Drug Monograph

A - Drug Name

daratumumab (subcut)

COMMON TRADE NAME(S): Darzalex® SC

back to top

B - Mechanism of Action and Pharmacokinetics

Daratumumab is an IgG1K human monoclonal antibody (mAb) that targets CD38 on the surface of cells in a variety of hematological malignancies. Based on in vitro studies, by binding to CD38, daratumumab induces immune mediated tumour cell death or apoptosis through Fc mediated cross-linking. The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20) to increase dispersion and absorption.

Absorption	Bioavailability	69% (multiple myeloma patients)
	T max	70-72 h
	Time to reach steady state	Approximately by the 21st infusion (in monotherapy dosing schedule)
Distribution	Daratumumab is primarily localized to the vascular system with limited extravascular tissue distribution.	
Metabolism	Likely metabolized via degradation into small peptides and amino acids via catabolic pathways	
Elimination	Cleared by parallel linear and nonlinear (saturable) target-mediated	

	clearances.	
	Half-life	20 days (multiple myeloma patients) 28 days (AL amyloidosis patients)

back to top

C - Indications and Status

Health Canada Approvals:

- Multiple myeloma
- AL amyloidosis

Refer to the product monograph for a full list and details of approved indications.

back to top

D - Adverse Effects

Emetogenic Potential: Minimal

The following table lists adverse effects that occurred in > 5% of patients in a Phase 3 non-inferiority study comparing daratumumab (subcut) 1800 mg with daratumumab (IV) 16 mg/kg. It also includes severe or life-threatening adverse effects from other sources and post-marketing.

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

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (1%)	E
	Cardiotoxicity (<1%)	E
	Hypertension (9%) (may be severe)	I E
	Tachycardia (1%)	E
Gastrointestinal	Abdominal pain (6%)	E
	Constipation (8%)	E

	Diarrhea (11%)	E
	Nausea, vomiting (11%)	I E
General	Edema - limbs (6%)	E
	Fatigue (16%)	E
Hematological	↓ Immunoglobulins (2%)	E
	Myelosuppression ± infection, bleeding (23%) (including anemia) (14% severe)	E D
Hepatobiliary	↑ LFTs (<5%) (may be severe)	E D
	Pancreatitis (1%)	E D
Hypersensitivity	Administration-related reactions (systemic) (13%) (2% severe) ^	I E
	Anaphylaxis (rare)	I
Immune	Antibody response (anti-daratumumab antibodies - <1%; anti-rHuPH20 antibodies - 7%) ^	D
Injection site	Injection site reaction (7%) ^	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (6%)	E
Musculoskeletal	Musculoskeletal pain (12%)	E
Nervous System	Headache (9%)	E
	Insomnia (5%)	E
Ophthalmic	Blurred vision (6%)	E
Renal	Renal failure (<2%)	E D
Respiratory	Cough, dyspnea (14%)	E
	Rhinitis (5%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for daratumumab (subcut) include myelosuppression ± infection, bleeding, fatigue, cough/dyspnea, administration-related reactions, musculoskeletal pain, diarrhea, and nausea/vomiting.

Daratumumab (subcut) may cause severe **administration-related reaction** (ARRs), including anaphylactic reactions. During clinical trials, most reactions occurred after the first injection and were mild to moderate. The majority of reactions occurred on the day of treatment (median was 3 hours). Delayed reactions have occurred in < 1% of patients.

Serious **cardiac adverse reactions** (16%), including fatal events (10%), have occurred in patients with AL amyloidosis who received daratumumab (subcut) in combination with bortezomib, cyclophosphamide, and dexamethasone. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at an increased risk for serious cardiac disorders.

Neutropenia, febrile neutropenia, and thrombocytopenia have been associated with daratumumab (subcut). Higher rates of neutropenia and thrombocytopenia, including Grade 3-4 events, were observed in lower body weight patients. Daratumumab (subcut) may worsen **myelosuppression** when used in combination with other chemotherapy agents.

Infections may be severe in patients treated with daratumumab (subcut). Opportunistic infections (e.g. cytomegalovirus) and herpes zoster virus reactivation, including fatal outcomes, were also reported. Hepatitis B reactivation has been observed post-marketing.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

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).

[†]For combination therapy, dexamethasone 20 mg IV/PO (or equivalent) is recommended. Refer to the respective regimen monographs.

[‡]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.

[¶]For combination therapy, consider low-dose oral methylprednisolone (≤ 20 mg) or equivalent for 1 day post-injection.

[‖]For combination therapy, consider adding an H1-receptor antagonist if the patient is at higher risk of respiratory complications.

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

For pre/post injection medications used in daratumumab combination regimens, see the respective regimen monographs.

Adults:

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

Monotherapy:

Subcutaneous: 1800 mg as per the following schedule:

Week	Schedule
1 - 8	Weekly (8 doses)
9 - 24	Every 2 weeks (8 doses)
25+	Every 4 weeks

Combination therapy:

Various schedules are used depending on the regimen. Refer to the product monograph or related regimen monographs for details.

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

Dosage with 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)	

Dosage with 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.

Dosage based on gender:

Gender had no clinically significant effect on PK parameter in patients with multiple myeloma.

Dosage based on ethnicity:

Based on PK analyses, no clinically significant differences were seen between white and non-white patients.

Children:

The safety and efficacy of daratumumab (subcut) have not been established in children < 18 years of age.

back to top

F - Administration Guidelines

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.

back to top

G - Special Precautions

Contraindications:

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

Other 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.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Crosses placental barrier: Likely
  Daratumumab (subcut) has not been studied in pregnant women. IgG1 monoclonal antibodies are known to transfer across the placenta.
- Fetotoxicity: Likely
  Based on its mechanism of action, daratumumab may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. If exposure to daratumumab occurred in utero, live vaccines should not be administered to the infant until a hematology evaluation has been completed.
  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: Not recommended
  It is not known whether daratumumab is excreted into breastmilk. Human IgG is excreted in breast milk.
- Fertility effects: Unknown

back to top

H - Interactions

- 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

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

Monitor Type	Monitor Frequency
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 (more frequent cardiac monitoring in patients with AL amyloidosis)

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Daratumumab in Combination with a Bortezomib-Based Regimen for Newly Diagnosed Transplant Ineligible Multiple Myeloma
- Daratumumab in Combination with Lenalidomide and Dexamethasone for Newly Diagnosed Transplant Ineligible Multiple Myeloma
- Daratumumab - In Combination with Bortezomib and Dexamethasone for Relapsed Multiple Myeloma
- Daratumumab - In Combination with Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma
- Daratumumab and Bortezomib in combo with Cyclophosphamide and Dexamethasone - Previously Untreated Light Chain (AL) Amyloidosis

back to top

K - References

Daratumumab drug monograph. 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.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Antiemesis. Version 2.2022, March 23, 2022.

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.

Prescribing information: Darzalex Faspro®. Janssen Pharmaceutical Companies. April 2022.

Product Monograph. Darzalex® SC (daratumumab). Janssen Inc. June 22, 2022.

September 2022 Updated pregnancy section; added NDFP forms

back to top

L - Disclaimer

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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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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back to top