Regimen Monograph

A - Regimen Name

DARA(MNT-SC) Regimen

Daratumumab (subcut) Maintenance

Disease Site

Hematologic
- Amyloidosis
- Multiple Myeloma

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

- As maintenance (after completion of combination treatment*) in patients with newly diagnosed (transplant ineligible) or relapsed multiple myeloma, who have good performance status
- As maintenance after completion of CYBORD in patients with light chain (AL) amyloidosis, who have good performance status

*Refer to NDFP forms in Supplementary Public Funding section for details on funded regimens.

Supplementary Public Funding

daratumumab (subcut)
New Drug Funding Program (Daratumumab in Combination with a

Bortezomib-Based Regimen for Newly Diagnosed Transplant Ineligible Multiple Myeloma) (NDFP Website)

daratumumab (subcut)
New Drug Funding Program (Daratumumab - In Combination with Bortezomib and Dexamethasone for Relapsed Multiple Myeloma) (NDFP Website)

daratumumab (subcut)
New Drug Funding Program (Daratumumab and Bortezomib in combo with Cyclophosphamide and Dexamethasone - Previously Untreated Light Chain (AL) Amyloidosis) (NDFP Website)

back to top

B - Drug Regimen

Note: Different daratumumab products are NOT INTERCHANGEABLE.

As maintenance treatment (after completion of daratumumab combination* therapy):

daratumumab (subcut)	1800 mg	Subcut	Day 1

*Refer to NDFP forms for details on funded regimens.

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

Multiple myeloma: Until disease progression or unacceptable toxicity.

Light chain amyloidosis: Up to 24 cycles of treatment (including CYBORD+DARA(SC) cycles) or until disease progression or unacceptable toxicity, whichever occurs first

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

- Also refer to CCO Antiemetic Recommendations.
- HBV screening should be performed in all patients prior to starting daratumumab.
- Consider antiviral prophylaxis for herpes zoster reactivation.
- Daratumumab can interfere with cross-matching for blood transfusions; type and screen and RBC genotyping tests should be done before starting this drug.

Pre-medications for daratumumab (subcut) monotherapy (prophylaxis for administration-related reactions (ARRs)):

To be given at least 1 hour prior to each dose:

- Corticosteroid IV/PO (e.g., methylprednisolone 100 mg or equivalent)*
- Oral antipyretic (e.g., acetaminophen 650-1000 mg)
- H1-receptor antagonist IV/PO (e.g., diphenhydramine 25-50 mg or equivalent)
- Montelukast 10 mg PO‡

*This dose may be reduced after the 2nd injection (e.g., methylprednisolone 60 mg IV or equivalent).

‡Montelukast 10 mg was optional on Cycle 1 Day 1 during clinical trials of daratumumab (subcut). The addition of montelukast given prior to the first daratumumab IV infusion numerically reduced the incidence of respiratory IRs in the study by Nooka et al.

Post-injection medications for daratumumab (subcut) monotherapy (prevention of delayed ARRs):

- Oral corticosteroid (e.g., methylprednisolone 20 mg or equivalent) for 2 days post-injection§
- Consider bronchodilators (e.g., short and long acting) and inhaled corticosteroids (for patients with a history of COPD)#

§These may be discontinued after the 3rd injection if no major systemic ARRs occurred.

#These may be discontinued after the 4th injection if no major ARRs occurred.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Dose Levels: No dose reductions of daratumumab (subcut) are recommended. Dose delays may be required.

Toxicity	Grade/Severity	Action
Neutropenia	Grade 4	Hold until ≤ Grade 2. Consider use of colony-stimulating factors (e.g., G-CSF).
Thrombocytopenia	Grade 3 or 4	Hold until ≤ Grade 2.
Hepatitis B virus (HBV) reactivation		Hold daratumumab, concomitant steroids and chemotherapy. Consult with an HBV expert and manage appropriately. Restart of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Management of Administration-Related Reactions (ARRs):

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the administration rate. • Manage the symptoms. **Restart:** • Consider restart if appropriate	• Consider rechallenge if appropriate.
3	• Stop treatment.	• Consider rechallenge if appropriate.

	• Aggressively manage symptoms. **Restart:** • Consider restart if appropriate	
4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Hepatic Impairment

Hepatic Impairment	Daratumumab (Subcut) Dose
Mild (total bilirubin 1 to 1.5 times ULN or AST > ULN)	No dose adjustment necessary.
Moderate (total bilirubin >1.5 to 3 times ULN and any AST)	Limited data.
Severe (total bilirubin >3 times ULN and any AST)	

Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

Dosage in the Elderly

No dose adjustment is required in patients ≥ 65 years of age. No overall differences in efficacy were observed but patients ≥ 65 years were more likely to experience serious adverse events (e.g., pneumonia) than those < 65 years.

back to top

F - Adverse Effects

Refer to daratumumab (subcut) drug monograph(s) for additional details of adverse effects.

The incidences below were mostly reported for daratumumab IV. Adverse events associated with the subcutaneous formulation are denoted with "^".

Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection, bleeding (may be severe, including opportunistic infection or viral reactivation) • Fatigue • Cough, dyspnea • Systemic administration-related reactions^ • Musculoskeletal pain • Diarrhea • Nausea, vomiting	• Injection site reaction^ • Cardiotoxicity • Atrial fibrillation • Hepatotoxicity • Pancreatitis • ↓ Immunoglobulins • Renal failure

back to top

G - Interactions

Refer to daratumumab (subcut) drug monograph(s) for additional details.

- Daratumumab interferes with the indirect antiglobulin (Coombs) test by binding to CD38 on RBCs. Daratumumab-mediated positive Coombs test may persist for up to 6 months after treatment completion. Patient's blood should be typed and screened prior to initiating treatment. Notify blood transfusion centres of this in the event of a planned transfusion and educate patients.

- Daratumumab may interfere with the serum protein electrophoreses (SPE) and immunofixation (IFE) assays used to monitor M-protein. This can impact the monitoring of response and disease progression in some patients with IgG kappa myeloma protein.

back to top

H - Drug Administration and Special Precautions

Refer to daratumumab (subcut) drug monograph(s) for additional details.

Administration:

Daratumumab IV and subcutaneous formulations are **not interchangeable**. The dosing and administration of these products are different.

- Daratumumab (subcut) does not require reconstitution or dilution.
- Compatible with polypropylene or polyethylene syringe material, polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets, and stainless steel transfer and injection needles.
- Administer by subcutaneous injection, over approximately 3-5 minutes.
- Inject into the abdominal wall only (approximately 7.5 cm to the right or left of the navel). Do not give in areas where the skin is red, bruised, tender, hard or where there are scars.
- If pain occurs during injection, pause or slow rate of injection. If pain is not improved, the remaining dose may be given at an alternate injection site (on the opposite side of the abdomen).
- If there are other subcutaneous medications, they should be given at separate sites.
- Do not shake vials.
- Store vials at 2-8°C. Bring vials to room temperature (15-30°C) before use. Keep out of direct sunlight.

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Warnings/Precautions:

- Daratumumab can cause severe administration-related reactions (ARRs), including anaphylaxis. It should only be administered by healthcare professionals with appropriate medical support to manage these reactions. Pre- and post-injection medications should be administered. Refer to Dosing section.
- Daratumumab (subcut) is not recommended for use in patients with AL amyloidosis with advanced cardiac disease.

Pregnancy/Lactation:

- Daratumumab (subcut) should not be used in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.
- Breastfeeding is not recommended.
- Fertility Effects: Unknown

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; Baseline and before each dose
- Blood; Type and screen prior to initiation. In the event of a planned transfusion, notify blood transfusion centres.
- Electrolytes, renal function tests; Baseline and as clinically indicated
- Liver function tests; Baseline and as clinically indicated
- Immunoglobulin levels; Baseline and as clinically indicated
- HBV serology; Baseline for all patients and as clinically indicated. For patients with evidence of HBV serology at baseline, monitor during treatment and for at least 6 months post treatment. Consult with an expert in HBV.
- Clinical toxicity assessment for systemic administration-related reactions, injection-site reactions, hypersensitivity, infection, bleeding, anemia, cardiac, and GI effects; Baseline and at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Administrative Information

Approximate Patient Visit	1.5 hours
Pharmacy Workload (average time per visit)	17.650 minutes
Nursing Workload (average time per visit)	42.333 minutes

back to top

K - References

Daratumumab drug monograph, Ontario Health (Cancer Care Ontario).

Daratumumab (subcut) drug monograph, Ontario Health (Cancer Care Ontario).

Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol. 2020 May;7(5):e370-e380.

Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet 2020 Jan 11;395(10218):132-41.

Nooka AK, Gleason C, Sargeant MO, et al. Managing infusion reactions to new monoclonal antibodies in multiple myeloma: daratumumab and elotuzumab. J Oncol Pract 2018 Jul;14(7):414-22.

Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med. 2021;385(1):46-58.

Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Aug 25;375(8):754-66.

pCODR Expert review committee final recommendation: Daratumumab for the treatment of patients with newly diagnosed multiple myeloma. Aug 29, 2019.

Yimer H, Melear J, Edward Faber E, et al. Lyra: a phase 2 study of daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (Cybord) in newly diagnosed and relapsed patients (Pts) with multiple myeloma. Blood 2018;132 (Supplement 1):152.

PEBC Advice Documents or Guidelines

- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

September 2022 Added NDFP forms; modified Rationale and uses, and Cycle frequency sections

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on

usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top