Drug Monograph

A - Drug Name

daratumumab

COMMON TRADE NAME(S): Darzalex®

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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.

Distribution	Daratumumab is primarily localized to the vascular system with limited extravascular tissue distribution. Time to steady state: Approximately by the 21st infusion (in monotherapy dosing schedule)	
Metabolism	Likely via degradation into small peptides and amino acids via catabolic pathways.	
Elimination	Cleared by parallel linear and nonlinear (saturable) target-mediated clearances.	
	Half-life	Terminal half-life increases with increasing dose and with repeated dosing Mean estimated terminal half-life following the 1st 16mg/kg dose: 9 Days

	Upon complete saturation of target mediated clearance and repeat dosing: 18 days

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C - Indications and Status

Health Canada Approvals:

- Multiple myeloma

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

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

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

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	Infusion related reaction (35%) (for first infusion) (including CRS and anaphylaxis - 5% severe)	I E
Immune	Antibody response (anti-daratumumab antibodies - <1%)	D
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 include infusion related reaction, myelosuppression ± infection, bleeding, fatigue, cough/dyspnea, musculoskeletal pain, diarrhea, and nausea/vomiting.

The majority (83%) of **infusion reactions (IRs)** occurred during the first infusion with incidence declining to 4% with subsequent infusions. Most reactions were grade 1 or 2, however, IRRs can be severe and include respiratory symptoms, cytokine release syndrome (CRS), anaphylaxis, nausea, rash and hypotension. Most reactions occurred during infusion or within 4 hours of completion (median onset was 1.5 h). Without post-infusion medications, infusion reactions can occur up to 48 hours post-infusion.

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

Daratumumab may worsen **myelosuppression** when used in combination with other chemotherapy agents for the treatment of multiple myeloma.

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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 (prophylaxis for infusion reaction) for daratumumab monotherapy:

To be given at least 1 hour prior to infusion:

- Corticosteroid IV (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)
- Famotidine 20 mg IV (or equivalent)
- Montelukast 10 mg PO[**]

[*]This dose may be reduced following the second infusion (i.e. IV methylprednisolone 60 mg or equivalent).

[†]For daratumumab combination therapy, corticosteroid IV/PO (e.g. dexamethasone 20 mg) is recommended. When dexamethasone is a regimen specific corticosteroid, the treatment dose will serve as pre-medication on infusion days. Additional regimen specific corticosteroids (e.g. prednisone) should not be taken on infusion days when dexamethasone is given as pre-medication.

[**]The addition of montelukast given prior to the first infusion numerically reduced the incidence of respiratory IRs in the study by Nooka et al.

Post-infusion medications for daratumumab monotherapy:

- Oral corticosteroid (e.g. methylprednisolone 20 mg or equivalent) for 2 days post-infusion[‡]
- Consider bronchodilators (e.g. short and long acting) and inhaled corticosteroids if chronic obstructive pulmonary disorder[&***]

‡For daratumumab combination therapy, corticosteroid PO (e.g. dexamethasone 20 mg) on the day after infusion is recommended. When a regimen specific corticosteroid (e.g. dexamethasone or prednisone) is given the day after infusion, additional post-infusion medications may not be needed.

&For daratumumab 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 infusion if no major IRs occurred.

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

Adults:

Monotherapy:

Daratumumab 16mg/kg* IV as per the following schedule:

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

*Splitting the first dose over 2 days has been described (8 mg/kg days 1 and 2) and may be considered. The same premedications listed above should be administered prior to both treatment days (Reece et al 2018).

Combination therapy:

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

Dosage with Toxicity:

No dose reductions of daratumumab are recommended. A dose delay may be required in case of myelosuppression. Consider supportive care with transfusions or growth factors, as needed.

Hepatitis B virus (HBV) reactivation: Hold daratumumab, concomitant steroids and chemotherapy. Consult with a 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.

Table 1: Management of Infusion Reactions:

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 infusion rate. • Manage the symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a rate of no more than 50% of the rate at which the reaction occurred. • If no reaction occurs, escalate the rate at no more than 50 mL/hour every hour.	• Re-challenge with pre-medications and with infusion rate modification (eg. Table 2 below).
3	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a rate of no more than 50% of the rate at which the reaction occurred. • If no reaction occurs, escalate the rate at no more than 50 mL/hour every hour.	• Re-challenge with pre-medications and with infusion rate modification (eg. Table 2 below). • If a grade 3 IR recurs for the 3rd time, discontinue permanently (do not re-challenge).
4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with Hepatic Impairment:

Hepatic Impairment	Daratumumab 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)	No data
Severe impairment (total bilirubin >3 times ULN and any AST)	

Dosage with Renal Impairment:

No dose adjustment is necessary. Formal studies have not been conducted; daratumumab is not renally cleared.

Dosage in the elderly:

No dose adjustments necessary. No overall differences in effectiveness was observed but the incidence of serious adverse reactions (e.g., pneumonia) was more frequent in older compared to younger patients.

Dosage based on gender:

Based on population PK analysis, there are no significant differences between genders.

Dosage based on ethnicity:

No significant differences were seen between white and non-white patients in the population PK analysis.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

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

- Daratumumab infusion should be administered at the appropriate initial infusion rate with incremental escalation. Subsequent infusion rate escalation or dilution reduction should only be considered if the previous infusion was well-tolerated (Table 2).

Table 2: Standard infusion rates

	Dilution volume	Initial Infusion Rate (1st hr)	Increments of infusion rate	Max infusion rate	Approximate infusion time
Week 1 (single dose infusion)	1000 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	6.5 hr
Week 1 (split dose infusion; applicable to days 1 and 2)	500 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	4 hr
Week 2[a]	500 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	4 hr
Subsequent Infusions[b, c]	500 mL	100 mL/hr	50 mL/hr every hour	200 mL/hr	3.25 hr

[a] If single dose infusion is used for week 1, the 500 mL dilution volume for the 16 mg/kg dose should be used only if there were no IRRs in the previous week.

[b] Initial infusion rate should only be modified if treatment in Weeks 1 and 2 were well-tolerated (no ≥ grade 1 IRRs during ≥100 mL/hr).

[c] If the patient did not experience an IR in the first 2 infusions of daratumumab, consideration can be given to administer daratumumab as a rapid infusion starting with the 3rd dose (20% of the dose over 30 minutes at 200 mL/hour, then the remaining 80% of the dose over 60 minutes at 450 mL/hour).

- Missed doses should be administered as soon as possible and the dosing schedule adjusted accordingly. The treatment interval should be maintained.
- Daratumumab should be diluted in 0.9% Sodium Chloride; remove a volume from the IV bag that is equal to the required volume of daratumumab solution.
- Daratumumab solution is colourless to yellow.
- The diluted solution may develop very small, translucent to white proteinaceous particles. Do not use if opaque particles, discolouration, or other foreign particles.
- Administer by IV infusion using an infusion set with a flow regulator and an in-line, low protein-binding filter (0.22 or 0.2 µm).
- The infusion bag must be made of PVC, polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE).
- Polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE administration sets must be used.
- Do not infuse concomitantly in the same IV line with other agents.
- Store vials at 2^{o}C - 8^{o}C
- Do not shake or freeze, protect from light.

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

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G - Special Precautions

Contraindications:

- Patients with a history of severe hypersensitivity to daratumumab or who have hypersensitivity to any ingredient in the formulation or component of the container.

Other Warnings/Precautions:

- Daratumumab can cause severe infusion-related reactions (IRRs), including anaphylaxis. It should only be administered by healthcare professionals with appropriate medical support to manage these reactions. Pre and post infusion medications should be administered (see Dosing section).

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Crosses placental barrier: Likely
  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 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

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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.

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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 starting daratumumab. 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 infusion-related reactions, hypersensitivity, infection, anemia, bleeding, GI and cardiac effects	Baseline and at each visit

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

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Daratumumab - In Combination with Bortezomib and Dexamethasone for Relapsed Multiple Myeloma
- Daratumumab - In Combination with Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma
- 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

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K - References

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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.

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.

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Reece DE, Phillips MJ. Infusion Reactions with Monoclonal Antibody Therapy in Myeloma: Learning from Experience. J Oncol Pract. 2018 Jul;14(7):425-6.

September 2022 Updated indications (to new format), adverse effects, dosing, administration, special precautions, and monitoring sections

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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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The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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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