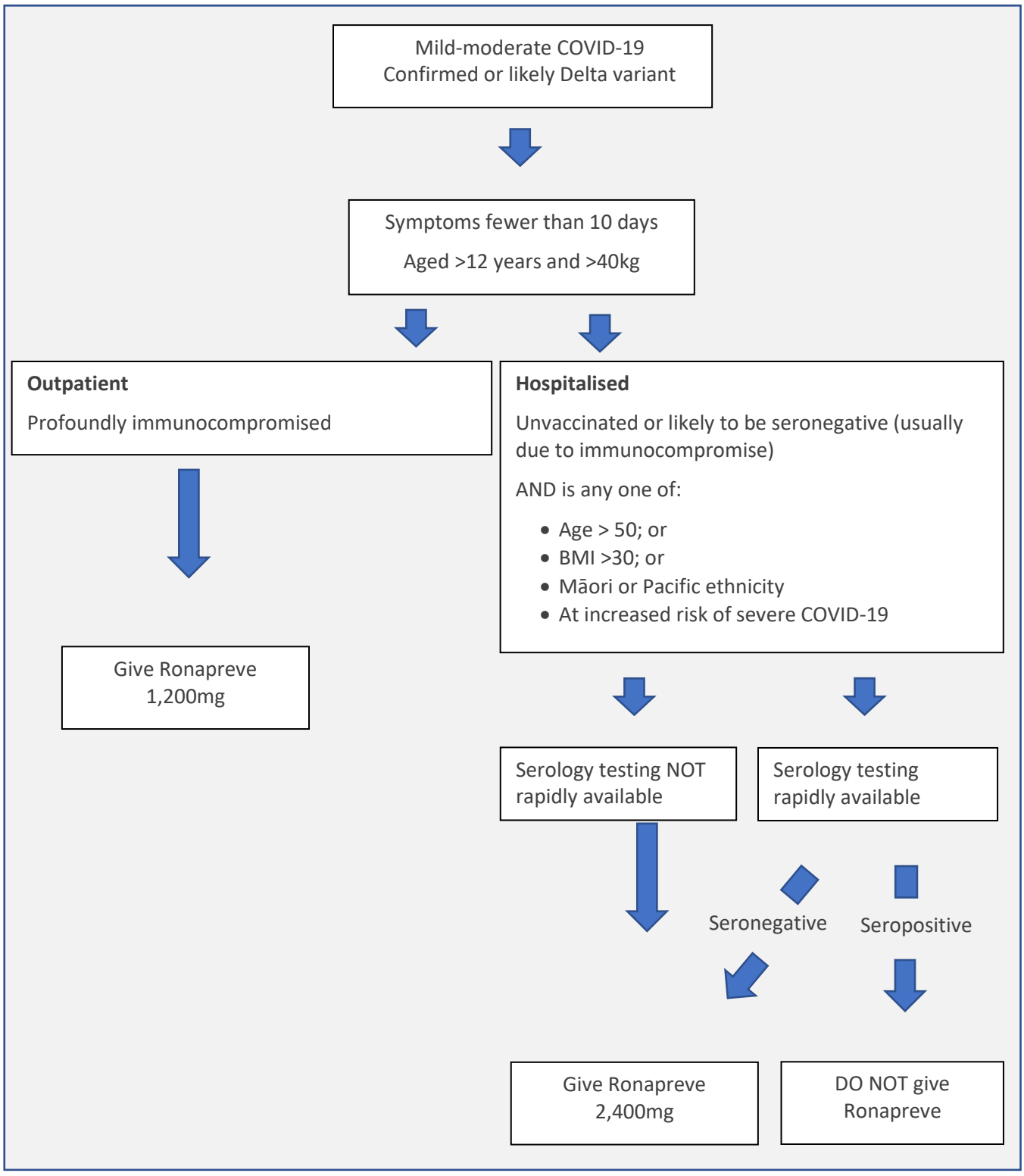
** Examples include B-cell depletive illnesses or patients receiving treatment that is B-cell depleting

*** (https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-information-specific-audiences/covid-19-advice-higher-risk-people)

How to decide if a patient will benefit and be eligible for Ronapreve

Synthesising Medsafe indication, Pharmac eligibility criteria and clinical evidence, the Therapeutics TAG recommend the use of Ronapreve in COVID-19 patients thought to be infected with the Delta variant, with symptoms for <10 days, and eligible to access Ronapreve (Figure 1). We would consider the patients to meet the criteria of profoundly immunocompromised if they met, or would now meet, the eligibility criteria for a third primary dose of COVID-19 vaccination (7), available at: https://www.health.govt.nz/system/files/documents/pages/third-primary-dose-policy-statement-clinical-guidance-25nov2021.pdf

Figure 1. Selecting which COVID-19 patients should be treated with Ronapreve



Dosing of Ronapreve

The recommendation of a 1,200mg dose in outpatients is based on existing trials of Ronapreve among outpatients (1), and is in keeping with the New Zealand Data Sheet supplied to Medsafe (8).

The Therapeutics TAG recommend 2,400mg for patients admitted to hospital due to COVID-19. Although this is a greater dose than stipulated in the New Zealand Data Sheet, it is based on data from the RECOVERY trial (2), additional work suggesting equivilance of 2,400mg with the higher dose (9), and recommendations in the United Kingdom (10). There is not currently evidence to support equivilance of 1,200mg among hospitalised patients.

Administration of Ronapreve (11)

The 2,400mg dose of Ronapreve can only be given via an intravenous infusion.

When Ronapreve is given at a dose of 1,200mg it can be given as either an intravenous infusion or 4 subcutaneous injections.

Regardless of the route of administration, patients must be clinically monitored during the administration and for 1 hour post-administration at 15-minute intervals. Check blood pressure, heart rate, oxygen saturation and temperature.

Intravenous infusion of 2,400mg

Preparation

1. Wash hands and remove casirivimab and imdevimab vials from the refrigerator.
2. Allow 20 minutes for the medication to equilibrate to room temperature. Ensure there is no discolouration or particulate matter in the preparation.
3. From a prefilled 250ml intravenous infusion bag of 0.9% sodium chloride or 5% dextrose solution, remove 20mL of solution using aseptic technique.
4. Using a separate syringe for each vial of casirivimab and imdevimab add 10mL (1,200mg) of EACH medication to the infusion bag
5. Gently mix the infusion bag by hand 10x to mix and administer immediately. It can be stored for up to 4 hours at room temperature and 36 hours in a refrigerator.

Administration

1. Attach a polyvinyl chloride or polyurethane infusion set to the prepared infusion.
2. Ensure there is an in-line or add-on 0.2 micron polyethersulfone filter attached and prime the infusion set.
3. Administer via intravenous infusion up to a maximum infusion rate of 500mL/hour, with a minimum infusion time of 30 minutes.
4. Do not administer the infusion solution with another medication
5. Once the infusion is complete, flush the line with 0.9% sodium chloride or 5% dextrose.

Intravenous infusion of 1,200mg

Preparation

1. Wash hands and remove casirivimab and imdevimab vials from the refrigerator.
2. Allow 20 minutes for the medication to equilibrate to room temperature. Ensure there is no discolouration or particulate matter in the preparation.
3. From a prefilled intravenous infusion bag of 0.9% sodium chloride or 5% dextrose solution, remove 10mL of solution using aseptic technique. 50 mL, 100mL, 150mL and 250mL bags of fluid are acceptable.
4. Using a separate syringe for each vial of casirivimab and imdevimab add 5mL (600mg) of EACH medication to the infusion bag
5. Gently mix the infusion bag by hand 10x to mix and administer immediately. It can be stored for up to 4 hours at room temperature and 36 hours in a refrigerator.

Administration

6. Attach a polyvinyl chloride or polyurethane infusion set to the prepared infusion.
7. Ensure there is an in-line or add-on 0.2 micron polyethersulfone filter attached and prime the infusion set.
8. Administer via intravenous infusion at these maximum infusion rates:

Size of prefilled infusion bag	Maximum infusion rate	Minimum infusion time
50 mL	150 mL/hour	20 min
100 mL	300 mL/hour	20 min
150 mL	450 mL/hour	20 min
250 mL	500 mL/hour	30 min

9. Do not administer the infusion solution with another medication
10. Once the infusion is complete, flush the line with 0.9% sodium chloride or 5% dextrose.

Sub-cutaneous (SC) injection if 1,200mg

Preparation

1. Wash hands and remove casirivimab and imdevimab vials from the refrigerator.
2. Allow 20 minutes for the medication to equilibrate to room temperature. Ensure there is no discolouration or particulate matter in the preparation.
3. Prepare 4 syringes to give in total 5ml of casirivimab and 5ml of imdevimab according to one of the 4 options below:

Option	Volume to be withdrawn to prepare 4 syringes
1	2.5 mL from two 6 mL single-use vials of casirivimab 2.5 mL from two 6 mL single-use vials of imdevimab
2	2.5 mL (2x) from one-20 mL multidose vial of casirivimab 2.5 mL (2x) from one 20 mL multidose vial of imdevimab
3	2.5 mL from two 6 mL single-use vials of casirivimab 2.5 mL (2x) from one 20 mL multidose vial of imdevimab
4	2.5 mL (2x) from one 20 mL multidose vial of casirivimab 2.5 mL from two 6 mL single-use vials of imdevimab

4. SC injections of casirivimab and imdevimab must be administered separately at different sites in the thighs, abdomen or upper arms. Avoid the waistline, 5cm around the navel, and any skin that is tender, damaged, bruised or scarred.

Accessing Ronapreve

District Health Board Pharmacies can order Ronapreve from HealthCare Logistics. Practitioners should access Ronapreve through District Health Board Pharmacies.

Potential adverse effects

Hypersensitivity – serious hypersensitivity reactions have been reported including anaphylaxis. Hypersensitivity reactions can occur >24 hours after administration. Anaphylaxis is rare and is usually reported within an hour of administration.

If patients develop symptoms or signs of serious hypersensitivity including anaphylaxis, stop the infusion and provide appropriate supportive care.

Infusion reactions – these can occur during the infusion and up to 24 hours after the infusion. These can include: difficulty breathing, irregular heart beat, fever, throat irritation, bronchospasm, reduced oxygenation, diaphoresis, nausea, hypotension, chest pain or discomfort, dizziness, fatigue, angioedema, hypertension, headache, weakness, syncope, chills, muscle aches, rash/pruritis.

If patients develop infusion reactions, consider slowing or stopping the infusion as well as providing supportive care.

Potential locations of care for administration

Individual District Health Boards will need to work with COVID-19 Co-ordination hubs and Primary Care to develop a strategy for administration of intravenous infusions or subcutaneous injections of COVID-19 medications including Ronapreve. Sites that may be considered for administration of Ronapreve include community sites (such as COVID-19 Hubs or GP practices, rural community hospitals or outreach services), in patients' homes, or in hospital. Particular consideration needs to be given to ensure timely assessment and access to treatment for at-risk people who live in areas of known low vaccination rates.

Venues and providers who administer Ronapreve will have:

1. Clinical skills to assess COVID-19 severity and eligibility for Ronapreve
2. Ability to prescribe Ronapreve
3. Skills and experience in the delivery of intravenous infusions or subcutaneous injections
4. Adequate infection control procedures and infrastructure to provide care to patients with COVID-19 infection
5. Suitable protocols to enable safe travel to and from the venue of administration
6. Ability to provide emergent care in the event of a severe adverse drug reaction

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