Pharmacy Guide

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

REMAP-CAP Pharmacy Guide Version 4 dated 26 October 2023

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1. CYSTEAMINE DOMAIN

1.1.1. Presentation

Cysteamine bitartrate vials are provided frozen and should be immediately stored in a freezer between -15°C to -25°C.

Cysteamine bitartrate IV vials contain 500mg/vial; 2.5mL fill volume of cysteamine bitartrate (200mg/mL).

1.1.1.1. *Packaging*

Boxes (box size of 20cm (L) x 7cm (W) x 7cm (H) containing 30 vials of frozen cysteamine bitartrate (sufficient for 10 days of treatment (3 vials per day)). The box and insert are white.

1.1.2. Warnings

Cysteamine bitartrate should be stored frozen at -15°C to -25°C. Cysteamine bitartrate is temperature sensitive and the administration guide in section 1.1.5 should be strictly adhered to.

If preparing at the bedside, face shields should be worn in addition to standard PPE. There is no data supporting the safety of handling or preparation of cysteamine bitartrate by people who are pregnant or trying to conceive. Cysteamine bitartrate should be handled and prepared in line with local guidelines.

1.1.3. Dosing

Cysteamine will be administered every 8 hours at a dose of 5 mg/kg of estimated or measured body weight, with each administered dose not to exceed 500 mg. The IMP solution will be diluted in 50 or 100 mL of 0.9% NaCl and administered as an intravenous infusion over 10 minutes via a central or peripheral venous catheter.

If clinically significant hypotension occurs during infusion, the infusion rate should be slowed and, if necessary, ceased.

Monitor patients for:

- Suspected or proven allergic or hypersensitivity reaction sufficient to require interruption of infusion or treatment or both. These may include one or more of the following clinical findings - urticaria, pruritus, facial flushing, wheezing, dyspnea, and hypotension

- Hypocalcemia* that is symptomatic or requires treatment or both
- Total neutrophil count less than 2.0 x 10^9 /L
- For any patients on glyceryl trinitrate – patients should be monitored for possible hypotension, which can be serious and may be indicated by headaches.

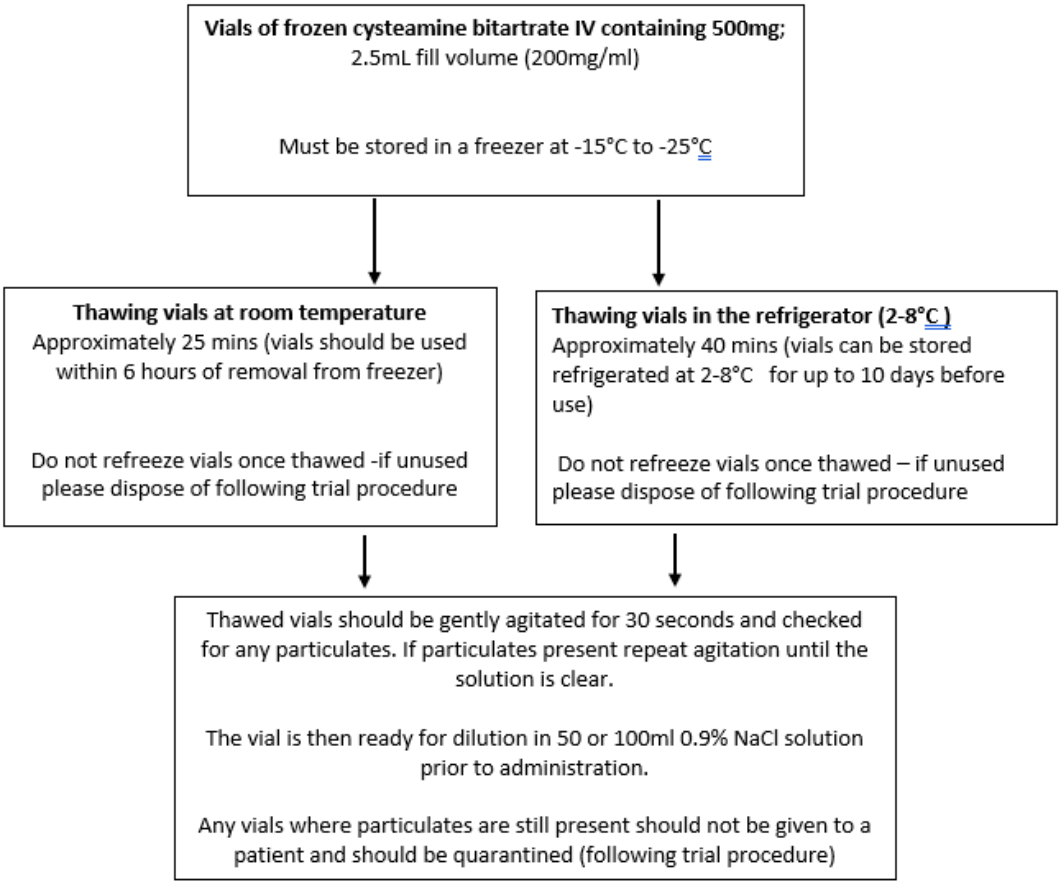
*Amifostine is an aminothiol drug that has been associated with hypocalcemia. As cysteamine is an aminothiol compound, hypocalcemia may be a potential side effect.

1.1.4. Duration of therapy

The duration of cysteamine administration is 10 days, i.e. 30 doses. Cysteamine may be ceased at the time of ICU discharge in patients who are discharged from ICU before completion of the 10-day course. Omission of three or more consecutive doses is a protocol deviation.

1.1.5. Preparation and administration

1.1.5.1. *Instructions for thawing and storage*



1.1.5.2. *Preparation of 5mg/kg dose for IV administration*

Cysteamine Bitartrate (200mg/mL) is a concentrated solution and should be diluted prior to administration intravenously (5mg/Kg of estimated/actual body weight, see dose banding table below) with each single administered dose not to exceed 500mg. Cysteamine bitartrate should be diluted in 50 mL or 100 mL 0.9% NaCl solution prior to administration and given as below.

The infusion may be made in an aseptic environment or at the bedside, depending on local regulations. If made at the bedside, administer infusion immediately after preparation and discard remaining vials following local guidance.

Calculate the volume (mL) of the thawed cysteamine bitartrate required (based on patient's estimated/actual body weight) of 200 mg/mL cysteamine bitartrate drug product (see dose banding table below for guidance).

1. Cysteamine bitartrate is very sensitive to air, therefore care should be taken not to introduce air bubbles while drawing the solution from the vial into the syringe and on transferring into the infusion bag. Withdraw the required volume of cysteamine bitartrate using a needle and 1 mL or 5 mL syringe and add to a 50 mL or 100 mL 0.9% NaCl solution infusion bag (Baxter is the preferred infusion bag but is not essential to use).

2. The remaining contents of the vial should be disposed of in pharmaceutical waste.

3. Invert the infusion bag 10 times to ensure homogenous solution.

4. Inspect the bag. Only bags which are clear and free of visible particles can be infused.

5. It is recommended to administer cysteamine bitartrate as soon as it is diluted in the 50mL or 100mL 0.9% NaCl solution. However, if made in an aseptic environment and there is a situation where cysteamine bitartrate cannot be administered immediately, the 50mL or 100mL 0.9% NaCl bags with diluted cysteamine bitartrate can be stored in refrigerator at 2-8°C for a maximum of 24 hours prior to administration.

6. Attach the bag to the administration set and prime the line with the cysteamine bitartrate infusion then administer infusion intravenously over set at a flow rate to administer the entire bag within 10- minutes. Please note cysteamine bitartrate should not be given via the same line as betalactams (see Potential drug interactions).

7. Flush line at the same rate as the infusion with 20mL of 0.9% sodium chloride.

Table 1. Dose banding table for Cysteamine bitartrate

Estimated or measured body weight (kg) Based on the upper weight in each 5kg band	Calculated dose in mgs (to give 5mg/Kg of body weight)	Required volume (mL) of 200mg/mL solution – rounded to nearest decimal point
35-40kg	200mg	1.0mL
41-45kg	225mg	1.1mL
46-50kg	250mg	1.3mL
51-55kg	275mg	1.4mL
56-60kg	300mg	1.5mL
61-65kg	325mg	1.6mL
66-70kg	350mg	1.8mL
71-75kg	375mg	1.9mL
76-80kg	400mg	2.0mL
81-85kg	425mg	2.1mL
86-90kg	450mg	2.25mL
91kg and over	475mg-500mg*	*Calculate the dose up to the extractable volume of the vial

*The total fill volume of each vial is 2.5 mL, however the total extractable volume varies between vials so for patients weighing 91kg and over use the maximum extractable volume from the vial.

1.1.6. Dose adjustment

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

1.1.7. Potential interactions

Beta-lactam antibiotics are not contraindicated, but co-administration of cysteamine with beta-lactams should be avoided (as direct mixing in a line can affect the chemistry of the drugs and potentially reduce beta-lactam potency). Cysteamine is an antibiotic potentiator and is designed for co-administration with antibiotics but:

- Through different lines if given concomitantly
- Through different ports of the same line sequentially

- If only a single line is available/accessible, cysteamine and beta-lactams should be administered at different times (a few minutes apart)

Glyceryl trinitrate (GTN): Simultaneous administration with cysteamine may increase the vasodilatory and platelet aggregation-inhibiting effect of glyceryl trinitrate. If such combined treatment is considered necessary, the patient should be monitored for possible hypotension, which can be serious and may be indicated by headaches.

1.1.8. Discontinuation

Cysteamine bitartrate should be discontinued if there is development of a serious adverse event.

For patients assigned to any intervention, occurrence of any of the following should be reported as an SAE:

- Suspected or proven allergic or hypersensitivity reaction sufficient to require interruption of infusion or treatment or both. These may include one or more of the following clinical findings - urticaria, pruritus, facial flushing, wheezing, dyspnea, and hypotension
- Hypocalcemia that is symptomatic or requires treatment or both
- Total neutrophil count less than 2.0×10^9 /L

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. INFLUENZA IMMUNE MODULATION DOMAIN

2.1. Tocilizumab

2.1.1. Presentation

The following preparations are available:

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

2.1.2. 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.

2.1.3. 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. In children weighing less than 30kg, the tocilizumab dose will be 12mg/kg.

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

To reduce wastage, the below dose banding table can be used at the discretion of the site:

Table 2. Dose banding table for Tocilizumab

Estimated or measured weight	Dose	Vials	Maximum dose variance
<30 kg	12mg/kg, rounded to nearest 10mg	As required	
≥30 and < 41 kg	8mg/kg, rounded to nearest 10mg	As required	
≥41 and ≤ 45 kg	360mg	1x 200mg + 2x 80mg	9%
≥ 46 and ≤ 55 kg	400mg	2x 200mg	9%
≥ 56 and ≤ 65 kg	480mg	2x 200mg + 1x 80mg	9%
≥ 66 and ≤ 80 kg	600mg	3x 200mg	14%
≥ 81 and ≤ 90 kg	680mg	3x 200mg + 1x 80mg	5%
≥ 91kg	800mg	4x 200mg	10%

2.1.4. Duration of therapy

A single dose of tocilizumab will be administered.

2.1.5. Preparation and administration

This infusion may be made in an aseptic environment or at the bedside, depending on local regulations. It is recommended that the tocilizumab infusion is prepared in 100mL sodium chloride 0.9% bag; however, for patients under 30kg, a 50mL sodium chloride 0.9% infusion bag may be used instead at the discretion of the treating clinician.

1. Calculate the volume (mL) required for the dose

    a. For adults and children weighing 30kg or more, the prescribed dose is 8 mg/kg estimated or measured body weight, with a maximum dose of 800 mg.

    b. For children < 30kg the prescribed dose is 12mg/kg estimated or measured body weight

    c. 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 recommended infusion speed must be 10mL per hour for 15 minutes and then increased to 130mL per hour for the next 45 minutes.

    b. If 50 ml bag is used, then infusion rate is half of that listed above.

    c. If local policies allow then the infusion can be administered as a fixed speed over 60 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.

2.1.6. 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.

2.1.7. Potential drug interactions

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

2.1.8. Discontinuation

Tocilizumab 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. Baricitinib

2.2.1. Presentation

The following preparations are available:

- Baricitinib 4mg tablet (Olumiant®)
- Baricitinib 2mg tablet (Olumiant®)
- Baricitinib 1mg tablet (Olumiant®) [Only in some countries]

2.2.2. Warnings

Staff should wear a mask and gloves when dispersing Baricitinib. Do not prepare or disperse Baricitinib tablets if pregnant.

If a 2mg tablet must be split to create a 1mg dose (see below), this should be performed in a pharmacy in a suitable powder containment cabinet (e.g., laminar flow hood). In areas where all staff are in full PPE, and if local policies allow, the 2mg tablet may be cut in half using a tablet cutter with a blade.

2.2.3. Dosing

Baricitinib dose is dependent on age and renal function, based on the table below:

Table 3. Baricitinib dosing by age and renal function

Age	eGFR	Baricitinib dose
2 – 9 years	≥60 mL/min/1.73m^2	2mg daily
	≥30 and < 60 mL/min/1.73m^2	1mg daily
	<30 mL/min/1.73m^2	Withhold dose
	Receiving renal replacement therapy	Withhold dose
≥ 9 years	≥60 mL/min/1.73m^2	4mg daily
	≥30 and < 60 mL/min/1.73m^2	2mg daily
	≥15 and <30 mL/min/1.73m^2	1mg daily
	<15 mL/min/1.73m^2	Withhold dose
	Receiving renal replacement therapy	Withhold dose

If a 1mg dose is required, but 1mg tablets are not available, a 2mg tablet can be split to administer half a 2mg tablet once daily. Alternatively, 2mg of Baricitinib can be given every second day.

If you intend to split Baricitinib tablets, please note the warnings above.

2.2.4. Duration of therapy

Baricitinib will be administered for 10 doses or until hospital discharge, whichever occurs first.

2.2.5. Preparation and administration

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

Preferred method of administration is tablets swallowed whole.

2.2.5.2. *For patients with swallowing difficulties*

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

1. Place the tablet(s) in sterile water in an enteral syringe.
    a. Use 15mL of water for a gastrostomy tube, or 30mL of water for a nasogastric tube
2. Swirl gently until completely dispersed and an even suspension is formed. The tablet may take 5 minutes to completely disperse.
3. Administer the solution via the tube soon after preparation.
4. Rinse the enteral syringe with 15mL of water to ensure the entire dose is given

Note that this solution may block tubes that are smaller than size 12 French.

2.2.6. Dose adjustment

Baricitinib dose is adjusted for renal function (see Table 3). There is no adjustment for liver impairment.

2.2.7. Potential interactions

The dose of baricitinib may need to be reduced in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors, such as probenecid.

2.2.8. Discontinuation

Baricitinib should be discontinued if there is development of a SAE which, in the opinion of the treating clinician, could be related to participation in this domain. 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.

APPENDIX 1. SUMMARY OF CHANGES FROM VERSION 1 TO VERSION 2

- Removal of Hydroxychloroquine. This agent has been removed from the COVID-19 Antiviral Domain of REMAP-CAP on the basis of results from the RECOVERY and WHO SOLIDARITY trials.
- Addition of Vitamin C and Simvastatin to reflect the addition of these domains to the platform.
- Clarification for duration of lopinavir/ritonavir, interferon, anakinra, and tocilizumab interventions to reflect the extension of these therapies to the Moderate Illness Severity State (i.e. patients not requiring organ support in ICU).
- Clarification of warnings regarding preparation for interferon, anakinra, and sarilumab.
- Clarification of preparation of infusions of interferon, anakinra, and sarilumab, particularly with reference to the use of Baxter Viaflex bags.
- Addition of a tocilizumab dose banding table, to be used at the discretion of sites to reduce wastage.

APPENDIX 2. SUMMARY OF CHANGES FROM VERSION 2 TO VERSION 2.1

- Updated advice about the preparation of IFN-β1a, anakinra, tocilizumab, and sarilumab by people who are pregnant or trying to conceive.

APPENDIX 3. SUMMARY OF CHANGES FROM VERSION 2.1 TO VERSION 3

- Removal of COVID-19 Immune Modulation Domain agents (anakinra, interferon-beta-1a, tocilizumab, and sarilumab). This domain has been closed.
- Removal of lopinavir/ritonavir from the COVID-19 Antiviral Domain, and addition of ivermectin to this domain.
- Addition of Cysteamine.

APPENDIX 4. SUMMARY OF CHANGES FROM VERSION 3 TO VERSION 4

- Removal of interventions specified in the COVID-19 Antiviral Domain (ivermectin), Simvastatin Domain (simvastatin), and Vitamin C Domain (vitamin C). These domains are now closed.
- Addition of interventions specified in the Influenza Immune Modulation Domain (tocilizumab and Baricitinib).