BC Cancer Protocol Summary for the Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Bortezomib and Dexamethasone With or Without Cyclophosphamide

Protocol Code	*UMYDARBD*
Tumour Group	*Myeloma*
Contact Physicians	*Dr. Kevin Song, Dr. Jesse Shustik*
Contact Pharmacist	*Louisa Pang*

ELIGIBILITY:

- For treatment of patients with multiple myeloma who have received at least one prior line of therapy.
- Patients must be sensitive to bortezomib or not previously exposed
- A BC Cancer "Compassionate Access Program" request with appropriate clinical information for each patient must be approved prior to treatment
- Patients are eligible for only one triplet therapy, i.e. either daratumumab (UMYDARBD, UMYDARLD) or carfilzomib (UMYCARLD) triplet therapy.

EXCLUSIONS:

- Disease refractory to bortezomib or unacceptable side effects from bortezomib.
- Disease refractory to another proteasome inhibitor
- Grade 2 or higher peripheral neuropathy or neuropathic pain
- Neutrophil of 1.0 x 10^9/L or less may be considered a relative contraindication. Consider giving filgrastim
- Hemoglobin level of 75 g/L or less may be considered a relative contraindication
- Platelet count of 75 x 10^9/L or less may be considered a relative contraindication.
- AST or ALT level of 2.5 times greater than the ULN
- Bilirubin of 1.5 or greater than the ULN

TESTS:

- Baseline (required before first treatment): Red Blood Cell phenotype and Group and Screen pre daratumumab (mark on requisition "patient to start daratumumab")
- Baseline (required before first treatment): CBC & diff, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin.
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with further treatment): HBsAg, HBcoreAb, serum protein electrophoresis ***and/or*** serum free light chain level

<u>Cycles 1 to 4</u>

- Day 1: CBC & diff, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin
- Day 1: (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis ***and/or*** free light chain levels.
- Day 15: CBC & diff, platelets. If clinically indicated, sodium, potassium, creatinine, ALT, serum bilirubin

Cycle 5 and subsequent

- Day 1**:** CBC & diff, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin
- Day 1: (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis ***and/or*** free light chain levels.

PREMEDICATIONS:

Prior to daratumumab infusion:

- acetaminophen 650 mg PO prior to each daratumumab . Repeat acetaminophen Q4H dose x 1 dose during the infusion on Day 1 of cycle 1 only, then Q4H PRN fever
- diphenhydrAMINE 50 mg PO/IV or loratadine 10mg PO prior to each daratumumab. Repeat diphenhydrAMINE 50 mg Q4H X 1 dose during the infusion on Day 1 of cycle 1 only, then diphenhydrAMINE 50 mg IV Q4H PRN allergic reaction
- montelukast 10 mg PO prior to each daratumumab for cycle 1, day 1 (and day 2 if on alternative regimen), then consider discontinuing if no infusion reactions
- dexamethasone 20-40 mg PO prior to daratumumab for cycle 1 only. (The therapeutic dose of dexamethasone is used as the premedication steroid to reduce the risk of reactions). If using daratumumab split dosing (i.e., the Alternative regimen), dexamethasone 20 mg should be given prior to daratumumab on days 1 and 2. After cycle 1, steroids are not required as a premedication as the risk of infusion reactions is significantly reduced after the third dose of daratumumab.[15] The therapeutic dexamethasone dose (if ordered) should be administered prior to daratumumab.
    - predniSONE may be used instead of dexamethasone as the therapeutic steroid. A minimum of 100mg of predniSONE is required for cycle 1. After cycle 1, a lower dose of prednisone may be used and administered prior to daratumumab

  Note: A minimum of 20mg of dexamethasone (or 100mg of prednisone) is not needed prior to each daratumumb infusion after cycle 1

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. (Complete special authority form)
- If Varicella-zoster Virus (VZV) seropositive, start valACYClovir 500 mg PO daily and continue for entire duration of bortezomib and/or daratumumab and for 4 weeks after discontinuation.
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone may be considered

TREATMENT:

1 cycle = 28 days. Treat until progression

There are 2 options for administering the first daratumumab infusion and the decision to use one over the other is centre-based:

1) **Standard regimen** – first infusion of daratumumab 16 mg/kg administered on Cycle 1 day 1. This is preferred where possible.

2) **Alternative regimen** – first dose of daratumumab is split over 2 days i.e., 8 mg/kg administered on Cycle 1 day 1 and again on day 2. Cycle 1 day 1 + day 2 is considered to be the first infusion. This regimen has been created to accommodate shorter clinic hours.

Drug	Dose	BC Cancer Administration Guideline
dexamethasone*	Cycle 1 to 8: 40 mg once weekly on days 1, 8, 15 and 22 For patients greater than 75 years of age (or younger than 75 years of age at MD's discretion), use dexamethasone 20 mg or lower Cycle 9 onwards: Optional at physician's discretion	PO prior to daratumumab, and on the weeks when daratumumab is not given, taken in the morning
cyclophosphamide (if using)**	Cycle 1 to 8: 300 mg/m^2*** (maximum 500 mg) once weekly on days 1, 8, 15 Cycle 9 onwards: Optional at physician's discretion	PO
bortezomib	Cycle 1 to 8: 1.3 mg/m^2 once weekly on days 1, 8, 15, 22	SC (abdomen or thigh)

*Therapeutic dose of dexamethasone is used as the premedication steroid to reduce the risk of infusion reactions. PredniSONE may be substituted for dexamethasone as the therapeutic steroid per physician preference. A minimum of 20mg dexamethasone or 100mg predniSONE is required for cycle 1 only to prevent infusion reactions. The risk of infusion reactions is significantly reduced after the third dose of daratumumab; therefore, premedication with steroids is not required after cycle 1.[15]

**If neutropenia is a concern consider a dose reduction of cyclophosphamide

***round dose to the nearest 25 mg

Cycle 1 DARATUMUMAB

Drug	Standard Regimen (Dose)	Alternative Regimen (Dose)	BC Cancer Administration Guideline
daratumumab	16 mg/kg on day 1		IV in 1000 mL NS (use 0.2 micron in-line filter) Start at 50 mL/h; if no reactions† after 60 minutes, increase rate by 50 mL/h every 60 minutes until maximum 200 mL/h
		8 mg/kg on days 1 and 2	IV in 500 mL NS (use 0.2 micron in-line filter) Start at 50 mL/h; if no reactions† after 60 minutes, increase by 50 mL/h every 60 minutes until maximum 200 mL/h
	16 mg/kg on day 8		IV in 500 mL‡ NS (use 0.2 micron in-line filter) If no reaction on Cycle 1 day 1, or Cycle 1 day 1 and 2, or reaction is Grade 2‡ or less: Start infusion at 200 mL/h. If no reaction† after 30 minutes, infuse the remainder at 450 mL/h (rapid infusion) **OR** If reaction on Cycle 1 day 1, or Cycle 1 day 1 and 2 is Grade 3‡: Start at 50 mL/h; if no reactions† after 60 minutes, increase by 50 mL/h every 60 minutes until maximum 200 mL/h (slow infusion)
	16 mg/kg on days 15 and 22		IV in 500 mL NS (use 0.2 micron in-line filter) If no reaction on Cycle 1 day 1, day 2 and day 8 or reaction is Grade 2‡ or less: Start infusion at 200 mL/h. If no reaction† after 30 minutes, infuse the remainder at 450 mL/h (rapid infusion) **OR** If reaction on Cycle 1 day 1, day 2 and day 8 is Grade 3‡: Start at 100 mL/h; if no reactions† after 60 minutes, increase by 50 mL/h every 60 minutes until maximum 200 mL/h (slow infusion)

† If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritis, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort occurs, stop daratumumab infusion and page physician. See Infusion Reaction section in protocol for when to resume infusion and rate.

‡ For CTCAE grading, see Appendix: Infusion Related Reaction

Cycle 2 plus DARATUMUMAB

Drug	Cycle	Dose	BC Cancer Administration Guideline
daratumumab	Cycle 2	16 mg/kg on days 1, 8, 15, 22	IV in 500 mL NS (use 0.2 micron in-line filter) If no reaction in the previous infusion or reaction is Grade 2‡ or less: Start infusion at 200 mL/h. If no reaction† after 30 minutes, infuse the remainder at 450mL/h (rapid infusion) **OR** If reaction in the previous infusion is Grade 3‡: Start at 100 mL/h; if no reactions† after 60 minutes, increase by 50 mL/h every 60 minutes until maximum 200 mL/h (slow infusion)
	Cycle 3 to 4	16 mg/kg on days 1 and 15	
	Cycle 5 and subsequent	16 mg/kg on day 1	

† If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritis, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort occurs, stop daratumumab infusion and page physician. See Infusion Reaction section in protocol for when to resume infusion and rate.

‡ For CTCAE grading, see Appendix: Infusion Related Reaction

For additional information on infusion rates, see Appendix: Daratumumab infusion rate titration table.

Vitals monitoring:

For infusions on Cycle 1 day 1 (and day 2 if using Alternative regimen)

Vital signs immediately before the start of the infusion, then every 30 minutes x 4, then every 1 to 2 hours until the end of the infusion. Post infusion at 30 minutes after the end of the infusion. Patient may leave when infusion is complete and patient is stable for 30 minutes.

For subsequent infusions i.e., Cycle 1 day 8 and beyond:

Vital signs immediately before the start, at the end of the infusion, and as needed. Patient may leave when infusion is complete and patient is stable for 30 minutes. Observation post-infusion not required after 3 treatments if patient did not experience any infusion reactions.

POST INFUSION MEDICATIONS:

Patients with a higher risk of respiratory complications (e.g., patients with chronic obstructive pulmonary disease (COPD) who have a forced expiratory volume in 1 second of less than 80%; patients with asthma) should be treated with post-infusion medication consisting of an antihistamine (diphenhydramine) on the first and second days after all infusions, short acting adrenergic receptor agonist (salbutamol inhaler) and control medications for lung disease (e.g., inhaled corticosteroids +/- long-acting β2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators +/- inhaled corticosteroids for patients with COPD.

OTHER OPTIONS FOR STEROID DOSING

Option A: Oral dexamethasone 20 mg once weekly on days 1, 8, 15 and 22
Option B: predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance.
Option C: No dexamethasone. Dexamethasone may need to be avoided in certain patients who are intolerant or have difficulty with side-effects. It is expected that the response will be inferior using bortezomib alone. Dexamethasone may be added for sub-optimal response

DOSE MODIFICATIONS:

I. CYCLOPHOSPHAMIDE DOSE MODIFICATIONS:

1. Hematological, for low counts due to treatment, not disease

For Cyclophosphamide lab on day 1 only

ANC ($x10^9$/L)	Platelets ($x10^9$/L)	Dose (cyclophosphamide)
greater or equal to 1.0	greater than or equal to 80	100%
less than 1.0	less than 80	Consider delay until recovery checking CBC weekly

2. Hepatic Impairment:

For Cyclophosphamide, no dose reduction is necessary for hepatic impairment.

3. Renal Failure:

For Cyclophosphamide, dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis. Physician may consider giving full dose of cyclophosphamide irrespective of renal function if deemed to be of benefit.

Creatinine clearance (mL/min)	Cyclophosphamide Dose
Greater than or equal to 10	100 %
Less than 10	75 %

Calculated creatinine clearance = $\frac{N \times (140 - Age) \times weight\ (kg)}{Serum\ Creatinine\ (micromols/L)}$

N = 1.04 (Females) and 1.23 (Males)

II. BORTEZOMIB DOSE MODIFICATIONS:

Dexamethasone should continue to be taken even if bortezomib is held due to a dose limiting toxicity.

1. Hematological¥:

ANC ($x10^9$/L)	Platelets ($x10^9$/L)	Bortezomib Dose
greater than or equal to 0.5	And greater than or equal to 30	100%
less than 0.5	Or less than 30	Consider delay until recovery checking CBC weekly or consider omit; reduce dose to 1 mg/m^2
reoccurrence of less than 0.5	reoccurrence of less than 30	Consider delay until recovery checking CBC weekly or consider omit; further reduce dose to 0.7 mg/m^2

¥Modify on day 1 only. MD may delay or consider omitting on other days.

2. Peripheral Neuropathy:

Severity of Peripheral Neuropathy Signs and Symptoms	Bortezomib Dose
Grade 1 (paresthesia and/or loss of reflexes) without pain or loss of function	100%
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 1 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living	Delay until recovery. When resolved, reduce dose to 0.7 mg/m^2 weekly
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

3. Hepatic Impairment:

	Bilirubin	ALT or AST	Bortezomib Dose
Mild	less than or equal to 1 x ULN	greater than ULN	100%
	greater than 1 – 1.5 x ULN	Any	100%
Moderate	greater than 1.5-3 x ULN	Any	▪ Reduce dose to 0.7 mg/m^2 in the first cycle. ▪ Consider dose escalation to 1 mg/m^2 *or* further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	greater than 3 x ULN	Any	

4. Renal Failure:

For bortezomib, no dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis.

5. Diarrhea management with bortezomib:

Diarrhea grading system

Grade 1	Grade 2	Grade 3	Grade 4
Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated for less than 24hrs; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of greater than 7 stools per day over baseline; incontinence; IV fluids for greater than 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)

Treatment of Diarrhea during cycle		
At first loose stool:	Start loperamide 2 mg PO q 2 h while awake and q4h while sleeping. Continue around the clock until 12 h diarrhea free	• If diarrhea free greater than 12 h, stop loperamide. If new episode, retreat with loperamide. • If grade 3 diarrhea or diarrhea accompanied by mucus or dehydration, hold doses of Bortezomib (if applicable) and hydrate.

Diarrhea management: Next Cycle Dosing Delay next cycle until diarrhea has resolved (less than 2 watery bowel movements / day)	
Severity of diarrhea with last cycle:	Bortezomib dose this cycle
less than or equal to grade 2	no change from previous cycle
greater than or equal to grade 3 or associated with mucus or dehydration	Reduce dose to 80% of that used in the last course or consider once a week dosing. (if two dose reductions have already occurred further treatment with Bortezomib must be individualized and should only continue if a clearly useful clinical response in the myeloma has occurred)

III. DARATUMUMAB DOSE MODIFICATIONS:

1. Infusion reactions

See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Chemotherapeutic Agents – SCDRUGRX.

Infusion reactions	Management
If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort, stop infusion and page physician	**Initial occurrence:** After recovery of symptoms, restart infusion at HALF the rate at which the infusion reactions occurred and continue with escalation of infusion rates on the appropriate schedule above. **Subsequent occurrence:** If the infusion must be stopped a second time, restart after recovery of symptoms, at HALF the rate at which the infusion reactions occurred and continue at that rate without further escalation

Infusion rate when resuming infusion after grade 1 or greater symptoms are resolved:

Infusion rate when reactions occur	Maximum infusion rate when resuming infusion*
50 mL/h	25 mL/h
100 mL/h	50 mL/h
150 mL/h	75 mL/h
200 mL/h	100 mL/h
450 mL/h	225 mL/h*

***Incremental increases remain at 50 mL/h for all resuming infusions

2. Hematological†, for low counts due to treatment, not disease

ANC($x10^9$/L)		Platelets ($x10^9$/L)	daratumumab
Greater than or equal to 1.0	and	Greater than or equal to 50	100 %
Less than 1.0	and/or	Less than 50	Delay until recovery

†Modify on day 1 only. MD may delay or consider omitting on other days.

Consider holding bortezomib and cyclophosphamide if daratumumab is delayed for cytopenias. Dexamethasone does NOT need to be held.

3. **Hepatic dysfunction**

Bilirubin (micromol/L)		ALT +/or AST	daratumumab
Less than 1.5 x ULN	or	less than or equal to 2.5 x ULN	100 %
Greater than or equal to 1.5 X ULN	or	Greater than 2.5 to 5 x ULN	Delay until recovery

4. Renal Failure:

For daratumumab, no dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis.

IV. STEROID DOSE MODIFICATIONS

Dexamethasone (or predniSONE) does NOT need to be held when cyclophosphamide, bortezomib or daratumumab are held.

PRECAUTIONS:

1. **Infusion reactions** occur in 50% of all patients and can be serious including bronchospasm, hypoxia and hypertension. These usually occur with the first dose and rarely after subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing the infusion. Other signs and symptoms include cough, wheezing, larynx and throat tightness/irritation, laryngeal edema, pulmonary edema, nasal congestion, and allergic rhinitis. Less commonly reported symptoms include hypotension, headache, urticarial rash, pruritus, nausea, vomiting, and chills. **Premedication** with antihistamines, antipyretics, and corticosteroids is required; stop infusion for any infusion reactions and manage as appropriate. Reduce the infusion rate for grade 1, 2, or 3 infusion reactions, see Common Terminology Criteria for Adverse Events (CTCAE) in appendix; permanently discontinue therapy for grade 4 infusion reactions. Administer in a facility with immediate access to resuscitative measures (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen). Administer oral corticosteroids on the first and second day after infusion to reduce the risk of delayed infusion reactions. Consider short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders; monitor closely. See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Chemotherapeutic Agents – SCDRUGRX.
2. **Interference with cross-matching and red blood cell antibody screening** occurs due to drug binding to CD38 on red blood cells (RBC) resulting in a positive Indirect Antiglobulin Test (Coombs test). This interference may persist for up to 6 months post last daratumumab treatment. Inform blood bank that a patient has received daratumumab. Type and screen patients prior to starting daratumumab.
3. **Interference with determination of myeloma response** as daratumumab (a human IgG kappa monoclonal antibody) may be detected on serum protein electrophoresis and

immunofixation assays which monitor for endogenous M-protein. Interference with these assays by daratumumab may affect the determination of complete response and disease progression in some patients with IgG kappa myeloma protein.

4. **Hepatitis B Reactivation**: All lymphoma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamiVUDine during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
5. **VZV prophylaxis:** Antiviral prophylaxis is recommended prior to initiating daratumumab and/or bortezomib for patients who are VZV seropositive. Patients should take valACYclovir 500 mg PO daily while taking daratumumab and for 4 weeks after its discontinuation. Of note, VZV serology is often not reliable, even in patients previously exposed. Most clinicians choose to prescribe valACYclovir without testing for VZV serology.
6. **Live vaccines**: Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
7. **Need for irradiated blood products:** Patients receiving an autotransplant require irradiated blood products from 7 days prior to collection to 3 months post transplant (6 months if total body irradiation conditioning) to eliminate the risk of potentially life-threatening transfusion-related graft-versus-host-disease. All other myeloma patients do not require irradiated blood products. .
8. **Green tea avoidance**: Some of the components in green tea and preparations made from green tea block the activity of bortezomib in in vitro experiments. Green tea or preparations made from green tea should be avoided by patients taking bortezomib.
9. **Diarrhea management with bortezomib:** see diarrhea management in bortezomib dose modification section.
10. **Peripheral Neuropathy:** occurs in 36–37% of patients receiving IV bortezomib with 8–14% resulting in grade 3–4 severity of symptoms. This is a common and often dose limiting side effect. Administration of bortezomib via the subcutaneous route instead of IV push significantly reduces the occurrence of peripheral neuropathy.

Call Dr. Kevin Song (Leukemia/BMT), Dr. Jesse Shustik or Dr Laurie Sehn (Lymphoma) or tumour group delegate with any problems or questions regarding this treatment program. (Leukemia/BMT at (604) 875-4863 or after hours (604) 875-4111; Lymphoma at (604) 877-6000 or 1-800-663-3333)

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Appendix:

Daratumumab infusion rate titration table

STANDARD Regimen Cycle 1: Day 1

Daratumumab 16 mg/kg IV in 1000 mL NS Total Volume (Refer to pharmacy label)		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
50 mL/h	1 h	50 mL
100 mL/h	1 h	100 mL
150 mL/h	1 h	150 mL
200 mL/h	3 h 30 min	700 mL

ALTERNATIVE Regimen Cycle 1: Day 1 and Day 2

Daratumumab 8 mg/kg IV in 500 mL NS Total Volume (Refer to pharmacy label)		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
50 mL/h	1 h	50 mL
100 mL/h	1 h	100 mL
150 mL/h	1 h	150 mL
200 mL/h	1 h	200 mL

Infusion rate is the same for both regimens thereafter.

Both regimens have same infusion rate for Cycle 1 Days 8, 15 and 22, and Cycle 2 and beyond.

Rapid Infusion: Cycle 1 Day 8 and beyond

Daratumumab 16 mg/kg IV in 500 mL NS **Total Volume (Refer to pharmacy label)**		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
200 mL/h	30 min	100 mL
450 mL/h	55 min	400 mL

Slow Infusion: Cycle 1: Day 8

Daratumumab 16 mg/kg IV in 500 mL NS **Total Volume (Refer to pharmacy label)**		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
50 mL/h	1 h	50 mL
100 mL/h	1 h	100 mL
150 mL/h	1 h	150 mL
200 mL/h	1 h	200 mL

Slow Infusion: Cycle 1: Day 15 and Day 22

Slow Infusion: Cycle 2 and beyond

Daratumumab 16 mg/kg IV in 500 mL NS **Total Volume (Refer to pharmacy label)**		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
100 mL/h	1 h	100 mL
150 mL/h	1 h	150 mL
200 mL/h	1 h 15 min	250 mL

Appendix: Infusion related Reaction

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg. antihistamines, NSAIDS, narcotics, iv fluids); prophylactic medications indicated for less than or equal to 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and /or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	**Death**

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