

DARZALEX® (daratumumab)

NCCN Compendia Communication – Option to Split First Dose Approved February 2019

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NCCN Guidelines® Panel: Multiple Myeloma

Dear NCCN,

On behalf of Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - Multiple Myeloma Panel review the enclosed data regarding the recently approved option to split the first prescribed DARZALEX® (daratumumab) 16 mg/kg dose at Week 1 over two consecutive days (8 mg/kg on Day 1 and Day 2, respectively).

Specific Change Requested: Recommend the inclusion of this dosage and administration option as a footnote to the relevant “Myeloma Therapy” tables.

FDA Clearance: The FDA has approved DARZALEX® (daratumumab) for the treatment of multiple myeloma (1) in combination with bortezomib, melphalan and prednisone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, (2) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone in patients who have received at least one prior therapy, (3) in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI), and (4) as a monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.¹

Rationale: Option to split the first prescribed 16 mg/kg dose at Week 1 over two consecutive days, to facilitate administration for clinical practices for which the long week 1 day 1 single dose infusion poses a significant barrier to patient treatment.

Summary of February 2019 Prescribing Information Changes

Section 2.1: Recommended Dose and Schedule, Infusion Rates and Management of Infusion Reactions

- The sentence “To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively, see Table 4 below.” was added
- Table 4 was changed to the following:

Table 4: Infusion rates for DARZALEX (16 mg/kg) administration

	Dilution volume	Initial rate (first hour)	Rate increment^a	Maximum rate
Week 1 Infusion				
Option 1 (Single dose infusion)				
Week 1 Day 1 (16 mg/kg)	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Option 2 (Split dose infusion)				
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour

Week 2 (16 mg/kg) infusion^b	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (Week 3 onwards, 16 mg/kg) infusions^c	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

^a Consider incremental escalation of the infusion rate only in the absence of infusion reactions.

^b Use a dilution volume of 500 mL for the 16 mg/kg dose only if there were no infusion reactions the previous week. Otherwise, use a dilution volume of 1000 mL.

^c Use a modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) only if there were no infusion reactions during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

Section 6.1: Adverse Reactions in Clinical Trials, Infusion Reactions

- Amendments were made in the first two paragraphs to clarify that they pertain to DARZALEX 16 mg/kg. Additional clarification was included regarding the infusion week.
- The following statement was added: In EQUULEUS, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Section 12.3: Pharmacokinetics

- The sentence "Split dosing of the first dose resulted in a different PK profile in the first day compared to single dosing; however, similar C_{max} and C_{min} concentrations were both predicted and observed following the administration of the second split dose on Week 1 Day 2." was added to the 2nd paragraph of this section.

Additional Supportive Data

The following poster presentation is submitted with the Full Prescribing Information.

- Xu XS, Moreau P, Usmani SZ, et al. Split first dose administration of daratumumab for the treatment of patients with multiple myeloma (MM): clinical pharmacology and population pharmacokinetic (PK) analyses. Poster presented at: 60th American Society of Hematology (ASH) Annual Meeting & Exposition; December 1-4, 2018; San Diego, CA.

I look forward to working with you as you consider the enclosed information. The information provided is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information, including the following sections: **INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.**

If you require further information, please feel free to contact me via the Janssen Medical Information Center at 1-800-JANSSEN (1-800-526-7736).

Sincerely,

Darren Piscitelli, PharmD

Associate Director, Hematologic Malignancies Medical Information and Knowledge Integration
Janssen Scientific Affairs, LLC

REFERENCES

- DARZALEX (daratumumab) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-dc33e1e3-dde0-4c18-b1e3-a3a79c07d600.
- Xu XS, Moreau P, Usmani SZ, et al. Split first dose administration of daratumumab for the treatment of patients with multiple myeloma (MM): clinical pharmacology and population pharmacokinetic (PK) analyses. Poster presented at: 60th American Society of Hematology (ASH) Annual Meeting & Exposition; December 1-4, 2018; San Diego, CA.