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February 01, 2021

Kristina Gregory
3025 Chemical Road
Plymouth Meeting, PA 19462
USA

Dear Ms. Gregory,

Please consider the following information.

Response(s):

- DARZALEX FASPRO - NCCN Compendium Communication - Amyloidosis Product Update - January 2021

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,

Cynthia Toso

Cynthia Toso, PharmD

Associate Director
Medical Information

Inquiry #:01940924

Enclosure(s)/Electronic Link(s):

- DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) Prescribing Information at https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-3da10f5e-7e32-4a75-996e-e511369c64b3
- Rapid and Deep Hematologic Responses Are Associated With Improved Major Organ Deterioration Progression-Free Survival in Newly Diagnosed AL Amyloidosis: Results From ANDROMEDA
- Outcomes by Cardiac Stage in Newly Diagnosed AL Amyloidosis: Results From ANDROMEDA
- Reduction in Absolute Involved Free Light Chain and Difference Between Involved and Uninvolved Free Light Chain Is Associated With Prolonged Major Organ Deterioration Progression-Free Survival in Patients With Newly Diagnosed AL Amyloidosis Receiving Bortezomib, Cyclophosphamide, and Dexamethasone With or Without Daratumumab: Results From ANDROMEDA
- DARZALEX FASPRO Prescribing Information

Need Help? If you have any additional questions, please contact us via:

1-800-JANSSEN
Monday - Friday, 9 am - 8 pm EST

24x7 Access to Medical Information
www.janssenmd.com

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Locate Medical Science Liaison
www.janssenmsl.com

To report a possible adverse event or product quality complaint, please call the Medical Information Center immediately, at 1-800-JANSSEN (1-800-526-7736).

DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj)
Compendium Communication – NCCN – Amyloidosis Product Update – January 2021

Name: Cindy Toso, PharmD
Company/Organization: Janssen Biotech, Inc.
Address: 850 Ridgeview Drive Horsham, PA 19044
Phone: 215-325-4244
E-mail: ctoso@its.jnj.com
Date of request: February 1, 2021
NCCN Guidelines® Panel: Systemic Light Chain Amyloidosis

Dear NCCN,

In follow up to our Janssen Biotech, Inc. submissions on 6/16/20, I respectfully request that the NCCN Guidelines® Systemic Light Chain Amyloidosis Panel review the enclosed FDA approved labeling for DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj), revised January 2021, and the provided summary of key changes.

Specific Change Requested: We request an update to the compendium monograph and the Systemic Light Chain Amyloidosis Guidelines (V.1.2021) to include DARZALEX FASPRO in combination with bortezomib, cyclophosphamide, and dexamethasone (VCd) for primary therapy of transplant and non-transplant candidates with newly diagnosed systemic light chain amyloidosis (AMYL-A, 1 of 4) as a preferred regimen with a Category 1 evidence level rating.

In addition, please align all related content currently in the Guidelines® Version 1.2021, NCCN Compendium®, NCCN Templates® and any other NCCN® publications or platforms with the current version of the DARZALEX FASPRO Prescribing Information, noting pertinent efficacy and safety updates related to the ANDROMEDA study. Key changes to the DARZALEX FASPRO Prescribing Information are summarized on pages 3-12 of this communication, including updates to the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY, and CLINICAL STUDIES sections.

FDA Clearance: DARZALEX FASPRO is approved for the treatment of adult patients with multiple myeloma: 1) in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant; 2) in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy; 3) in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant; 4) in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; 5) as monotherapy, in patients who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.[1]

DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone is indicated for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).[1]

Limitations of Use: DARZALEX FASPRO is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials.[1]

Rationale: The FDA has approved DARZALEX FASPRO in combination with VCd (D-VCd) in newly diagnosed patients with light chain amyloidosis based on the ANDROMEDA study. ANDROMEDA is an ongoing, phase 3, randomized, open-label study evaluating the safety and efficacy of D-VCd (n=195) compared with VCd alone (n=193) in patients with newly diagnosed AL amyloidosis. Primary results after a median follow-up of 11.4 months were included in our previous submission from 6/16/20. These results included an overall hematologic complete response (CR) rate (primary endpoint) of 53% for D-VCd vs 18% for VCd (odds ratio [OR]: 5.1; 95% confidence interval [CI]: 3.2-8.2; $P<0.0001$).[2]

Three subsequent analyses of the ANDROMEDA study after a median follow-up of 15.7 months were recently presented at the 2020 Virtual 62nd American Society of Hematology (ASH) Annual Meeting & Exposition. One of these analyses revealed that hematologic CR rates were higher with D-VCd vs VCd in patients with baseline cardiac stage I (51.1% vs 27.9%; OR: 2.70; 95% CI, 1.12-6.49), cardiac stage II (56.6% vs 21.3%; OR: 4.83; 95% CI, 2.39-9.74), and cardiac stage III (61.1% vs 10.0%; OR: 14.14; 95% CI, 5.67-35.25). Cardiac and renal response rates at 6 months were also higher with D-VCd compared with VCd regardless of baseline cardiac stage. In both treatment groups, rates of serious adverse events increased with worsening baseline cardiac stage.[3] In the second analysis, D-VCd resulted in increased rates of deep hematologic responses as measured by various hematologic response criteria (involved free light chain [iFLC]; difference between involved and uninvolved free light chains [dFLC]; International Society of Amyloidosis [ISA] criteria), which were associated with prolonged major organ deterioration progression-free survival.[4] The third analysis revealed that CR or very good partial response (VGPR) at 1 and 3 months was associated with reduced risk of death or major organ deterioration in a multivariate analysis adjusting for dFLC and cardiac stage.[5]

The following presentations are submitted with the Full Prescribing Information:

Minnema MC, Dispenzieri A, Merlini G, et al. Outcomes by cardiac stage in newly diagnosed AL amyloidosis: results from ANDROMEDA. Poster presented at: Virtual 62nd American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2020.

Comenzo RL, Kastritis E, Minnema MC, et al. Reduction in absolute involved free light chain and difference between involved and uninvolved free light chain is associated with prolonged major organ deterioration progression-free survival in patients with newly diagnosed AL amyloidosis receiving bortezomib, cyclophoshpamide, and dexamethasone with or without daratumumab: results from ANDROMEDA. Oral presentation presented at: Virtual 62nd American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2020.

Wechalekar AD, Palladini G, Merlini G, et al. Rapid and deep hematologic responses are associated with improved major organ deterioration progression-free survival in newly diagnosed AL amyloidosis: results from ANDROMEDA. Poster presented at: Virtual 62nd American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2020.

Sincerely,
Cindy Toso, PharmD
Associate Director, Payer & Health Systems, Medical Information and Knowledge Integration
Janssen Scientific Affairs, LLC

REFERENCES

1. DARZALEX FASPRO (daratumumab and hyaluronidase-fihj) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-3da10f5e-7e32-4a75-996e-e511369c64b3
2. Kastritis E, Palladini G, Minnema MC, et al. Subcuteanous Daratumumab + Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD) in Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Primary Results from the Phase 3 ANDROMEDA Study. Oral Presentation presented at: 25th Congress of the European Hematology Association (EHA) Virtual Scientific Program; June 11-14, 2020. Subcuteanous Daratumumab + Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD) in Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Primary Results from the Phase 3 ANDROMEDA Study.
3. Minnema MC, Dispenzieri A, Merlini G, et al. Outcomes by cardiac stage in newly diagnosed AL amyloidosis: results from ANDROMEDA. Poster presented at: Virtual 62nd American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2020.
4. Comenzo RL, Kastritis E, Minnema MC, et al. Reduction in absolute involved free light chain and difference between involved and uninvolved free light chain is associated with prolonged major organ deterioration progression-free survival in patients with newly diagnosed AL amyloidosis receiving bortezomib, cyclophoshpamide, and dexamethasone with or without daratumumab: results from ANDROMEDA. Oral presentation presented at: Virtual 62nd American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2020.
5. Wechalekar AD, Palladini G, Merlini G, et al. Rapid and deep hematologic responses are associated with improved major organ deterioration progression-free survival in newly diagnosed AL amyloidosis: results from ANDROMEDA. Poster presented at: Virtual 62nd American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2020.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj)
Compendia Communication – Product Update – January 2021

SUMMARY

- The current DARZALEX FASPRO Prescribing Information is dated January 2021.
- In addition to the HIGHLIGHTS OF PRESCRIBING INFORMATION, the following sections of the Prescribing Information were revised:
  - Section 1: INDICATIONS AND USAGE
  - Section 2: DOSAGE AND ADMINISTRATION
  - Section 5: WARNING AND PRECAUTIONS
  - Section 6: ADVERSE REACTIONS
  - Section 8: USE IN SPECIFIC POPULATION
  - SECTION 12 CLINICAL PHARMACOLOGY
  - SECTION 14 CLINICAL STUDIES
  - SECTION 17 PATIENT COUNSELING INFORMATION
  - PATIENT INFORMATION
- Please note, minor textual changes and omissions (e.g., table/figure numbers, section/subsection numbers, relocation of information within the document) may not be included in the description of changes below.
- Please ensure monograph alignment with the current DARZALEX FASPRO Full Prescribing Information Version January 2021.

DARZALEX FASPRO PRESCRIBING INFORMATION JANUARY 2021 KEY CHANGES

SECTION 1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

- The following information was added:
  - "In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant."

1.2 Light Chain Amyloidosis

- New section was added:
  - "DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone is indicated for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis."
  - "This indication is approved under accelerated approval based on response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)."
  - Limitations of Use:
    - "DARZALEX FASPRO is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials [see Warnings and Precautions (5.2)]."

SECTION 2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dosage for Multiple Myeloma

- New "In combination with Bortezomib, Thalidomide, and Dexamethasone" section added:
  - "Use the dosing schedule in Table 3 when DARZALEX FASPRO is administered in combination with bortezomib, thalidomide, and dexamethasone (4-week cycle)."
  - "Table 3: DARZALEX FASPRO dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle)"

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16[a]	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8[b]	every two weeks (total of 4 doses)

[a] First dose of the every-2-week dosing schedule is given at Week 9

[b] First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT

When DARZALEX FASPRO is administered as part of a combination therapy, see the prescribing information for dosage recommendations for the other drugs.

- The following information was deleted:
  - Missed DARZALEX FASPRO Doses
    - "If a dose of DARZALEX FASPRO is missed, administer the dose as soon as possible and adjust the dosing schedule to maintain the dosing interval."

2.3 Recommended Dosage for Light Chain Amyloidosis

- New section was added:
  - "Use the dosing schedule provided in Table 5 when DARZALEX FASPRO is administered in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle)."
  - "Table 5: DARZALEX FASPRO dosing schedule in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle)"

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks (total of 8 doses)
Week 25 onwards until disease progression or a maximum of 2 years[b]	every four weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9

[b] First dose of the every-4-week dosing schedule is given at Week 25

When DARZALEX FASPRO is administered as part of a combination therapy, *see Clinical Studies (14.2)* and the prescribing information for dosage recommendations for the other drugs.

2.4 Administration

- New section added:
  - "If a dose of DARZALEX FASPRO is missed, administer the dose as soon as possible and adjust the dosing schedule to maintain the dosing interval."

SECTION 5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity and Other Administration Reactions

- The following information was updated for "Systemic Reactions":
  - "In a pooled safety population of 683 patients with multiple myeloma (N=490) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 10% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 1%). Systemic administration-related reactions occurred in 9% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 9 minutes to 3.5

days). Of the 117 systemic administration-related reactions that occurred in 66 patients, 100 (85%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients."

- The following information was updated for "Local Reactions":
  - "In this pooled safety population, injection-site reactions occurred in 9% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management."

5.2 Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

- The following information was added:
  - "Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone [see Adverse Reactions (6.1)]. Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage III A disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied."
  - "Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate."

5.5 Embryo-Fetal Toxicity

- The following information was added:
  - "The combination of DARZALEX FASPRO with lenalidomide or thalidomide is contraindicated in pregnant women, because lenalidomide and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide or thalidomide prescribing information on use during pregnancy."

SECTION 6 ADVERSE REACTIONS

- "Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis *[see Warning and Precautions (5.2)]*."

6.1 Clinical Trial Experience

- New section was added on "Light Chain Amyloidosis- In Combination with Bortezomib, Cyclophosphamide and Dexamethasone"
  - "The safety of DARZALEX FASPRO with bortezomib, cyclophosphamide and dexamethasone (D-VCd) was evaluated in ANDROMEDA *[see Clinical Studies (14.2)]*. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity or a maximum of 2 years. Among patients who received D-VCd, 74% were exposed for 6 months or longer and 32% were exposed for greater than one year."
  - "Serious adverse reactions occurred in 43% of patients who received DARZALEX FASPRO in combination with VCd. Serious adverse reactions that occurred in at least 5% of patients in the D VCd arm were pneumonia (9%), cardiac failure (8%), and sepsis (5%). Fatal adverse reactions occurred in 11% of patients. Fatal adverse reactions that occurred in more than one patient included cardiac arrest (4%), sudden death (3%), cardiac failure (3%), and sepsis (1%)."
  - "Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 5% of patients. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than one patient were pneumonia, sepsis, and cardiac failure."
  - "Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 36% of patients who received DARZALEX FASPRO. Adverse reactions which required a dosage interruption in ≥3% of patients included upper respiratory tract infection

(9%), pneumonia (6%), cardiac failure (4%), fatigue (3%), herpes zoster (3%), dyspnea (3%), and neutropenia (3%)."

- "The most common adverse reactions (≥20%) were upper respiratory tract infection, diarrhea, peripheral edema, constipation, fatigue, peripheral sensory neuropathy, nausea, insomnia, dyspnea, and cough."
- "Table 12 below summarizes the adverse reactions in patients who received DARZALEX FASPRO with VCd in ANDROMEDA."

Table 12: Adverse Reactions (≥10%) in Patients with AL Amyloidosis Who Received DARZALEX FASPRO with Bortezomib, Cyclophosphamide and Dexamethasone (D-VCd) with a Difference Between Arms of >5% Compared to VCd in ANDROMEDA

	D-VCd (N=193)		VCd (N=188)	
Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Infections				
Upper respiratory tract infection[a]	40	1#	21	1#
Pneumonia[b]	15	10	9	5
Gastrointestinal disorders				
Diarrhea	36	6#	30	4
Constipation	34	2#	29	0
Nervous system disorders				
Peripheral sensory neuropathy	31	3#	20	2#
Respiratory, thoracic and mediastinal disorders				
Dyspnea[c]	26	4	20	4#
Cough[d]	20	1#	11	0
Musculoskeletal and connective tissue disorders				
Back pain	12	2#	6	0
Arthralgia	10	0	5	0
Muscle spasms	10	1#	5	0
Cardiac disorders				
Arrhythmia[e]	11	4	5	2
General disorders and administration site conditions				
Injection site reactions[f]	11	0	0	0

Only grade 3 adverse reactions occurred.

[a] Upper respiratory tract infection includes laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection, upper respiratory tract infection bacterial, and viral upper respiratory tract infection.

[b] Pneumonia includes lower respiratory tract infection, pneumonia, pneumonia aspiration, and pneumonia pneumococcal.

[c] Dyspnea includes dyspnea, and dyspnea exertional.

[d] Cough includes cough, and productive cough.

[e] Arrhythmia includes atrial flutter, atrial fibrillation, supraventricular tachycardia, bradycardia, arrhythmia, bradyarrhythmia, cardiac flutter, extrasystoles, supraventricular extrasystoles, ventricular arrhythmia, ventricular extrasystoles, atrial tachycardia, ventricular tachycardia

[f] Injection site reactions includes terms determined by investigators to be related to daratumumab injection.

- "Clinically relevant adverse reactions not included in Table 12 and occurred in patients who received DARZALEX FASPRO with bortezomib, cyclophosphamide and dexamethasone (D VCd) included:
  - **"Skin and subcutaneous tissue disorders:** rash, pruritus; **Nervous system disorders:** paresthesia; **General disorders and administration site conditions**: infusion reaction, chills; **Cardiac disorders**: cardiac failurea, cardiac arrest; **Metabolism and nutrition disorders**: hyperglycemia, hypocalcemia, dehydration; **Infections**: bronchitis, herpes zoster, sepsis, urinary tract infection, influenza; **Vascular disorders**: hypertension; **Musculoskeletal and connective tissue disorders**: musculoskeletal chest pain; **Gastrointestinal disorders**: pancreatitis; **Respiratory, thoracic and mediastinal disorders**: pulmonary edema."
  - "[a] Cardiac failure includes cardiac dysfunction, cardiac failure, cardiac failure congestive, cardiovascular insufficiency, diastolic dysfunction, pulmonary edema, and left ventricular dysfunction occurred in 11% of patients."
- "Table 13 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with VCd in ANDROMEDA."

Table 13: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Cyclophosphamide and Dexamethasone (D-VCd) in ANDROMEDA

	D-VCd		VCd	
Laboratory Abnormality	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Decreased lymphocytes	81	54	71	46
Decreased hemoglobin	66	6	70	6
Decreased leukocytes	60	7	46	4
Decreased platelets	46	3	40	4
Decreased neutrophils	30	6	18	4

Denominator is based on the number of patients with a baseline and post-baseline laboratory value for each laboratory test, N=188 for D-VCd and N=186 for VCd.

- New Section added on "Cardiac Adverse Reactions in Light Chain (AL) Amyloidosis"
  - "Among patients who received DARZALEX FASPRO in combination with VCd, 72% of patients had baseline cardiac involvement with Mayo Cardiac Stage I (3%), Stage II (46%) and Stage III (51%). Serious cardiac disorders occurred in 16% of patients (8% of patients with Mayo Cardiac Stage I and II and 28% of patients with Stage III). Serious cardiac disorders in >2% of patients included cardiac failure (8%), cardiac arrest (4%) and arrhythmia (4%). Fatal cardiac disorders occurred in 10% of patients (5% of patients with Mayo Cardiac Stage I and II and 19% of patients with Stage III) who received DARZALEX FASPRO in combination with

VCd. Fatal cardiac disorders that occurred in more than one patient in the D-VCd arm included cardiac arrest (4%), sudden death (3%), and cardiac failure (3%)."

6.2 Immunogenicity

- "In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 633 patients developed treatment-emergent anti-daratumumab antibodies."
- "In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 628 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies."

SECTION 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- The following information was updated for "Risk Summary":
  - "The combination of DARZALEX FASPRO and lenalidomide or thalidomide is contraindicated in pregnant women, because lenalidomide and thalidomide may cause birth defects and death of the unborn child. Lenalidomide and thalidomide are only available through a REMS program. Refer to the lenalidomide or thalidomide prescribing information on use during pregnancy."

8.2 Lactation

- The following information was updated for "Risk Summary"
  - Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide or "thalidomide" and dexamethasone, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide or "thalidomide" prescribing information for additional information."

8.3 Females and Males of Reproductive Potential

- The following information was updated for "Pregnancy Testing"
  - With the combination of DARZALEX FASPRO with lenalidomide or "thalidomide", refer to the lenalidomide or "thalidomide" labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.
- The following information was updated for "Contraception"
  - Additionally, refer to the lenalidomide or "thalidomide" labeling for additional recommendations for contraception.

8.5 Geriatric Use

- "Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension."
- "No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3)]."

SECTION 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

- The following information was added:
  - CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, "including clonal plasma cells in" multiple myeloma and "light chain (AL) amyloidosis, as well as other cell types." "Surface CD38" has multiple functions, including receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity.

12.3 Pharmacokinetics

- The following information was deleted:
  - "Following the administration of the recommended dose of DARZALEX FASPRO 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) subcutaneously once weekly for 8 weeks, the mean ± standard deviation (SD) maximum trough concentrations (C_{trough} following the 8th dose) were 593±306 µg/mL compared to 522±226 µg/mL for daratumumab 16mg/kg administered intravenously, with a geometric mean ration of 108% (90% CI: 96, 122). The estimated median daratumumab area under the concentration-time curves ($AUC_{0\text{-}7\ days}$) and daratumumab peak concentration (C_{max}) following the 8th dose were comparable between DARZALEX FASPRO and intravenous daratumumab (4017 µg/mL•day vs. 4,019 µg/mL•day for $AUC_{0\text{-}7\ days}$ and 592 µg/mL vs. 688 µg/mL for C_{max})
- The following information was added:
  - "Table 14 lists the observed mean (±SD) maximum trough concentrations (C_{trough}) after the 8th dose, simulated median (5th 95th percentiles) maximum C_{trough} after the 8th dose, simulated median (5th 95th percentiles) Cmax after the 8th dose, and simulated median (5th 95th percentiles) area under the curve (AUC0-7day) after the 8th dose following DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously in patients with multiple myeloma or light chain (AL) amyloidosis."

Table 14: Daratumumab Exposure for Patients with Multiple Myeloma or Light Chain (AL) Amyloidosis

Parameter	Intravenous Daratumumab 16 mg/kg in Patients with Multiple Myeloma	DARZALEX FASPRO 1,800 mg/30,000 units in Patients with Multiple Myeloma	DARZALEX FASPRO 1,800 mg/30,000 units in Patients with Light Chain (AL) Amyloidosis
Observed mean±SD max C_{trough} after 8th dose (µg/mL)	522±226[a,b]	593±306[a,b]	597±232[c]
Simulated median (5th-95th percentiles) max C_{trough} after 8th dose (µg/mL)	472 (144-809)[d]	563 (177-1063)[d]	662 (315-1037)[e]
Simulated median (5th-95th percentiles) C_{max} after 8th dose (µg/mL)	688 (369-1061)[d]	592 (234-1114)[d]	729 (390-1105)[e]
Simulated median (5th-95th percentiles) $AUC_{0\text{-}7days}$ after 8th dose (µg/mL•day)	4019 (1740-6370)[d]	4017 (1515-7564)[d]	4855 (2562-7522)[e]

[a] Geometric mean ratio between 1,800 mg SC and 16 mg/kg was 108% (90% CI: 96, 122) in patients with multiple myeloma.

[b] Source: MMY3012 Primary Analysis Clinical Study Report

[c] Source: AMY3001 Primary Analysis Clinical Study Report

[d] Source: Population Pharmacokinetics and Exposure-response Analysis Report for Subcutaneously Administered Daratumumab in Multiple Myeloma Subjects

[e] Source: Population Pharmacokinetics and Exposure-response Analysis Report for Daratumumab Subcutaneous Administration for the Treatment of Subjects with AL Amyloidosis

- The following information was added for "absorption":
  - "Peak concentrations occurred around 4 days in patients with light chain (AL) amyloidosis."
- The following information was added for "distribution":

- "The estimated mean volume of distribution was 10.8 L (28%) in patients with light chain (AL) amyloidosis."

- The following information was added for "elimination":
  - The estimated mean (CV%) linear clearance of daratumumab "(59%) in patients with multiple myeloma and is 210 mL/day (42%) in patients with light chain (AL) amyloidosis"
  - The estimated (CV%) elimination half-life associated with linear clearance "in patients with multiple myeloma and 28 days (74%) in patients with light chain (AL) amyloidosis."
- New section was added on "Racial or Ethnic Groups"
  - "Of 190 patients with light chain (AL) amyloidosis who received DARZALEX FASPRO and had a maximum C_{trough} after the 8th dose, African-Americans (4%) had 24% higher daratumumab mean maximum C_{trough} after the 8th dose compared to that of Whites (83%) and Asians (10%) had 16% higher mean maximum C_{trough} after the 8th dose compared to that of Whites. The difference in exposure between that of Asians and Whites could be explained in part by differences in body size. The effect of African-American race on exposure and related safety and efficacy of daratumumab is unknown."
- New Section was added on "Body Weight"
  - "In patients with light chain (AL) amyloidosis who received DARZALEX FASPRO 1,800 mg/30,000 units in combination and had a maximum Ctrough after the 8th dose, the mean maximum Ctrough after the 8th dose was 22% lower in the higher BW group (>85 kg), while the mean maximum Ctrough was 37% higher in the lower BW group (≤50 kg) compared to the patients with body weight of 51-85 kg."

SECTION 14 CLINICAL STUDIES

14.3 Light Chain Amyloidosis

- New section on "In Combination with Bortezomib, Cyclophosphamide and Dexamethasone"
  - "The efficacy of DARZALEX FASPRO with VCd was evaluated in ANDROMEDA (NCT03201965), an open-label, randomized, active-controlled trial. Eligible patients were required to have newly diagnosed light chain (AL) amyloidosis with at least one affected organ, measurable hematologic disease, Cardiac Stage I IIIA (based on European Modification of Mayo 2004 Cardiac Stage), and NYHA Class I-IIIA. Patients with NYHA Class IIIB and IV were excluded. Patients were randomized to receive bortezomib 1.3 mg/m2 administered subcutaneously, cyclophosphamide 300 mg/m2 (max dose 500 mg) administered orally or intravenously, and dexamethasone 40 mg (or a reduced dose of 20 mg for patients >70 years or body mass index <18.5 or who have hypervolemia, poorly controlled diabetes mellitus or prior intolerance to steroid therapy) administered orally or intravenously on Days 1, 8, 15, and 22 of each 28-day cycle with or without DARZALEX FASPRO 1,800 mg/30,000 units subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or a maximum of two years. When DARZALEX FASPRO and dexamethasone were administered on the same day, dexamethasone 20 mg was administered before DARZALEX FASPRO with the remaining dose of dexamethasone administered after DARZALEX FASPRO if applicable. The major efficacy outcome measure was confirmed hematologic complete response (HemCR) rate based on Consensus Criteria as determined by the Independent Review Committee (negative serum and urine immunofixation, involved free light chain level decrease to less than the upper limit of normal, and normal free light chain ratio). Randomization was stratified by Cardiac Stage (European Modification of Mayo 2004 Cardiac Stage) countries that typically offer autologous stem cell transplant (ASCT) for patients with light chain (AL) amyloidosis, and renal function."
  - "A total of 388 patients were randomized: 195 to D-VCd and 193 to VCd. The median patient age was 64 years (range: 34 to 87 years); 58% were male; 76% White, 17% Asian, and 3% Black or African American; 23% had light chain (AL) amyloidosis Cardiac Stage I, 40% had Stage II, and 37% had Stage IIIA. The median number of organs involved was 2 (range: 1-6) and 66% of patients had 2 or more organs involved. Vital organ involvement was: cardiac 71%, renal 59% and hepatic 8%. The majority (79%) of patients had lambda free light chain disease."
  - "Efficacy results are summarized in Table 18."

Table 18: Efficacy results from ANDROMEDA[a]

	D-VCd (n=195)	VCd (n=193)
Hematologic complete response (HemCR), n (%)	82 (42%)	26 (13%)
p-value[b]	<0.0001	
Very good partial response (VGPR), n (%)	71 (36%)	69 (36%)
Partial response (PR), n (%)	26 (13%)	53 (27%)
Hematologic VGPR or better (HemCR + VGPR), n (%)	153 (78%)	95 (49%)
Major organ deterioration progression-free survival[c], Hazard ratio with 95% CI	0.58 (0.37, 0.92)	

D-VCd=daratumumab-bortezomib-cyclophosphamide-dexamethasone; VCd=bortezomib-cyclophosphamide-dexamethasone

[a] Based on intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

[c] Major organ deterioration-PFS defined as hematologic progression, major organ (cardiac or renal) deterioration or death

- "The median time to HemCR was 59 days (range: 8 to 299 days) in the D-VCd arm and 59 days (range: 16 to 340 days) in the VCd arm. The median time to VGPR or better was 17 days (range: 5 to 336 days) in the D-VCd arm and 25 days (range: 8 to 171 days) in the VCd arm. The median duration of HemCR had not been reached in either arm."
- "The median follow-up for the study is 11.4 months. Overall survival (OS) data were not mature. A total of 56 deaths were observed [N=27 (13.8%) D-VCd vs. N=29 (15%) VCd group]."

SECTION 17 PATIENT COUNSELING INFORMATION

- New section on "Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis"
  - "Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see Warnings and Precautions (5.2)]."
- The following information was updated for "Embryo-Fetal Toxicity":
  - Advise patients that lenalidomide and "thalidomide" have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide and "thalidomide" are only available through a REMS program [see Use in Specific Populations (8.1, 8.3)].

PATIENT INFORMATION

- The following information was updated:
  - DARZALEX FASPRO may be used with other medicines called lenalidomide or "thalidomide" and dexamethasone. You should also read **the Medication Guide that comes with lenalidomide or "thalidomide"** if you use DARZALEX FASPRO with lenalidomide or "thalidomide".
- The following information was added in the **"What is DARZALEX FASPRO?"** section:
  - "in combination with the medicines bortezomib, thalidomide, and dexamethasone in newly diagnosed people who are eligible to receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant)."
  - "DARZALEX FASPRO is a prescription medicine also used in combination with the medicines bortezomib, cyclophosphamide and dexamethasone in patients with newly diagnosed light chain (AL) amyloidosis."
- The following changes were made in the **"Before you receive DARZALEX FASPRO, tell your healthcare provider about all of your medical conditions, including if you"**:

- Updated: Before starting DARZALEX FASPRO in combination with lenalidomide or "thalidomide" and dexamethasone, females and males must agree to the instructions in the lenalidomide or "thalidomide" REMS program.
  - The lenalidomide and "thalidomide" REMS have more information about effective methods of birth control, pregnancy testing, and blood donation for females who can become pregnant.
  - For males who have female partners who can become pregnant, there is information in the lenalidomide and "thalidomide" REMS about sperm donation and how lenalidomide and "thalidomide" can pass into human semen.
- Added: "Before you receive DARZALEX FASPRO for light chain (AL) amyloidosis, tell your healthcare provider if you have a history of heart problems. DARZALEX FASPRO should not be used in light chain (AL) amyloidosis patients with highly advanced heart disease outside of clinical trials."

- The following changes were made to the "**What are the possible side effects of DARZALEX FASPRO?":**
  - Added: "**Heart problems in patients with light chain (AL) amyloidosis**. Heart problems, in some cases fatal, have occurred. Your healthcare provider will monitor you closely during treatment with DARZALEX FASPRO. Call your healthcare provider right away if any of the following symptoms occur: chest pain, feeling faint, swollen legs, shortness of breath, or abnormal heart rhythm."