



COVID-19 Pharmacy Guide

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

REMAP-CAP COVID-19 Domain Pharmacy Guide Version 1.0 dated 13th May 2020

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1. COVID-19 ANTIVIRAL DOMAIN

1.1. *Hydroxychloroquine*

1.1.1. Presentation

Hydroxychloroquine 200mg tablet

1.1.2. Warnings

Do not crush the tablet if you are pregnant. Consider local handling precautions for hazardous medicines.

1.1.3. Dosing

Dosing will be hydroxychloroquine administered by the enteral route. Loading doses of 800mg will be administered 6-hourly until two doses have been administered. Subsequently, starting 12 hours after the first dose, 400mg will be administered 12-hourly for 12 doses.

1.1.4. Duration of therapy

If ICU discharge occurs before the end of the treatment course, the remaining doses should be prescribed unless the treating clinicians considers this not to be in the patient's best interest. Discontinuation at the time of or after ICU discharge will not be considered a protocol deviation.

1.1.5. Preparation and administration

1.1.5.1. *For patients who are able to swallow whole tablets*

Preferred method of administration is tablets swallowed whole.

1.1.5.2. *For patients with swallowing difficulties*

For patients who are unable to swallow whole tablets and do not have a gastric tube in situ:

1. Crush the tablet with a mortar and pestle or a tablet crusher
2. Add 10 to 20mL of sterile water and mix well
3. Draw the mixture into an oral dispenser/syringe

4. Rinse the crushing device with 10mL of sterile water, then repeat with another 10mL (total of 20mL) and draw into the oral dispenser/syringe, to ensure that all of the medicine is removed
5. Give the mixture immediately
6. Rinse the oral dispenser/syringe with a further 10mL of sterile water and give to the patient, to ensure the entire dose is given

If the person cannot swallow thin fluids (i.e. is at risk of aspiration) or the very bitter taste is unacceptable, crush the tablet and mix with a spoonful of yoghurt or fruit puree.

1.1.5.3. *For patients with gastric feeding tubes*

For patients who are unable to swallow whole tablets and have an enteral tube in situ:

1. Give immediately after a bolus feed or stop the continuous feed
2. Flush the tube with 30mL of sterile water
3. Crush the tablet to a fine powder using a mortar and pestle or a tablet crusher
4. Add 10mL of sterile water to the powder and mix well (the tablet does not disperse easily)
5. Draw the mixture into the **enteral** syringe
6. Rinse the crushing device with 10mL of sterile water, then repeat with another 10mL (total of 20mL) and draw into the **enteral** syringe, to ensure that all of the medicine is removed
7. Give the mixture (~30mL) immediately into the enteral feeding tube
8. Rinse the **enteral** syringe with a further 10mL of sterile water to ensure the entire dose is given
9. If other medicines are given, flush the tube with at least 5 mL of sterile water between each medicine
10. After the final medicine is given, flush the tube with 30mL of sterile water
11. Restart the continuous feed immediately after dosing

Smaller volumes can be used to accommodate fluid-restriction.

1.1.1. Dose adjustment in renal impairment

There are varying published recommendations on dosing in renal impairment. For the purposes of this trial, no dose adjustment is made for impaired renal function or concomitant use of renal replacement therapy. For patients with renal transplants, no dose adjustments of hydroxychloroquine are required however therapeutic drug monitoring should be considered for other agents. Decision to enroll patients with renal transplants should occur in consultation with a nephrologist.

1.1.2. Potential drug interactions

Concomitant treatment with drugs that are known to interact with hydroxychloroquine should be avoided. If possible, an alternative agent should be considered, allowing for continuation of study drug. If no alternative is acceptable, the treating clinician will need to choose either to not administer the interacting medication or hydroxychloroquine, based on clinical priority.

1.1.3. Discontinuation

An antiviral agent for COVID-19 should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

1.2. *Lopinavir/ritonavir*

1.2.1. Presentation

The following preparations are available:

- Lopinavir 200mg/Ritonavir 50mg per tablet
- Lopinavir 80mg/Ritonavir 20mg per 1mL suspension

The following instructions apply to both the Kaletra® and Aluvia® brand.

1.2.2. Warnings

Nil.

1.2.3. Dosing

Dosing will be lopinavir/ritonavir 400/100mg, administered by the enteral route every 12 hours.

1.2.4. Duration of therapy

Lopinavir/ritonavir will be administered for a minimum of five days, including if the patient is discharged from ICU before the end of study day 5. If the patient is discharged from ICU between study day 6 and the end of study day 14, lopinavir/ritonavir is ceased at ICU discharge. If the patient remains in ICU, lopinavir/ritonavir should be ceased at the end of study day 14. If the patient is readmitted to ICU prior to the end of study day 14, lopinavir/ritonavir should be recommenced.

1.2.5. Preparation and administration

1.2.5.1. For patients who are able to swallow whole tablets

Preferred method of administration for patients who are able to swallow whole tablets is to administer two 200/50mg tablets, swallowed whole. Do not crush, chew or break the tablet due to the film coating.

1.2.5.2. For patients with swallowing difficulties or gastric feeding tubes

Preferred route of administration for patients who are unable to swallow whole tablets is to administer 5mL of suspension orally. Note that the liquid has an unpleasant taste. The use of ice chips before and after the dose may numb the taste buds or mix the dose with chocolate syrup to mask the taste.

For patients with a gastric feeding tube:

1. Give immediately after a bolus feed or stop the continuous feed
2. Flush the tube with 30mL of sterile water
3. Draw 5mL into an **enteral** syringe and dilute with at least an equal volume of sterile water
4. Mix well and give via the gastric feeding tube
5. A white residue or cloudy solution may be seen but will not clog the tube
6. Flush the tube with 30 mL of sterile water and restart the feed

Note that due to the high content of propylene glycol and ethanol in the oral suspension, a PVC / silicone feeding tube should be used due to incompatibility with polyurethane.

There is adequate absorption of lopinavir when the oral liquid is given through nasogastric or PEG tubes and reduced absorption when given through jejunal tubes.

If suspension is unavailable, the preference is then to dissolve whole tablets according to the following instructions:

1. It is recommended to initiate preparation 6-12 hours prior to the prescribed administration time. It is recommended to prepare the next dose at the time of administering the current dose. Unused solution must be discarded within 24 hours. The dose should be stored safely per institutional requirements during the dissolution process
2. Label an **enteral** syringe with the preparation time, cap the syringe then remove the plunger
3. Place 2 tablets in the syringe barrel. **Do not crush or grind the tablet prior to mixing with sterile water as this will affect bioavailability**
4. Add 20mL of sterile water to the syringe barrel and replace plunger
5. Allow tablets to fully dissolve at room temperature (takes at least 4 hours). No agitation or stirring is required during this time
6. Carefully swirl. The resulting suspension will have a milky appearance
7. Administer to patient:

- a. For patients with swallowing difficulties but no gastric feeding tube, give orally
 - b. For patients with a gastric tube, administer immediately after a bolus feed or stop the continuous feed. Flush the tube with 30mL of sterile water then administer the dose. If other medicines are given, flush the tube with at least 5mL of sterile water between each dose
8. Rinse the **enteral** syringe with a further 20mL of sterile water to ensure the entire dose is given.
 9. After the medicine is given, flush the tube with 30mL of sterile water.

For a patient who cannot swallow and when the suspension is not available or tablets cannot be dissolved, four crushed tablets (double dose) may be administered via gastric tube:

1. Crush 4 tablets using a mortar and pestle or a tablet crusher
2. Add 10mL of sterile water to the powder and mix well
3. Draw the mixture into the **enteral** syringe
4. Rinse the crushing device with 10mL of sterile water, then repeat with another 10mL (total of 20mL) and draw into the **enteral** syringe to ensure that all of the medicine is removed from the device
5. Administer to the patient:
 - a. For patients with swallowing difficulties, give orally
 - b. For patients with a gastric tube, give immediately after a bolus feed or stop the continuous feed. Flush the tube with 30mL of sterile water then administer the dose. If other medicines are given, flush the tube with at least 5mL of sterile water between each dose
6. Rinse the enteral syringe with a further 20mL of sterile water to ensure the entire dose is given
7. After the medicine is given, flush the tube with 30mL of sterile water

Note that systemic absorption is reduced by approximately 50% using this method. This method of administration should only be used when it is not possible to dissolve whole tablets.

Administering crushed tablets via nasogastric tube may cause blockage of the tube. Consider using a wide-bore nasogastric tube and flush thoroughly after administration.

1.2.1. Dose adjustment in renal impairment:

No dose adjustment is required due to renal dysfunction or concomitant use of renal replacement therapy. Clinically significant drug interactions may occur between lopinavir/ritonavir and immunosuppressant agents for patients with renal transplants. A decision to enroll such patients should occur in consultation with a nephrologist.

Clinicians should consider a dose adjustment in the presence of liver failure, however no dose adjustment is necessary for abnormal liver function tests in the absence of liver failure.

1.2.2. Potential drug interactions

Concomitant treatment with drugs that are known to interact with lopinavir/ritonavir should be avoided. If possible, an alternative agent should be considered, allowing for continuation of study drug. If no alternative is acceptable, the treating clinician will need to choose either not to administer the interacting medication or lopinavir/ritonavir based on clinical priority.

A list of medications known to interact with lopinavir/ritonavir can be found at <http://www.covid19-druginteractions.org/>

1.2.3. Discontinuation

An antiviral agent for COVID-19 should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

Patients with known HIV infection at the time of enrollment are excluded from receiving lopinavir/ritonavir. Any patient who is discovered to be HIV positive after enrollment may have lopinavir/ritonavir ceased if the treating clinician believes that this is clinically appropriate.

2. COVID-19 IMMUNE MODULATION DOMAIN:

2.1. *Interferon-β1A*

2.1.1. Presentation

The following presentations are available:

- Interferon beta-1α 44mcg/0.5mL prefilled syringe (PFS) (Rebif®)
- Interferon beta-1α 22mcg/0.5mL syringe PFS (Rebif®)*

**Note that the 22mcg syringe is not currently available in Australia.*

2.1.2. Warnings

Prefilled syringes and auto-injectors should be protected from light and heat. Face shields in addition to standard PPE should be worn. Do not prepare if pregnant or trying to conceive.

2.1.3. Dosing

IFN-β1a 11mcg will be diluted in 0.9% saline. The diluted IFN-β1a solution will be administered as an intravenous bolus injection via a central or peripheral line.

The injection should be given at the same time each day, up to one hour either side of the prescribed administration time. If for any reason this is not possible, the treatment window may be extended by up to 4 hours. If study drug is not administered within this 4-hour period it should be omitted for that day and administered at the prescribed administration time on the following day.

2.1.4. Duration of therapy

IFN-β1a will be administered once daily for 6 days or until ICU discharge, whichever occurs first.

2.1.5. Preparation and administration

2.1.5.1. *Preparing the 11mcg dose using a 44mcg/0.5mL PFS:*

Preferred method of preparation using sodium chloride 0.9% 100mL vial (i.e. Phebra brand or equivalent):

1. Uncap the 44mcg/0.5mL Rebif® PFS
2. Inject the entire syringe (44mcg/0.5mL) into a sodium chloride 0.9% 100mL vial

3. Mix gently by inverting 10 times
4. Withdraw 25mL (11mcg) into a syringe
5. Ensure the remaining contents of the vial are discarded into pharmaceutical waste (the remaining contents of the vial may only be used for other patients located in the same area and due for administration at the same time, and if there is a drug shortage. This should be considered with regards to local policies)
6. Administer the contents of the syringe (11mcg/25mL) intravenously as a 5-minute slow IV bolus via the central or peripheral line.
7. Flush line with 10-20mL of sodium chloride 0.9%

Second preference (only if 100mL sodium chloride 0.9% vials are unavailable):

1. Select a Baxter Viaflex sodium chloride 0.9% 100mL bag and add a 3-way adaptor to the injection port (if possible, to allow multiple entry into the port)
2. Remove 8 mL from the injection port and discard (approximate bag overage volume). This will give an approximate final volume of 100mL
3. Uncap the 44mcg/0.5mL Rebif® PFS
4. Inject the entire syringe (44mcg/0.5mL) into the sodium chloride 0.9% 100mL bag
5. Mix gently by inverting 10 times
6. Withdraw 25mL (11mcg) into a syringe
7. Ensure the remaining contents of the bag are discarded into pharmaceutical waste (the remaining contents of the bag may only be used to dose other patients located in the same area and due for administration at the same time, and if there is a drug shortage. This should be considered with regards to local policies)
8. Administer the contents of the syringe (11mcg/25mL) intravenously as a 5-minute slow IV bolus via the central or peripheral line
9. Flush line with 10-20mL of sodium chloride 0.9%.

2.1.5.2. *Preparing the 11mcg dose using 22mcg/0.5mL PFS*

Preferred method of preparation using sodium chloride 0.9% 50mL vial:

1. Uncap the 22mcg/0.5mL Rebif® PFS
2. Inject the entire syringe (22mcg/0.5mL) into a sodium chloride 0.9% 50mL vial
3. Mix gently by inverting 10 times
4. Withdraw 25mL (11mcg) into a syringe
5. Ensure the remaining contents of the vial are discarded into pharmaceutical waste (the remaining contents of the vial may only be used to dose other patients located in the same area and due for administration at the same time, and if there is a drug shortage. This should be considered with regards to local policies)
6. Administer the contents of the syringe (11mcg/25mL) intravenously as a 5-minute slow IV bolus via the central or peripheral line
7. Flush line with 10-20mL of sodium chloride 0.9%

Second preference (only if 50mL sodium chloride 0.9% vials are unavailable):

1. Select a Baxter Viaflex sodium chloride 0.9% 50mL bag and add a 3-way adaptor to the injection port (if possible, to allow multiple entry into the port)
2. Remove 7mL from the injection port and discard (approximate bag overage volume). This will give an approximate final volume of 50mL
3. Uncap the 22mcg/0.5mL Rebif® PFS
4. Inject the entire syringe (22mcg/0.5mL) into the sodium chloride 0.9% 50mL bag
5. Mix gently by inverting 10 times
6. Withdraw 25mL (11mcg) into a syringe
7. Ensure the remaining contents of the bag are discarded into pharmaceutical waste (the remaining contents of the bag may only be used for other patients located in the same area)

and due for administration at the same time, and if there is a drug shortage. This should be considered with regards to local policies)

8. Administer the contents of the syringe (11mcg/25mL) intravenously as a 5-minute slow IV bolus via the central or peripheral line
9. Flush line with 10-20mL of sodium chloride 0.9%

2.1.6. Dose adjustment in renal or liver impairment

No dose adjustment is made for impaired renal function or concomitant use of renal replacement therapy.

2.1.7. Potential drug interactions

Additional agents that are intended to modulate the immune response against COVID-19 infection, other than those included in the REMAP-CAP platform, should not be administered.

2.1.8. Discontinuation

An immunomodulatory agent for COVID-19 infection should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

2.2. *Anakinra*

2.2.1. Presentation

Anakinra 100mg/0.5mL prefilled syringe (PFS) (Kineret®)

2.2.2. Warnings

Prefilled syringes should be protected from light and heat.

Face shields in addition to standard PPE should be worn. Do not prepare if pregnant or trying to conceive.

2.2.3. Dosing

Anakinra will be administered as intravenously via a central or peripheral line. A loading dose of 300mg will be administered, followed by maintenance doses of 100mg of anakinra administered every 6 hours. In patients with creatinine clearance of less than 30mL/min or who are receiving renal replacement therapy, anakinra will be administered every 12 hours.

2.2.4. Duration of therapy

For patients who are not receiving invasive mechanical ventilation, anakinra will be ceased on ICU discharge or after 14 days, whichever occurs first.

For patients who are receiving invasive mechanical ventilation, anakinra will be administered until the patient has been breathing without receiving invasive mechanical ventilation for more than 24 hours. For patients who continue to receive invasive mechanical ventilation, anakinra will be ceased after 14 days.

2.2.5. Preparation and administration

To prepare the infusion using 100mg PFS:

1. Uncap the 100mg PFS
2. Inject required number of 100mg syringes into a 50mL sodium chloride 0.9% infusion bag
3. Mix gently by inverting 10 times
4. Prime the line with the Anakinra infusion then administer infusion intravenously over 60 minutes via a central or peripheral line

5. Flush line at the same rate as the Anakinra infusion with 10-20mL of sodium chloride 0.9%.

2.2.6. Dose adjustment in renal or liver impairment

In patients with creatinine clearance of less than 30 mL/min or who are receiving renal replacement therapy, anakinra will be administered every 12 hours.

2.2.7. Potential drug interactions

Additional agents that are intended to modulate the immune response against COVID-19 infection, other than those included in the REMAP-CAP platform, should not be administered.

2.2.8. Discontinuation

An immunomodulatory agent for COVID-19 infection should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

2.3. Tocilizumab

2.3.1. Presentation

- Tocilizumab 400mg/20mL vial and 200mg/10mL vial (RoActemra® /Actemra®)
- Tocilizumab 80mg/4mL vial (RoActemra® /Actemra®)

2.3.2. Warnings

Tocilizumab vials should be protected from light and heat.

If made at the bedside, consider donning a face shield in addition to standard PPE. Do not prepare if pregnant or trying to conceive.

2.3.3. Dosing

Tocilizumab will be administered intravenously at a dose of 8mg/kg based on measured or estimated body weight, with a total dose not exceeding 800 mg.

Doses should be rounded to the nearest 10mg (which represents the nearest 0.5mL measurable volume).

2.3.4. Duration of therapy

A single dose of tocilizumab will be administered. If the treating clinician believes there has not been sufficient clinical improvement, a second dose may be administered between 12 and 24 hours after the initial dose.

2.3.5. Preparation and administration

This infusion may be made in an aseptic environment or at the bedside, depending on local regulations.

1. Calculate the volume (mL) required for the dose
 - a. Prescribed dose is 8 mg/kg estimated or measured body weight, with a maximum dose of 800 mg
 - b. Round dose to the nearest 10mg (0.5 mL)
2. Withdraw this volume from a 100mL sodium chloride 0.9% infusion bag

3. Discard the volume withdrawn from the sodium chloride 0.9% infusion bag. This will ensure that the final volume is 100mL after the drug has been added
4. Withdraw the required volume of tocilizumab solution for the patient dose
5. Add the tocilizumab solution to the 100mL sodium chloride 0.9% infusion bag
6. Gently invert the bag to mix, do not shake
7. Inspect the bag. Only bags which are clear to opalescent, colorless to pale yellow and free of visible particles can be infused
8. Prime the line with the tocilizumab infusion then administer infusion intravenously over 60 minutes via a central or peripheral line
 - a. The infusion speed must be 10mL per hour for 15 minutes and then increased to 130mL per hour for the next 45 minutes
9. Flush line at the same rate as the tocilizumab infusion with 10-20mL of sodium chloride 0.9%

If made at the bedside, administer infusion immediately after preparation and discard remaining vials. If made in an aseptic environment, the diluted solution may be stored at 2-8°C for 24 hours prior to administration.

2.3.6. Dose adjustment in renal or liver impairment

For the purposes of this trial, no dose adjustment is made for impaired renal function or concomitant use of renal replacement therapy.

2.3.7. Potential drug interactions

Additional agents that are intended to modulate the immune response against COVID-19 infection, other than those included in the REMAP-CAP platform, should not be administered.

2.3.8. Discontinuation

An immunomodulatory agent for COVID-19 infection should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

2.4. Sarilumab

2.4.1. Presentation

Sarilumab 200mg/1.14mL prefilled syringe (PFS) (Kevzara®)

2.4.2. Warnings

Prefilled syringes should be protected from light and heat.

The solution should not be used if it is cloudy, discolored, or contains particles, or if any of the device appears to be damaged.

Face shields in addition to standard PPE should be worn. Do not prepare if pregnant or trying to conceive.

2.4.3. Dosing

Sarilumab will be administered as a single dose of 400mg as an intravenous infusion via a central or peripheral line over a one-hour period.

2.4.4. Duration of therapy

A single dose of 400 mg Sarilumab will be administered.

2.4.5. Preparation and administration

Preparation of Sarilumab infusion using 200mg PFS:

1. If using Baxter Viaflex sodium chloride 0.9% infusion bags, it is suggested to pre-pierce the internal septum on the drug injection port of the IV bag as the half-inch attached needle on the sarilumab PFS may not be long enough to pierce the internal septum of this IV bag
2. Uncap the 200mg PFS
3. Inject 2 x 200mg syringes into a 100mL sodium chloride 0.9% infusion bag
4. Mix gently by inverting 10 times
5. Prime the line with the sarilumab infusion then administer the infusion intravenously over 60 minutes via a central or peripheral line

- a. The infusion speed must be 10mL/hour for 15 minutes, then increased to 130mL/hour for the next 45 minutes
 - b. The infusion set must contain a 0.2-micron inline filter
6. Flush the line at the same rate as the sarilumab infusion with 20mL sodium chloride 0.9%

The infusion should be prepared and administered immediately. The infusion should be commenced within a maximum of 4 hours after preparation.

2.4.6. Dose adjustment in renal or liver impairment

For the purposes of this trial, no dose adjustment is made for impaired renal function or concomitant use of renal replacement therapy.

2.4.7. Potential drug interactions

Additional agents that are intended to modulate the immune response against COVID-19 infection, other than those included in the REMAP-CAP platform, should not be administered.

2.4.1. Discontinuation

An immunomodulatory agent for COVID-19 infection should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.