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----------

Dosage and Administration (2.1) 02/2019

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

DARZALEX is a CD38-directed cytolytic antibody indicated:

- in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy
- in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor
- as monotherapy, 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)

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

- Pre-medicate with corticosteroids, antipyretics and antihistamines. (2.2)
- Dilute and administer as an intravenous infusion. (2.4, 2.5)
- Recommended dose is 16 mg/kg actual body weight. See full prescribing information for drugs used in combination and schedule (2.1)
- 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----------

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

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

- Infusion reactions: Interrupt DARZALEX infusion for infusion reactions of any severity. Permanently discontinue the infusion in case of anaphylactic reactions or life-threatening infusion reactions and institute appropriate emergency care. (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)
- 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)

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

The most frequently reported adverse reactions (incidence ≥20%) were: infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, constipation, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy 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 FDA-approved patient labeling.

Revised: 07/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose and Schedule
2.2 Recommended Concomitant Medications
2.3 Dose Modifications
2.4 Preparation for Administration
2.5 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Infusion Reactions
5.2 Interference with Serological Testing
5.3 Neutropenia
5.4 Thrombocytopenia
5.5 Interference with Determination of Complete Response
6 ADVERSE REACTIONS
6.1 Adverse Reactions in Clinical Trials
6.2 Immunogenicity
6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Effects of Daratumumab on Laboratory Tests
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Newly Diagnosed Multiple Myeloma
14.2 Relapsed/Refractory Multiple Myeloma
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Stability
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 4462732

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DARZALEX is indicated:

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

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 in 0.9% Sodium Chloride Injection, USP *[see Dosage and Administration (2.4, 2.5)]*.
- 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)]*.

Newly Diagnosed Multiple Myeloma

Dosing Schedule for DARZALEX in Combination with Bortezomib, Melphalan and Prednisone (6-week cycle regimen) for Patients Ineligible for Autologous Stem Cell Transplant

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule in Table 1.

Reference ID: 4462732

Table 1: DARZALEX dosing schedule in combination with bortezomib, melphalan and prednisone ([VMP], 6-week cycle dosing regimen)

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).*

Relapsed/Refractory Multiple Myeloma

Monotherapy and Combination Therapy with Lenalidomide or Pomalidomide and Low-Dose Dexamethasone (4-week cycle regimens)

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule in Table 2:

Table 2: DARZALEX dosing schedule for monotherapy and in combination with lenalidomide or pomalidomide (4-week cycle dosing regimens)

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 (14.2)* and manufacturer's prescribing information.

Combination Therapy with Bortezomib and Dexamethasone (3-week cycle regimen)

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule in Table 3:

Table 3: DARZALEX dosing schedule with bortezomib (3-week cycle dosing regimen)

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.

Reference ID: 4462732

Missed DARZALEX Doses

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.

Infusion Rates and Management of Infusion Reactions

Administer DARZALEX infusion intravenously at the infusion rate described below in Table 4. Consider incremental escalation of the infusion rate only in the absence of infusion reactions.

To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively, see Table 4 below.

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

	Dilution volume	**Initial rate (first hour)**	**Rate increment[a]**	**Maximum rate**
Week 1 Infusion				
Option 1 (Single dose infusion)				
Week 1 Day 1 (16 mg/kg)	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Option 2 (Split dose infusion)				
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 2 (16 mg/kg) infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (Week 3 onwards, 16 mg/kg) infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

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

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

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

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 clinically appropriate up to the maximum rate of 200 mL/hour (Table 4).

- 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

Reference ID: 4462732

additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 4. 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 the following pre-infusion medications to reduce the risk of infusion reactions to all patients 1-3 hours prior to every infusion of DARZALEX:

- Corticosteroid (long-acting or intermediate-acting)

  Monotherapy:

  Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg).

  Combination therapy:

  Administer 20 mg dexamethasone (or equivalent) prior to every DARZALEX infusion *[Clinical Studies (14)]*.

  Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions. Additional background regimen-specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX infusion days when patients receive dexamethasone (or equivalent) as a pre-medication.

- Antipyretics (oral acetaminophen 650 to 1000 mg)

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

Post-infusion Medication

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

Reference ID: 4462732

Monotherapy:

Administer oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) on each of the 2 days following all DARZALEX infusions (beginning the day after the infusion).

Combination therapy:

Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent, the day after the DARZALEX infusion.

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

In addition, for any patients with a history of chronic obstructive pulmonary disease, 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 after starting DARZALEX and continue for 3 months following treatment *[see Adverse Reactions (6.1)]*.

2.3 Dose Modifications

No dose reductions of DARZALEX are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of hematological toxicity *[see Warnings and Precautions (5.3, 5.4)]*. For information concerning drugs given in combination with DARZALEX, see manufacturer's prescribing information.

2.4 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.
- 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.

Reference ID: 4462732

- 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 4 *[see Dosage and Administration (2.1)]*. 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.

2.5 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 <u>in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer)</u>. 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.

Reference ID: 4462732

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) and Adverse Reactions (6.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

DARZALEX can cause severe and/or serious infusion reactions including anaphylactic reactions. In clinical trials, approximately half of all patients experienced an infusion reaction. Most infusion reactions occurred during the first infusion and were Grade 1-2 *[see Adverse Reactions (6.1)]*.

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.

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)]*.

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 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 (2.1)]*.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.2)]*. 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.

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)]*.

Reference ID: 4462732

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 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. DARZALEX dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX is recommended. Consider supportive care with growth factors.

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. DARZALEX dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions.

5.5 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 clinically significant adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Warning and Precautions (5.1)]*.
- Neutropenia *[see Warning and Precautions (5.3)]*.
- Thrombocytopenia *[see Warning and Precautions (5.4)]*.

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.

Reference ID: 4462732

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 1166 patients with multiple myeloma including 872 patients from three Phase 3 active-controlled trials who received DARZALEX in combination with either lenalidomide and dexamethasone (DRd, n=283; POLLUX), bortezomib and dexamethasone (DVd, n=243; CASTOR) or bortezomib, melphalan and prednisone (D-VMP, n=346; ALCYONE), and five open-label, clinical trials in which patients received DARZALEX either in combination with pomalidomide and dexamethasone (DPd, n=103; EQUULEUS), in combination with lenalidomide and dexamethasone (n=35), or as monotherapy (n=156).

Newly Diagnosed Multiple Myeloma

Combination Treatment with Bortezomib, Melphalan and Prednisone

Adverse reactions described in Table 5 reflect exposure to DARZALEX (D-VMP arm) for a median treatment duration of 14.7 months (range: 0 to 25.8 months) and median treatment duration of 12 months (range: 0.1 to 14.9 months) for the VMP group in ALCYONE. The most frequent adverse reactions (≥20% with at least 5% greater frequency in the D-VMP arm) were infusion reactions, upper respiratory tract infection and edema peripheral. Serious adverse reactions with at least a 2% greater incidence in the D-VMP arm compared to the VMP arm were pneumonia (D-VMP 11% vs VMP 4%), upper respiratory tract infection (D-VMP 5% vs VMP 1%), and pulmonary edema (D-VMP 2% vs VMP 0%).

Table 5: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the D-VMP arm in ALCYONE

Body System Adverse Reaction	**D-VMP (N=346)**			**VMP (N=354)**		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**Any Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Infusion reactions[a]	28	4	1	0	0	0
General disorders and administration site conditions						
Edema peripheral[b]	21	1	< 1	14	1	0
Infections and infestations						
Upper respiratory tract infection[c]	48	5	0	28	3	0
Pneumonia[d]	16	12	< 1	6	5	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[e]	16	< 1	0	8	< 1	0
Dyspnea[f]	13	2	1	5	1	0
Vascular disorders						
Hypertension[g]	10	4	< 1	3	2	0

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] edema peripheral, generalized edema, peripheral swelling

[c] upper respiratory tract infection, bronchitis, bronchitis bacterial, epiglottitis, laryngitis, laryngitis bacterial, metapneumovirus infection, nasopharyngitis, oropharyngeal candidiasis, pharyngitis, pharyngitis streptococcal, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, tracheitis, tracheobronchitis, viral pharyngitis, viral rhinitis, viral upper respiratory tract infection.

[d] pneumonia, lung infection, pneumonia aspiration, pneumonia bacterial, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, and pulmonary sepsis

[e] cough, productive cough

[f] dyspnea, dyspnea exertional

[g] hypertension, blood pressure increased

Reference ID: 4462732

Laboratory abnormalities worsening during treatment from baseline listed in Table 6.

Table 6: Treatment-emergent hematology laboratory abnormalities in ALCYONE

	D-VMP (N=346) %			VMP (N=354) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anemia	47	18	0	50	21	0
Thrombocytopenia	88	27	11	88	26	16
Neutropenia	86	34	10	87	32	11
Lymphopenia	85	46	12	83	44	9

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide

Adverse reactions described in Table 7 reflect exposure to DARZALEX (DRd arm) for a median treatment duration of 13.1 months (range: 0 to 20.7 months) and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide group (Rd) in POLLUX. The most frequent adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 42% for the Rd group. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 7: Adverse reactions reported in ≥ 10% of patients and with at least a 5% greater frequency in the DRd arm in POLLUX

Adverse Reaction	DRd (N=283) %			Rd (N=281) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0

Reference ID: 4462732

Dyspnea[d]	21	3	< 1	12	1	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 8.

Table 8: Treatment-emergent hematology laboratory abnormalities in POLLUX

	DRd (N=283) %			**Rd (N=281) %**		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grades**	**Grade 3**	**Grade 4**
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib

Adverse reactions described in Table 9 reflect exposure to DARZALEX (DVd arm) for a median treatment duration of 6.5 months (range: 0 to 14.8 months) and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in CASTOR. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each).

Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Reference ID: 4462732

Table 9: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the DVd arm CASTOR

Adverse Reaction	DVd (N=243) %			Vd (N=237) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reactions[a]	45	9	0	0	0	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[c]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[d]	27	0	0	14	0	0
Dyspnea[e]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] edema peripheral, edema, generalized edema, peripheral swelling

[c] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[d] cough, productive cough, allergic cough

[e] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 10.

Table 10: Treatment-emergent hematology laboratory abnormalities in CASTOR

	DVd (N=243) %			Vd (N=237) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	< 1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Combination Treatment with Pomalidomide

Adverse reactions described in Table 11 reflect exposure to DARZALEX, pomalidomide and dexamethasone (DPd) for a median treatment duration of 6 months (range: 0.03 to 16.9 months) in EQUULEUS. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, constipation, nausea, vomiting, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, back pain, arthralgia, dizziness, insomnia, cough and dyspnea. The overall incidence of serious

Reference ID: 4462732

adverse reactions was 49%. Serious adverse reactions reported in ≥5% patients included pneumonia (7%). Adverse reactions resulted in discontinuations for 13% of patients.

Table 11: Adverse reactions with incidence ≥10% reported in EQUULEUS

Body System Adverse Reaction	**DPd (N=103)**		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**
Infusion reactions[a]	50	4	0
Gastrointestinal disorders			
Diarrhea	38	3	0
Constipation	33	0	0
Nausea	30	0	0
Vomiting	21	2	0
General disorders and administration site conditions			
Fatigue	50	10	0
Pyrexia	25	1	0
Chills	20	0	0
Edema peripheral[b]	17	4	0
Asthenia	15	0	0
Non-cardiac chest pain	15	0	0
Pain	11	0	0
Infections and infestations			
Upper respiratory tract infection[c]	50	4	1
Pneumonia[d]	15	8	2
Metabolism and nutrition disorders			
Hypokalemia	16	3	0
Hyperglycemia	13	5	1
Decreased appetite	11	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	26	1	0
Back pain	25	6	0
Arthralgia	22	2	0
Pain in extremity	15	0	0
Bone pain	13	4	0
Musculoskeletal chest pain	13	2	0
Nervous system disorders			
Dizziness	21	2	0
Tremor	19	3	0
Headache	17	0	0
Psychiatric disorders			
Insomnia	23	2	0
Anxiety	13	0	0

Reference ID: 4462732

Respiratory, thoracic and mediastinal disorders			
Cough[e]	43	1	0
Dyspnea[f]	33	6	1
Nasal congestion	16	0	0

Key: D=Daratumumab, Pd=pomalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] edema, edema peripheral, peripheral swelling.

[c] acute tonsillitis, bronchitis, laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection

[d] lung infection, pneumonia, pneumonia aspiration

[e] cough, productive cough, allergic cough

[f] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 12.

Table 12: Treatment-emergent hematology laboratory abnormalities in EQUULEUS

	DPd (N=103) %		
	Any Grade	**Grade 3**	**Grade 4**
Anemia	57	30	0
Thrombocytopenia	75	10	10
Neutropenia	95	36	46
Lymphopenia	94	45	26

Key: D=Daratumumab, Pd=pomalidomide-dexamethasone.

Monotherapy

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 20.04 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 13. Table 14 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Reference ID: 4462732

Table 13: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

	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 14: Treatment emergent Grade 3-4 laboratory abnormalities (≥10%)

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

Infusion Reactions

In clinical trials (monotherapy and combination treatments; N=1166) the incidence of any grade infusion reactions was 40% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with

Reference ID: 4462732

the Week 2 infusion, and 4% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion reaction at Week 2 or subsequent infusions. Grade 4 infusion reactions were reported in 2/1166 (0.2%) of patients.

The median time to onset of a reaction was 1.4 hours (range: 0 to 72.8 hours). The incidence of infusion modification due to reactions was 37%. Median durations of 16 mg/kg infusions for the 1st week, 2nd week and subsequent infusions were 7.0, 4.3, and 3.4 hours respectively.

Severe infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea.

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

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported with DARZALEX combinations and background therapies (DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%; D-VMP:23%, VMP:15%; DPd: 28%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 3% versus 2% of patients in the DRd and Rd groups respectively, 4% versus 3% of patients in the DVd and Vd groups respectively, 1% each in the D-VMP and VMP groups respectively, and in 5% of patients receiving DPd. Fatal infections were generally balanced between the DARZALEX containing regimens and active control arms (<2%) in the controlled studies and were primarily due to pneumonia and sepsis.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials.

Reference ID: 4462732

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to daratumumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. 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 411 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 DARZALEX. 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

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, 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

Reference ID: 4462732

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.

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. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

8.2 Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed child, 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.

Reference ID: 4462732

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 1166 patients that received DARZALEX at the recommended dose, 46% were 65 to 75 years of age, and 15% 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)]*.

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 (2.4)]*.

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). A subset of myeloid derived suppressor cells

Reference ID: 4462732

(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.

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

Over the dose range from 1 to 24 mg/kg as monotherapy or 1 to 16 mg/kg of DARZALEX in combination with other treatments, increases in area under the concentration-time curve (AUC) were more than dose-proportional.

Following the recommended dose of 16 mg/kg when DARZALEX was administered as monotherapy or in combination therapy, the mean serum maximal concentration (C_{max}) value at the end of weekly dosing, was approximately 2.7 to 3-fold higher compared to the mean serum C_{max} following 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), and the mean ± SD ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 ± 0.5.

Distribution

At the recommended dose of 16 mg/kg, the mean ± SD central volume of distribution was 4.7 ± 1.3 L when DARZALEX was administered as monotherapy and 4.4 ± 1.5 L when DARZALEX was administered as combination therapy.

Elimination

Daratumumab clearance decreased with increasing dose and with multiple dosing. At the recommended dose of 16 mg/kg of DARZALEX as monotherapy, the mean ± SD linear clearance was estimated to be 171.4 ± 95.3 mL/day. The mean ± SD estimated terminal half-life

Reference ID: 4462732

associated with linear clearance was 18 ± 9 days when DARZALEX administered as monotherapy and a mean of 22-23 days when DARZALEX was administered as combination therapy.

Specific Populations

The following population characteristics have no clinically meaningful effect on the pharmacokinetics of daratumumab in patients administered DARZALEX as monotherapy or as combination therapy: 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 is unknown. Increasing body weight increased the central volume of distribution and clearance of daratumumab, supporting the body weight-based dosing regimen.

Drug Interactions

Effect of Other Drugs on Daratumumab

The coadministration of lenalidomide, pomalidomide or bortezomib with DARZALEX did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs

The coadministration of DARZALEX with bortezomib or pomalidomide did not affect the pharmacokinetics of bortezomib or pomalidomide.

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

14.1 Newly Diagnosed Multiple Myeloma

Combination Treatment with Bortezomib, Melphalan and Prednisone (VMP) in Patients Ineligible for Autologous Stem Cell Transplant

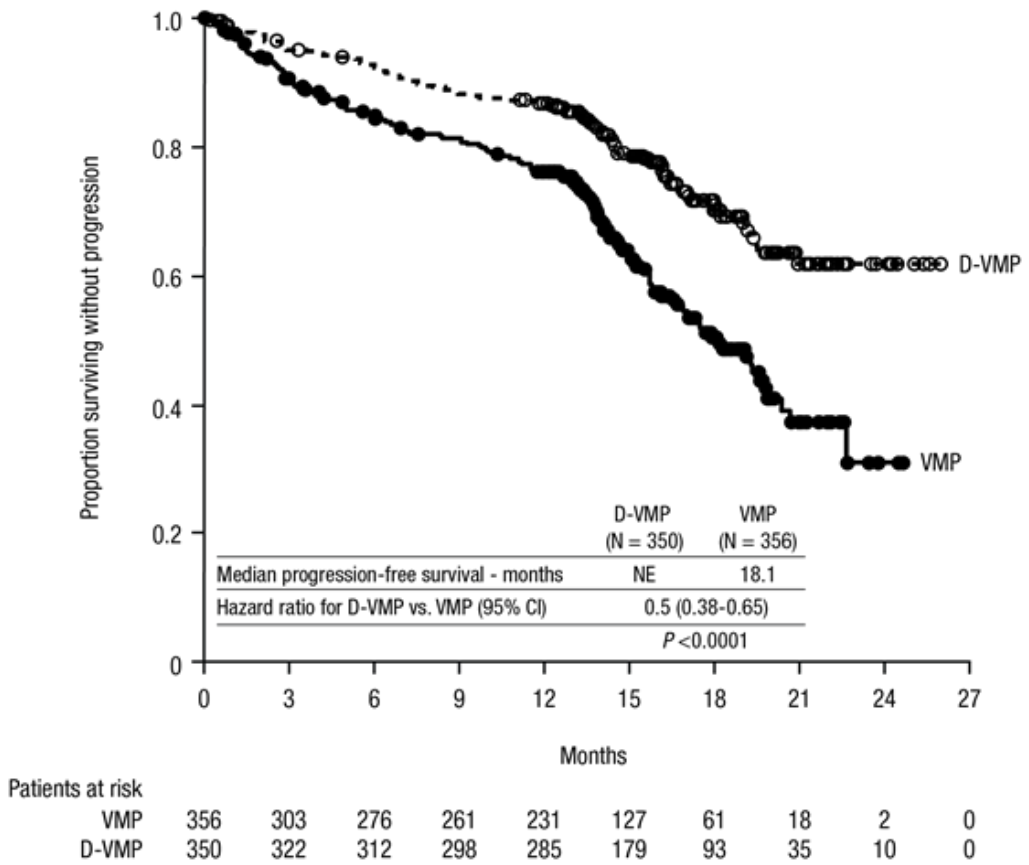
ALCYONE (NCT02195479), an open-label, randomized, active-controlled Phase 3 study, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous (SC) injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX treatment was continued until disease progression or unacceptable toxicity.

Reference ID: 4462732

A total of 706 patients were randomized: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%), female (54%), 25% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Nineteen percent of patients had ISS Stage I, 42% had ISS Stage II and 38% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

ALCYONE demonstrated an improvement in PFS in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months (95% CI:16.53, 19.91) in the VMP arm (hazard ratio [HR]=0.5; 95% CI: 0.38, 0.65; p<0.0001), representing 50% reduction in the risk of disease progression or death in patients treated with D-VMP.

Figure 1: Kaplan-Meier Curve of PFS in ALCYONE



Additional efficacy results from ALCYONE are presented in Table 15 below.

Reference ID: 4462732

Table 15: Additional efficacy results from ALCYONE

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) n(%)[a]	318 (90.9%)	263 (73.9%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	63 (18.0%)	25 (7.0%)
Complete response (CR)	86 (24.6%)	62 (17.4%)
Very good partial response (VGPR)	100 (28.6%)	90 (25.3%)
Partial response (PR)	69 (19.7%)	86 (24.2%)
MRD negativity rate[a, c] n(%)	78 (22.3%)	22 (6.2%)
95% CI (%)	(18.0, 27.0)	(3.9, 9.2)
p-value[d]	<0.0001	
MRD negativity rate in patients with CR or better[c] n(%)	74 (49.7%)	22 (25.3%)
95% CI (%)	(41.4, 58.0)	(16.6, 35.7)

D-VMP = daratumumab-bortezomib-melphalan-prednisone; VMP = bortezomib-melphalan-prednisone; MRD = minimal residual disease; CI = confidence interval

[a] Based on intent-to-treat population

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

[c] Based on threshold of 10^{-5}

[d] p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21.3 months (range: 0.5+, 23.7+) in the VMP group.

14.2 Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

POLLUX (NCT02076009), an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

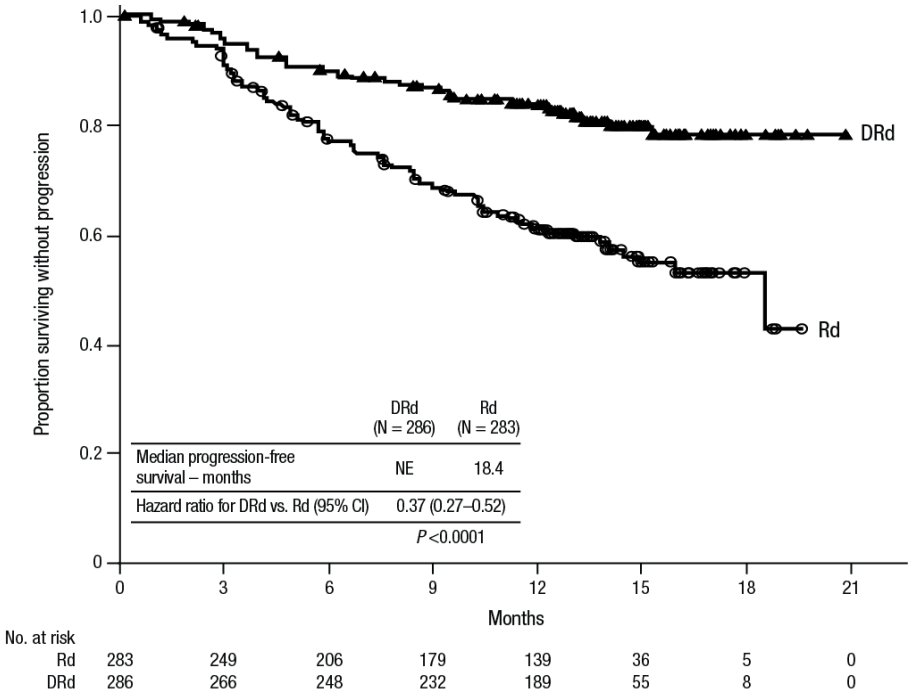
A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 65 years (range 34 to 89 years), 11% were ≥75 years, 59% were male; 69% Caucasian, 18% Asian, and 3% African American. Patients had received a median of 1 prior line of therapy. Sixty-three percent (63%) of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior PI, 55% of patients had received a prior immunomodulatory agent, including 18% of patients who

Reference ID: 4462732

had received prior lenalidomide; and 44% of patients had received both a prior PI and immunomodulatory agent. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

POLLUX demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (hazard ratio [HR]=0.37; 95% CI: 0.27, 0.52; p<0.0001), representing 63% reduction in the risk of disease progression or death in patients treated with DRd.

Figure 2: Kaplan-Meier Curve of PFS in POLLUX



Additional efficacy results from POLLUX are presented in Table 16 below.

Table 16: Additional efficacy results from POLLUX[a]

	DRd (n=286)	**Rd (n=283)**
Overall response (sCR+CR+VGPR+PR)	261 (91.3%)	211 (74.6%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	51 (17.8%)	20 (7.1%)
Complete response (CR)	70 (24.5%)	33 (11.7%)
Very good partial response (VGPR)	92 (32.2%)	69 (24.4%)
Partial response (PR)	48 (16.8%)	89 (31.4%)

DRd = daratumumab- lenalidomide-dexamethasone; Rd = lenalidomide-dexamethasone

[a] Based on Intent-to-treat population

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

Reference ID: 4462732

In responders, the median time to response was 1 month (range: 0.9 to 13 months) in the DRd group and 1.1 months (range: 0.9 to 10 months) in the Rd group. The median duration of response had not been reached in the DRd group (range: 1+ to 19.8+ months) and was 17.4 months (range: 1.4 to 18.5+ months) in the Rd group.

With a median follow-up of 13.5 months, 75 deaths were observed; 30 in the DRd group and 45 in the Rd group.

Combination Treatment with Bortezomib and Dexamethasone

CASTOR (NCT02136134), an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV infusion at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms; whereas DARZALEX was given until disease progression. However, dexamethasone 20 mg was continued as a DARZALEX pre-infusion medication in the DVd arm. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

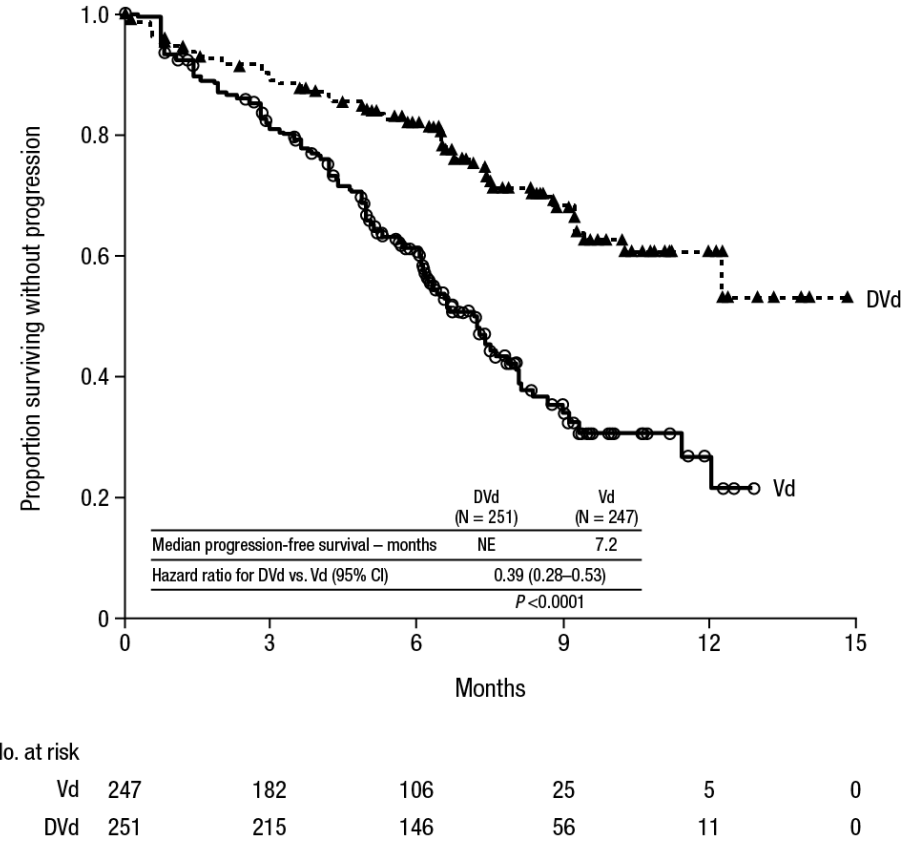
A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years); 12% were ≥75 years, 57% were male; 87% Caucasian, 5% Asian and 4% African American. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior autologous stem cell transplantation (ASCT). Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an immunomodulatory agent (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment and the proportions of patients refractory to any specific prior therapy were in general well balanced between the treatment groups. Thirty-three percent (33%) of patients were refractory to an immunomodulatory agent only, with 24% patients in the DVd arm and 33% of patients in the Vd arm respectively refractory to lenalidomide. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

CASTOR demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95%

Reference ID: 4462732

CI]: 0.39 [0.28, 0.53]; p-value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd.

Figure 3: Kaplan-Meier Curve of PFS in CASTOR



Additional efficacy results from CASTOR are presented in Table 17 below.

Table 17: Additional efficacy results from CASTOR[a]

	DVd (n=251)	**Vd (n=247)**
Overall response (sCR+CR+VGPR+PR)	199 (79.3%)	148 (59.9%)
P-value[b]	<0.0001	
Stringent complete response (sCR)	11 (4.4%)	5 (2.0%)
Complete response (CR)	35 (13.9%)	16 (6.5%)
Very good partial response (VGPR)	96 (38.2%)	47 (19.0%)
Partial response (PR)	57 (22.7%)	80 (32.4%)

DVd = daratumumab- bortezomib-dexamethasone; Vd = bortezomib-dexamethasone

[a] Based on Intent-to-treat population

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

In responders, the median time to response was 0.8 months (range: 0.7 to 4 months) in the DVd group and 1.5 months (range: 0.7 to 5 months) in the Vd group. The median duration of response had not been reached in the DVd group (range: 1.4+ to 14.1+ months) and was 7.9 months (1.4+ to 12+ months) in the Vd group.

Reference ID: 4462732

With a median follow-up of 7.4 months, 65 deaths were observed; 29 in the DVd group and 36 in the Vd group were observed.

Combination Treatment with Pomalidomide and Dexamethasone

EQUULEUS (NCT01998971) was an open-label trial in which 103 patients with multiple myeloma who had received a prior PI and an immunomodulatory agent, received 16 mg/kg DARZALEX in combination with pomalidomide and low-dose dexamethasone until disease progression. Pomalidomide (4 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/ week (reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.

The median patient age was 64 years (range: 35 to 86 years) with 8% of patients ≥75 years of age. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent (74%) of patients had received prior ASCT. Ninety-eight percent (98%) of patients received prior bortezomib treatment, and 33% of patients received prior carfilzomib. All patients received prior lenalidomide treatment, with 98% of patients previously treated with the combination of bortezomib and lenalidomide. Eighty nine percent (89%) of patients were refractory to lenalidomide and 71% refractory to bortezomib; 64% of patients were refractory to bortezomib and lenalidomide.

Efficacy results were based on overall response rate as determined by Independent Review Committee using IMWG criteria (see Table 18).

Table 18: Efficacy results for EQUULEUS

	N=103
Overall response rate (ORR) 95% CI (%)	61 (59.2%) (49.1, 68.8)
Stringent complete response (sCR)	8 (7.8%)
Complete response (CR)	6 (5.8%)
Very good partial response (VGPR)	29 (28.2%)
Partial response (PR)	18 (17.5%)

ORR = sCR+CR+VGPR+PR
CI = Confidence Interval

The median time to response was 1 month (range: 0.9 to 2.8 months). The median duration of response was 13.6 months (range: 0.9+ to 14.6+ months).

Monotherapy

SIRIUS (NCT01985126), 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-

Reference ID: 4462732

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 19).

Table 19: Efficacy results for SIRIUS

	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

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 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 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).

Reference ID: 4462732

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 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).

<u>Infusion Reactions</u>

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)]*.

<u>Neutropenia</u>

- Advise patients that if they have a fever, they should contact their healthcare professional *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

<u>Thrombocytopenia</u>

- Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.

Reference ID: 4462732

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 *[see Warnings and Precautions (5.2) and Drug Interactions (7.1)]*.

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) and Drug Interactions (7.1)]*.

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)]*.

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 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 lenalidomide and dexamethasone, **or** bortezomib and dexamethasone, in people who have received at least one prior medicine 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 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.

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.
  - 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 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 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 or serious**.** Your healthcare provider may temporarily stop your infusion or completely stop treatment with DARZALEX if you have infusion 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

Reference ID: 4462732

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
- trouble sleeping
- fever
- cough
- muscle spasms
- back pain
- joint pain
- vomiting
- cold-like symptoms (upper respiratory infection)
- nerve damage causing tingling, numbness or pain
- swollen hands ankles or feet
- constipation
- chills
- dizziness

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: July/2019

Reference ID: 4462732