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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

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

DARZALEX is a human CD38-directed monoclonal antibody indicated for the treatment of patients with multiple myeloma 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)

This indication is approved under accelerated approval based on response rate (14). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

Pre-medicate with corticosteroids, antipyretics and antihistamines. (2.2)
Dilute and administer as an intravenous infusion. (2.3, 2.4)
Recommended dose is 16 mg/kg body weight:

Weekly	Weeks 1 to 8
Every two weeks	Weeks 9 to 24
Every four weeks	Week 25 onwards until disease progression

Administer post-infusion medications. (2.2)

----------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----------

None. (4)

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

- Infusion reactions: Interrupt DARZALEX infusion for infusion reactions of any severity. Permanently discontinue the infusion in case of life-threatening infusion reactions. (2.1, 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)

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

The most frequently reported adverse reactions (incidence ≥20%) were: infusion reactions, fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection. (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 Patient Information.

Revised: 11/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DARZALEX is indicated for the treatment of patients with multiple myeloma 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.

This indication is approved under accelerated approval based on response rate *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

- Administer pre-infusion and post-infusion medications *[see Dosage and Administration (2.2)]*.
- Administer only as an intravenous infusion after dilution *[see Dosage and Administration (2.4)]*.
- DARZALEX should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion reactions if they occur *[see Warnings and Precautions (5.1)]*.

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

Table 1: DARZALEX dosing schedule

Schedule	Weeks
Weekly	Weeks 1 to 8
Every two weeks	Weeks 9 to 24
Every four weeks	Week 25 onwards until disease progression

If a planned dose of DARZALEX is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

Administer DARZALEX infusion intravenously at the appropriate infusion rate. Consider incremental escalation of the infusion rate only in the absence of infusion reactions with the previous infusion of DARZALEX as defined in Table 2.

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Table 2: Infusion rates for DARZALEX administration

	Dilution volume	Initial rate (first hour)	Rate increment	Maximum rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.

[b] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions.

For infusion reactions of any grade/severity, immediately interrupt the DARZALEX infusion and manage symptoms. Management of infusion 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 appropriate (Table 2).

- Grade 3 (severe): If the intensity of the reaction decreases to Grade 2 or lower, 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 2. 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 reaction.

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

2.2 Recommended Concomitant Medications

Pre-infusion Medication

Administer pre-infusion medications to reduce the risk of infusion reactions to all patients approximately 1 hour prior to every infusion of DARZALEX as follows:

- intravenous corticosteroid (methylprednisolone 100 mg, or equivalent dose of an intermediate-acting or long-acting corticosteroid), plus

- oral antipyretics (acetaminophen 650 to 1000 mg), plus

- oral or intravenous antihistamine (diphenhydramine 25 to 50 mg or equivalent).

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Following the second infusion, the dose of corticosteroid may be reduced (methylprednisolone 60 mg intravenously).

Post-infusion Medication

Administer post-infusion medication to reduce the risk of delayed infusion reactions to all patients as follows:

- oral corticosteroid (20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local standards) on the first and second day after all infusions.

For patients with a history of obstructive pulmonary disorder, consider prescribing post-infusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids. Following the first four infusions, if the patient experiences no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

Prophylaxis for Herpes Zoster Reactivation

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

2.3 Preparation for Administration

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.
- Using aseptic technique, 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 2 *[see Dosage and Administration (2.1)]*. Infusion bags/containers must be made of 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.
- Following dilution the infusion bag/container may be stored for up to 24 hours in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF), protected from light. Do not freeze. After allowing

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the bag/container to come to room temperature, use immediately since DARZALEX solutions do not contain a preservative.

- 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.

2.4 Administration

- 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). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.

- Infusion should be completed within 15 hours.

- 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

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

DARZALEX can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion.

Infusion reactions can also occur with subsequent infusions. 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 reactions occurred up to 48 hours after infusion.

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

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.1)]*.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients the first and second day after all infusions. Patients with a history of obstructive pulmonary disorders may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders.

5.2 Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (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[1] *[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.

5.3 Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions (7.1)]*. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

6 ADVERSE REACTIONS

The following serious adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Warning and Precautions (5.1)]*.

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6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.4 months).

Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 3. Table 4 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

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Table 3: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

System Organ Class	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see below
[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia

Table 4: Treatment Emergent Grade 3-4 laboratory abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	All Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

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Infusion Reactions

The incidence of any grade infusion reactions was 46% with the first infusion of DARZALEX, 5% with the second infusion, and 4% with subsequent infusions. None of the reactions with second or subsequent infusions were Grade 3 or higher.

The median time to onset of a reaction was 1.5 hours (range: 0.02 to 9.3 hours). The incidence of infusion interruptions due to reactions was 37%. Median durations of infusion for the 1st, 2nd and subsequent infusions were 7.0, 4.6 and 3.4 hours respectively.

Severe infusion reactions included bronchospasm, dyspnea, hypoxia, and hypertension (<2% each). Common any grade adverse infusion reactions (≥5%) were nasal congestion, cough, chills, rhinitis allergic, throat irritation, dyspnea, and nausea.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. Systemic anti-viral medications were used in 73% of patients. Herpes zoster was reported in 3% of patients.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In an open-label, clinical trial of patients with relapsed or refractory multiple myeloma treated with DARZALEX, 111 patients were evaluated for anti-therapeutic antibody (ATA) responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment using an electrochemiluminescence-based immunoassay. Following the start of DARZALEX treatment, none of the patients tested positive for anti-daratumumab antibodies. 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.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No drug interaction studies have been performed.

7.1 Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (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[1] *[see*

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References (15)] or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given 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). This can lead to false positive SPE and IFE assay results 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, consider other methods to evaluate the depth of response.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations *[see Clinical Considerations]*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

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8.2 Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed child from DARZALEX or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 156 patients on the recommended dose, 45% were 65 years of age or older, and 10% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients *[see Clinical Studies (14)]*.

8.6 Renal Impairment

Based on a population pharmacokinetic (PK) analysis no dosage adjustment is necessary for patients with pre-existing renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Based on a population PK analysis, no dosage adjustments are necessary for patients with mild hepatic impairment (Total Bilirubin [TB] 1.0× to 1.5× upper limit of normal [ULN] or aspartate aminotransferase [AST] >ULN). Daratumumab has not been studied in patients with moderate to severe hepatic impairment (TB >1.5× ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The dose of DARZALEX at which severe toxicity occurs is not known.

In the event of an overdose, monitor patients for any signs or symptoms of adverse effects and provide appropriate supportive treatment.

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11 DESCRIPTION

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.

DARZALEX is supplied as a colorless to pale yellow preservative-free solution for intravenous infusion in single-dose vials. The pH is 5.5. DARZALEX must be diluted with 0.9% Sodium Chloride Injection, USP *[see Dosage and Administration (2.3, 2.4)]*.

Each DARZALEX single-dose 20 mL 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.

Each DARZALEX single-dose 5 mL 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.

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). Myeloid derived suppressor cells (MDSCs) and a subset of regulatory T cells ($CD38+T_{regs}$) express CD38 and are susceptible to daratumumab mediated cell lysis.

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.

CD4+ and CD8+ T cell absolute counts, as well as their percentage of total lymphocytes, increased with DARZALEX treatment in both the peripheral blood and bone marrow.

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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

The pharmacokinetics (PK) of daratumumab following intravenous administration were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg, and included the recommended 16 mg/kg dose and regimen. The population PK analysis included 223 patients with multiple myeloma receiving DARZALEX in two clinical trials (150 subjects received 16 mg/kg).

Over the dose range from 1 to 24 mg/kg, increases in area under the concentration-time curve (AUC) were more than dose-proportional. Clearance decreased with increasing dose and repeated dosing, indicating target-mediated pharmacokinetics.

Following the recommended schedule and dose of 16 mg/kg, the mean [standard deviation (SD)] serum C_{max} value was 915 (410) µg/mL at the end of weekly dosing, approximately 2.9-fold higher than following the first infusion. The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (332) µg/mL.

Based on the population PK analysis, daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean (SD) ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 (0.5). The mean (SD) linear clearance and mean (SD) central volume of distribution are estimated to be 171.4 (95.3) mL/day and 4.7 (1.3 L), respectively. The mean (SD) estimated terminal half-life associated with linear clearance was approximately 18 (9) days.

Population PK analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Population PK analyses also showed that age (31 to 84 years) and gender do not have clinically important effects on the pharmacokinetics of daratumumab.

Special Populations

Renal Impairment

The population PK analysis included 71 patients with normal renal function (creatinine clearance [CrCL] ≥90 mL/min), 78 patients with mild renal impairment (CrCL <90 and ≥60 mL/min), 68 patients with moderate renal impairment (CrCL <60 and ≥30 mL/min), and 6 patients with severe renal impairment or end stage renal disease (CrCL <30 mL/min). No clinical differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function *[see Use in Specific Populations (8.6)]*.

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Hepatic Impairment

The population PK analysis included 189 patients with normal hepatic function (TB and AST ≤ULN) and 34 with mild hepatic impairment (TB 1.0× to 1.5× ULN or AST>ULN) patients. No clinical differences in the exposure to daratumumab were observed between patients with mild hepatic impairment and those with normal hepatic function. Daratumumab has not been studied in patients with moderate (TB>1.5× to 3× ULN and any AST) or severe (TB>3× ULN and any AST) hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with daratumumab. No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development, or to determine potential effects on fertility in males or females.

14 CLINICAL STUDIES

Study 1, was an open-label trial evaluating DARZALEX monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor and an immunomodulatory agent. In 106 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 63.5 years (range: 31 to 84 years), 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent, and 77% were refractory to alkylating agents.

Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 5).

Table 5: Efficacy results for Study 1

	N=106
Overall response rate (ORR) 95% CI (%)	31 (29.2%) (20.8, 38.9)
Stringent complete response (sCR)	3 (2.8%)
Complete response (CR)	0
Very good partial response (VGPR)	10 (9.4%)
Partial response (PR)	18 (17.0%)

ORR = sCR+CR+VGPR+PR
CI = confidence interval

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The median time to response was 1 month (range: 0.9 to 5.6 months). The median duration of response was 7.4 months (range: 1.2 to 13.1+ months).

Study 2 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 Caucasian. 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

16.1 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

16.2 Storage and Stability

Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF).

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).

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Infusion Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

- itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)]*.

Interference with Laboratory Tests

Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion.

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.

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

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

What is DARZALEX?

DARZALEX is a prescription medicine used to treat a type of cancer called multiple myeloma in people who:

- have received at least three prior medicines to treat multiple myeloma, 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.

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)
- are pregnant or plan to become pregnant. DARZALEX may harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control 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.
- 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 will be given to you by intravenous (IV) infusion into your vein. The infusion should be completed within 15 hours.
- DARZALEX is usually given weekly for the first 8 weeks, then every 2 weeks for 16 weeks, and then every 4 weeks after that.
- Your healthcare provider will decide how many treatments you will receive.
- Your healthcare provider will give you medicines before each dose of DARZALEX and on the first and second day after each dose of DARZALEX to help reduce the risk of infusion 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 reactions.** Infusion reactions are common with DARZALEX and can be severe**.** Your healthcare provider may temporarily stop your infusion or completely stop treatment with DARZALEX if you have infusion reactions. Tell your healthcare provider 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
  - rash or hives
  - itching
  - nausea
  - vomiting
  - chills
- **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.**

The most common side effects of DARZALEX include:

- tiredness
- nausea
- back pain
- fever
- cough
- cold-like symptoms (upper respiratory infection)

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 Informa ion has been approved by the U.S. Food and Drug Administration. Issued: November/2015

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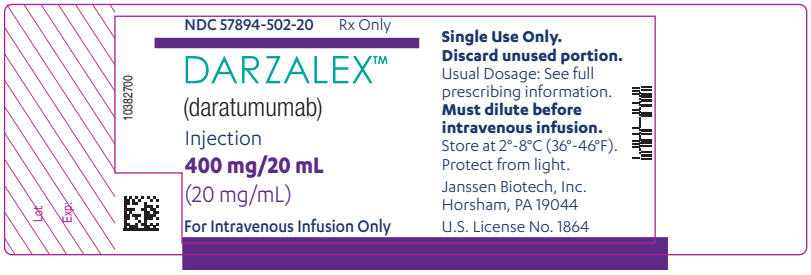

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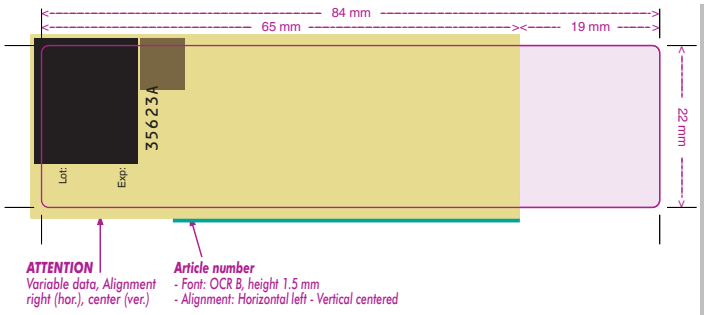

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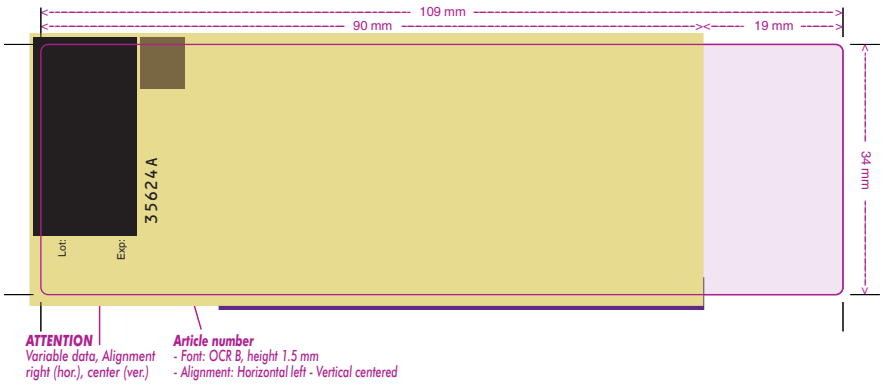

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/s/

RICHARD PAZDUR
11/16/2015