HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DARZALEX® safely and effectively. See full prescribing information for DARZALEX.

DARZALEX® (daratumumab) injection, for intravenous use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	8/2020
Dosage and Administration (2.1, 2.2, 2.4)	8/2020
Dosage and Administration (2.3)	6/2020
Warnings and Precautions (5.1, 5.3, 5.4, 5.6)	6/2020

----------INDICATIONS AND USAGE----------

DARZALEX is a CD38-directed cytolytic antibody indicated for the treatment of adult patients with multiple myeloma:

- 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
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- in combination with carfilzomib and dexamethasone in patients who have received one to three prior lines of therapy
- in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor
- as monotherapy, in patients who have received at least three 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)

----------DOSAGE AND ADMINISTRATION----------

- Pre-medicate with corticosteroids, antipyretics and antihistamines. (2.3)
- Dilute and administer as an intravenous infusion. (2.5)
- Recommended dose is 16 mg/kg actual body weight. See full prescribing information for drugs used in combination and schedule (2.2)
- Administer post-infusion medications. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection:

- 100 mg/5 mL solution in a single-dose vial (3)
- 400 mg/20 mL solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------

Patients with a history of severe hypersensitivity to daratumumab or any of the components of the formulation. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infusion-related reactions: Interrupt DARZALEX infusion for infusion-related reactions of any severity. Permanently discontinue the infusion in case of anaphylactic reactions or life-threatening infusion-related reactions and institute appropriate emergency care. (2.4, 5.1)
- Interference with cross-matching and red blood cell antibody screening: Type and screen patients prior to starting treatment. Inform blood banks that a patient has received DARZALEX. (5.2, 7.1)
- Neutropenia: Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Dose delay may be required to allow recovery of neutrophils. (5.3)
- Thrombocytopenia: Monitor complete blood cell counts periodically during treatment. Dose delay may be required to allow recovery of platelets. (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception (5.6, 8.1, 8.3).

----------ADVERSE REACTIONS----------

The most frequently reported adverse reactions (incidence ≥20%) were: upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DARZALEX is indicated for the treatment of adult patients with multiple myeloma:

- 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.
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.
- in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- as monotherapy, in patients who have received at least three 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

- Administer pre-infusion and post-infusion medications *[see Dosage and Administration (2.3)]*.
- Administer only as an intravenous infusion after dilution in 0.9% Sodium Chloride Injection, USP *[see Dosage and Administration (2.5)]*.
- DARZALEX should be administered by a healthcare provider, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions if they occur *[see Warnings and Precautions (5.1)]*.
- Type and screen patients prior to starting DARZALEX *[see Warnings and Precautions (5.2)]*.

2.2 Recommended Dosage

Monotherapy and In Combination with Lenalidomide (D-Rd) or Pomalidomide (D-Pd) and Dexamethasone

The DARZALEX dosing schedule in Table 1 is for combination therapy (4-week cycle regimens) and monotherapy as follows:

- combination therapy with lenalidomide and low-dose dexamethasone for newly diagnosed patients ineligible for autologous stem cell transplant (ASCT) and in patients with relapsed/refractory multiple myeloma
- combination therapy with pomalidomide and low-dose dexamethasone for patients with relapsed/refractory multiple myeloma
- monotherapy for patients with relapsed/refractory multiple myeloma.

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule:

Table 1: DARZALEX Dosing Schedule in Combination With Lenalidomide or Pomalidomide (4-Week Cycle) and Low-Dose Dexamethasone and for Monotherapy

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[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

For dosing instructions of combination agents administered with DARZALEX, *see Clinical Studies (14)* and manufacturer's prescribing information.

In Combination with Bortezomib, Melphalan and Prednisone (D-VMP)

The DARZALEX dosing schedule in Table 2 is for combination therapy with bortezomib, melphalan and prednisone (6-week cycle regimen) for patients with newly diagnosed multiple myeloma ineligible for ASCT.

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule:

Table 2: DARZALEX Dosing Schedule in Combination With Bortezomib, Melphalan and Prednisone ([VMP], 6-Week Cycle)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54[a]	every three weeks (total of 16 doses)
Week 55 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at Week 7
[b] First dose of the every-4-week dosing schedule is given at Week 55

For dosing instructions of combination agents administered with DARZALEX *see Clinical Studies (14.1).*

In Combination with Bortezomib, Thalidomide and Dexamethasone (D-VTd)

The DARZALEX dosing schedule in Table 3 is for combination therapy with bortezomib, thalidomide, and dexamethasone (4-week cycle regimen) for patients with newly diagnosed multiple myeloma eligible for ASCT.

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule:

Table 3: DARZALEX Dosing Schedule in Combination With Bortezomib, Thalidomide and Dexamethasone ([VTd]; 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

For dosing instructions of combination agents administered with DARZALEX, *see Clinical Studies (14.1)* and the manufacturer's prescribing information.

In Combination with Bortezomib and Dexamethasone (D-Vd)

The DARZALEX dosing schedule in Table 4 is for combination therapy with bortezomib and dexamethasone (3-week cycle) for patients with relapsed/refractory multiple myeloma.

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule:

Table 4: DARZALEX Dosing Schedule With Bortezomib and Dexamethasone (3-Week Cycle)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24[a]	every three weeks (total of 5 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at Week 10
[b] First dose of the every-4-week dosing schedule is given at Week 25

For dosing instructions of combination agents administered with DARZALEX *see Clinical Studies (14.2)* and manufacturer's prescribing information.

In Combination with Carfilzomib and Dexamethasone (DKd)

The recommended dosage for DARZALEX when administered in combination with carfilzomib and dexamethasone (4-week cycle) for patients with relapsed/refractory multiple myeloma is provided in Table 5.

Table 5: DARZALEX Dosing Schedule With Carfilzomib and Dexamethasone (4-Week Cycle)

Weeks	DARZALEX Dose[c]	Schedule
Week 1	8 mg/kg	days 1 and 2 (total 2 doses)
Weeks 2 to 8	16 mg/kg	weekly (total of 7 doses)
Weeks 9 to 24[a]	16 mg/kg	every two weeks (total of 8 doses)
Week 25 onwards until disease progression[b]	16 mg/kg	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
[c] Based on actual body weight

For dosing instructions of combination agents administered with DARZALEX *see Clinical Studies (14.1)* and manufacturer's prescribing information.

Infusion Rates

Administer DARZALEX intravenously at the infusion rate described below in Table 6. Consider incremental escalation of the infusion rate only in the absence of infusion-related reactions.

The recommended dose of 16 mg/kg to be administered on Day 1 when DARZALEX is administered as monotherapy or in combination may be split over two consecutive days, such that an 8 mg/kg dose is administered on Day 1 and Day 2, respectively.

Table 6: 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)	1,000 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)[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 3 onwards (16 mg/kg)[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-related reactions.

[b] Use a dilution volume of 500 mL for the 16 mg/kg dose only if there were no infusion-related reactions the previous week. Otherwise, use a dilution volume of 1,000 mL.

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

Missed DARZALEX Doses

If a dose of DARZALEX is missed, administer the dose as soon as possible and adjust the dosing schedule to maintain the dosing interval.

2.3 Recommended Concomitant Medications

Pre-infusion Medication

Administer the following pre-infusion medications 1-3 hours before every DARZALEX infusion:

- Corticosteroid (long- or intermediate-acting)

Monotherapy:

Administer methylprednisolone 100 mg (or equivalent) intravenously. Following the second infusion, consider reducing the dose to 60 mg (or equivalent) administered either orally or intravenously.

In Combination:

Administer dexamethasone 20 mg (or equivalent) orally or intravenously.

When dexamethasone is the background regimen-specific corticosteroid, the dexamethasone dose that is part of the background regimen will serve as pre-medication on DARZALEX infusion days *[see Clinical Studies (14)]*.

Do not administer background regimen-specific corticosteroids (e.g. prednisone) on DARZALEX infusion days when patients have received dexamethasone (or equivalent) as a pre-medication.

- Acetaminophen 650 to 1,000 mg orally
- Diphenhydramine 25 to 50 mg (or equivalent) orally or intravenously.

Post-infusion Medication

Administer the following post-infusion medications:

Monotherapy:

Administer methylprednisolone 20 mg (or an equivalent dose of an intermediate- or long-acting corticosteroid) orally for 2 days starting the day after the administration of DARZALEX.

In Combination:

Consider administering oral methylprednisolone at a dose of less than or equal to 20 mg (or an equivalent dose of an intermediate- or long-acting corticosteroid) beginning the day after the administration of a DARZALEX infusion.

If a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX infusion, additional corticosteroids may not be needed *[see Clinical Studies (14)]*.

For patients with a history of chronic obstructive pulmonary disease, consider prescribing short and long-acting bronchodilators and inhaled corticosteroids. Following the first 4 DARZALEX infusions, consider discontinuing these additional post-infusion medications, if the patient does not experience a major infusion-related reaction.

Prophylaxis for Herpes Zoster Reactivation

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting DARZALEX and continue for 3 months following the end of treatment *[see Adverse Reactions (6.1)]*.

2.4 Dosage Modifications for Adverse Reactions

No dose reductions of DARZALEX are recommended. Consider withholding DARZALEX to allow recovery of blood cell counts in the event of myelosuppression *[see Warnings and Precautions (5.3, 5.4)]*.

For information concerning drugs given in combination with DARZALEX, see manufacturer's prescribing information.

Infusion-Related Reactions

For infusion-related reactions of any grade/severity, immediately interrupt the DARZALEX infusion and manage symptoms. Management of infusion-related reactions may further require reduction in the rate of infusion, or treatment discontinuation of DARZALEX as outlined below *[see Warnings and Precautions (5.1)]*.

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 6).

- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 6. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARZALEX upon the third occurrence of a Grade 3 or greater infusion-related reaction.

- Grade 4 (life-threatening): Permanently discontinue DARZALEX.

2.5 Preparation and Administration

Preparation

DARZALEX is for single use only.

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient actual body weight.

- Check that the DARZALEX solution is colorless to pale yellow. Do not use if opaque particles, discoloration or other foreign particles are present.

- Remove a volume of 0.9% Sodium Chloride Injection, USP from the infusion bag/container that is equal to the required volume of DARZALEX solution.

- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to the infusion bag/container containing 0.9% Sodium Chloride Injection, USP as specified in Table 6 *[see Dosage and Administration (2.2)]*. Infusion bags/containers must be made of either polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.

- Gently invert the bag/container to mix the solution. Do not shake.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

- Since DARZALEX does not contain a preservative, administer the diluted solution immediately at room temperature 15°C–25°C (59°F–77°F) and in room light. Diluted solution may be kept at room temperature for a maximum of 15 hours (including infusion time).
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions 2°C–8°C (36°F–46°F) and protected from light. Do not freeze.

Administration

- If stored in the refrigerator, allow the solution to come to room temperature. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP or PE.

- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.

3 DOSAGE FORMS AND STRENGTHS

DARZALEX is a colorless to pale yellow, preservative-free solution available as:

Injection:

- 100 mg/5 mL (20 mg/mL) in a single-dose vial.

- 400 mg/20 mL (20 mg/mL) in a single-dose vial.

4 CONTRAINDICATIONS

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

DARZALEX can cause severe and/or serious infusion-related reactions including anaphylactic reactions. In clinical trials (monotherapy and combination: N=2,066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension *[see Adverse Reactions (6.1)]*.

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4:<1%) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg 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-related 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 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion *[see Dosage and Administration (2.3)]*. Interrupt DARZALEX

infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.4)]*.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.3)]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease *[see Dosage and Administration (2.3)]*.

5.2 Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References (15)]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions (7.1)]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX *[see Dosage and Administration (2.1)]*.

5.3 Neutropenia

DARZALEX may increase neutropenia induced by background therapy *[see Adverse Reactions (6.1)]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

5.4 Thrombocytopenia

DARZALEX may increase thrombocytopenia induced by background therapy *[see Adverse Reactions (6.1)]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 1,383 evaluable combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System disorders: Anaphylactic reaction
Gastrointestinal disorders: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

7 DRUG INTERACTIONS

7.1 Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References (15)]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for additional information.

8.3 Females and Males of Reproductive Potential

DARZALEX can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

8.4 Pediatric Use

Safety and effectiveness of DARZALEX in pediatric patients have not been established.

8.5 Geriatric Use

Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients *[see Adverse Reactions (6.1)]*. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

11 DESCRIPTION

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody that binds to CD38 antigen. It is produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.

DARZALEX® (daratumumab) injection is supplied as a colorless to pale yellow preservative-free solution for intravenous use in a single-dose vial. The pH is 5.5.

Each DARZALEX 20 mL single-dose vial contains 400 mg daratumumab, glacial acetic acid (3.7 mg), mannitol (510 mg), polysorbate 20 (8 mg), sodium acetate trihydrate (59.3 mg), sodium chloride (70.1 mg), and Water for Injection, USP.

Each DARZALEX 5 mL single-dose vial contains 100 mg daratumumab, glacial acetic acid (0.9 mg), mannitol (127.5 mg), polysorbate 20 (2 mg), sodium acetate trihydrate (14.8 mg), sodium chloride (17.5 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other cell types and tissues and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab.

12.2 Pharmacodynamics

NK cells express CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+$CD56^{dim}$) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX treatment.

Exposure-Response Relationship

The exposure-response relationship and time course of pharmacodynamics of DARZALEX have not been fully characterized.

Cardiac Electrophysiology

DARZALEX as a large protein has a low likelihood of direct ion channel interactions. There is no evidence from non-clinical or clinical data to suggest that DARZALEX has the potential to delay ventricular repolarization.

12.3 Pharmacokinetics

Daratumumab area under the concentration-time curve (AUC) increases more than proportionally over a dosage range from 1 to 24 mg/kg (0.06 to 1.5 times the approved recommended dosage) as monotherapy or 1 to 16 mg/kg (0.06 to 1 time the approved recommended dosage) as combination therapy.

Following administration of the approved recommended dosage of DARZALEX as monotherapy or in combination therapy, the mean serum maximal concentration (C_{max}) was approximately 2.7 to 3-fold higher at the end of weekly dosing compared to the first dose. The mean ± standard deviation (SD) trough serum concentration (C_{min}) at the end of weekly dosing was 573 ± 332 µg/mL when DARZALEX was administered as monotherapy and 502 ± 196 to 607 ± 231 µg/mL when DARZALEX was administered as combination therapy. 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.

When DARZALEX was administered as monotherapy, daratumumab steady state was achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion). At steady state, daratumumab mean ± SD accumulation ratio for C_{max} was 1.6 ± 0.5.

Distribution

Daratumumab volume of distribution was 4.7 ± 1.3 L as monotherapy and 4.4 ± 1.5 L as combination therapy following administration of the approved dosage.

Elimination

Daratumumab clearance decreased with increasing dose and with multiple dosing. The mean ± SD linear clearance was estimated to be 171.4 ± 95.3 mL/day and the mean ± SD estimated terminal half-life associated with linear clearance was 18 ± 9 days following administration of the approved recommended dosage of DARZALEX as monotherapy. Terminal half-life was similar when DARZALEX was administered as combination therapy.

Specific Populations

No clinically significant differences in the pharmacokinetics of daratumumab as monotherapy or as combination therapy were observed based on sex, age (31 to 93 years), mild [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate aminotransaminase (AST)>ULN] and moderate (total bilirubin 1.5 to 3 times ULN and any AST) hepatic impairment, or renal impairment [Creatinine clearance (CLcr) 15-89 mL/min]. The effect of severe (total bilirubin >3 times ULN and any AST) hepatic impairment on daratumumab pharmacokinetics is unknown.

Body Weight

The central volume of distribution and clearance of daratumumab increased with increasing body weight.

Study GEN501 (NCT00574288) was an open-label dose escalation trial evaluating DARZALEX monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 2 different cytoreductive therapies. In 42 patients, DARZALEX 16 mg/kg was administered with pre- and post-infusion medication. Treatment continued until unacceptable toxicity or disease progression.

The median patient age was 64 years (range: 44 to 76 years), 64% were male and 76% were White. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% of patients were refractory to both, a PI and an immunomodulatory agent, and 60% of patients were refractory to alkylating agents.

Overall response rate was 36% (95% CI: 21.6, 52.0%) with 1 CR and 3 VGPR. The median time to response was 1 month (range: 0.5 to 3.2 months). The median duration of response was not estimable (range: 2.2 to 13.1+ months).

15 REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

DARZALEX® is a colorless to pale yellow, preservative-free solution for intravenous infusion supplied as:

NDC 57894-502-05 contains one 100 mg/5 mL single-dose vial

NDC 57894-502-20 contains one 400 mg/20 mL single-dose vial

Storage and Stability

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).

Do not freeze or shake. Protect from light. This product contains no preservative.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Infusion-Related Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Warnings and Precautions (5.1)]*.

Neutropenia

Advise patients to contact their healthcare provider if they have a fever *[see Warnings and Precautions (5.3)]*.

Thrombocytopenia

Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding *[see Warnings and Precautions (5.4)]*.

Interference with Laboratory Tests

Advise patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion *[see Warnings and Precautions (5.2)]*.

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions (5.5)]*.

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX and for at least 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

Advise patients that lenalidomide, pomalidomide, or thalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program *[see Use in Specific Populations (8.1, 8.3)]*.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864

PATIENT INFORMATION
DARZALEX® (Dar'-zah-lex)
(daratumumab)
injection, for intravenous use

What is DARZALEX?

DARZALEX is a prescription medicine used to treat adults with multiple myeloma:

- in combination with the medicines lenalidomide and dexamethasone in people with newly diagnosed multiple myeloma who cannot receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant) and in people who have received at least one prior medicine to treat multiple myeloma.
- in combination with the medicines bortezomib, melphalan and prednisone, in people with newly diagnosed multiple myeloma who cannot receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant).
- 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).
- in combination with the medicines bortezomib and dexamethasone, in people who have received at least one prior medicine to treat multiple myeloma.
- in combination with the medicines carfilzomib and dexamethasone, in people who have received one to three prior medicines to treat multiple myeloma.
- in combination with the medicines pomalidomide and dexamethasone in people who have received at least two prior medicines to treat multiple myeloma, including lenalidomide and a proteasome inhibitor.
- alone in people who have received at least three prior medicines, including a proteasome inhibitor and an immunomodulatory agent, **or** did not respond to a proteasome inhibitor and an immunomodulatory agent.

It is not known if DARZALEX is safe and effective in children.

Do not receive DARZALEX:

- if you have a history of a severe allergic reaction to daratumumab or any of the ingredients in DARZALEX. See the end of this leaflet for a complete list of ingredients in DARZALEX.

Before you receive DARZALEX, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of breathing problems
- have had shingles (herpes zoster)
- have ever had or might now have a hepatitis B infection as DARZALEX could cause hepatitis B virus to become active again. Your healthcare provider will check you for signs of this infection before, during and for some time after treatment with DARZALEX. Tell your healthcare provider right away if you get worsening tiredness or yellowing of your skin or white part of your eyes.
- are pregnant or plan to become pregnant. DARZALEX may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think that you may be pregnant during treatment with DARZALEX.
  - Females who are able to become pregnant should use an effective method of birth control (contraception) during treatment and for at least 3 months after your final dose of DARZALEX. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Before starting DARZALEX in combination with lenalidomide, pomalidomide, or thalidomide, females and males must agree to the instructions in the lenalidomide, pomalidomide, or thalidomide REMS program.
    - The lenalidomide, pomalidomide, and thalidomide REMS has 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, pomalidomide, and thalidomide REMS about sperm donation and how lenalidomide, pomalidomide, and thalidomide can pass into human semen.
- are breastfeeding or plan to breastfeed. It is not known if DARZALEX passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive DARZALEX?

- DARZALEX may be given alone or together with other medicines used to treat multiple myeloma.
- DARZALEX will be given to you by your healthcare provider by intravenous (IV) infusion into your vein.
- Your healthcare provider will decide the time between doses as well as how many treatments you will receive.
- Your healthcare provider will give you medicines before each dose of DARZALEX and after each dose of DARZALEX to help reduce the risk of infusion-related reactions.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of DARZALEX?

DARZALEX may cause serious reactions, including:

- **Infusion-related reactions.** Infusion-related reactions are common with DARZALEX and can be severe or serious**.** Your healthcare provider may temporarily stop your infusion or completely stop treatment with DARZALEX if you have infusion-related reactions. Get medical help right away if you get any of the following symptoms:
  - shortness of breath or trouble breathing
  - dizziness or lightheadedness (hypotension)
  - cough
  - wheezing
  - throat tightness
  - runny or stuffy nose
  - headache
  - itching
  - nausea
  - vomiting
  - chills
  - fever
- **Changes in blood tests.** DARZALEX can affect the results of blood tests to match your blood type. These changes can last for up to 6 months after your final dose of DARZALEX. Your healthcare provider will do blood tests to match your blood type before you start treatment with DARZALEX. **Tell all of your healthcare providers that you are being treated with DARZALEX before receiving blood transfusions.**
- **Decreases in blood cell counts.** DARZALEX can decrease white blood cell counts which help fight infections and blood cells called platelets which help to clot blood. Your healthcare provider will check your blood cell counts during treatment with DARZALEX. Tell your healthcare provider if you develop fever or have signs of bruising or bleeding.

The most common side effects of DARZALEX include:

- tiredness
- nausea
- diarrhea
- shortness of breath
- feeling weak
- fever
- cough
- cold-like symptoms (upper respiratory infection)
- nerve damage causing tingling, numbness or pain
- swollen hands ankles or feet
- constipation

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of DARZALEX. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of DARZALEX

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about DARZALEX that is written for health professionals.

What are the ingredients in DARZALEX?

Active ingredient: daratumumab

Inactive ingredients: glacial acetic acid, mannitol, polysorbate 20, sodium acetate trihydrate, sodium chloride, and water for injection

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044 U.S. License Number 1864
For more information, call 1-800-526-7736 or go to www.DARZALEX.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 3/2021