เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

DARZALEX SC™

FULL PRESCRIBING INFORMATION

1. Name of the Medicinal Product

1.1 Product Name

DARZALEX SC™ (daratumumab)

1.2 Strength

Injection: 1,800 mg daratumumab per 15 mL (120 mg/mL) solution in a single-dose vial.

1.3 Pharmaceutical Dosage Form

Solution for subcutaneous injection

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

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

Hyaluronidase (recombinant human) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is a glycosylated single-chain protein produced by Chinese Hamster Ovary cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (recombinant human) has a molecular weight of approximately 61 kDa.

DARZALEX SC (daratumumab) injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution supplied in a single-dose vial for subcutaneous administration.

2.2 Quantitative Declaration

Each DARZALEX SC 15 mL single-dose vial contains 1,800 mg of daratumumab and 30,000 units of hyaluronidase, L-histidine (4.9 mg), L-histidine hydrochloride monohydrate (18.4 mg), L-methionine (13.5 mg), polysorbate 20 (6 mg), sorbitol (735.1 mg), and Water for Injection, USP.

3. Pharmaceutical Form

DARZALEX SC (daratumumab) injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution supplied in a single-dose vial for subcutaneous administration.

4. Clinical Particulars

4.1 Therapeutic Indications

4.1.1 Multiple Myeloma

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

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

4.1.2 Light Chain Amyloidosis

DARZALEX SC in combination with bortezomib, cyclophosphamide and dexamethasone is indicated for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis.

This indication is approved under accelerated approval based on response rate *[see Clinical Studies (5.1.3.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use

DARZALEX SC is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials *[see Special Warnings and Precautions for Use (4.4.2)]*.

4.2 Posology and Method of Administration

4.2.1 Important Dosing Information

- **DARZALEX SC is for subcutaneous use only.**

- Administer medications before and after administration of DARZALEX SC to minimize administration-related reactions *[see Posology and Method of Administration (4.2.5)]*.
- Type and screen patients prior to starting DARZALEX SC.

4.2.2 Recommended Dosage for Multiple Myeloma

The recommended dose of DARZALEX SC is 1,800 mg (1,800 mg daratumumab) administered subcutaneously over approximately 3-5 minutes. Tables 1, 2, 3, 4, and 5 provide the recommended dosing schedule when DARZALEX SC is administered as monotherapy or as part of a combination therapy.

Monotherapy and In Combination with Lenalidomide and Dexamethasone (DARZALEX SC-Rd) or Pomalidomide and Dexamethasone (DARZALEX SC-Pd) or Carfilzomib and Dexamethasone (Darzalex SC-Kd)

Use the dosing schedule provided in Table 1 when DARZALEX SC is administered:

- in combination with lenalidomide and dexamethasone (4-week cycle) OR
- in combination with pomalidomide and dexamethasone (4-week cycle) OR
- in combination with carfilzomib and dexamethasone (4-week cycle) OR
- as monotherapy.

Table 1: DARZALEX SC dosing schedule in combination with lenalidomide, pomalidomide or carfilzomib and dexamethasone (4-week cycle) and for monotherapy

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

[a] First dose of the every-2-week dosing schedule is given at Week 9
[b] First dose of the every-4-week dosing schedule is given at Week 25

When DARZALEX SC is administered as part of a combination therapy, *see Clinical Studies (5.1.3.2)* and the prescribing information for dosage recommendations for the other drugs.

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

Use the dosing schedule provided in Table 2 when DARZALEX SC is administered in combination with bortezomib, melphalan and prednisone (6-week cycle).

Table 2: DARZALEX SC dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle)

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

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

When DARZALEX SC is administered as part of a combination therapy, *see Clinical Studies (5.1.3.1)* and the prescribing information for dosage recommendations for the other drugs.

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

Use the dosing schedule in Table 3 when DARZALEX SC is administered in combination with bortezomib, thalidomide, and dexamethasone (4-week cycle).

Table 3: DARZALEX SC dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle)

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

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

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

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

In Combination with Bortezomib, Lenalidomide, and Dexamethasone (DARZALEX SC-VRd)

Use the dosing schedule in Table 4 when DARZALEX SC is administered in combination with bortezomib, lenalidomide, and dexamethasone (4-week cycle) for treatment of newly diagnosed multiple myeloma patients eligible for autologous stem cell transplant (ASCT).

Table 4: DARZALEX SC dosing schedule in combination with bortezomib, lenalidomide and dexamethasone (4-week cycle)

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

[a] First dose of the every-2-week dosing schedule is given at Week 9
[b] First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT

When DARZALEX SC is administered as part of a combination therapy, *see Clinical Studies (5.1.3.1)* and the prescribing information for dosage recommendations for the other drugs.

In Combination with Bortezomib and Dexamethasone (DARZALEX SC-Vd)

Use the dosing schedule in Table 5 when DARZALEX SC is administered in combination with bortezomib and dexamethasone (3-week cycle).

Table 5: DARZALEX SC dosing schedule in combination with bortezomib and dexamethasone (3-week cycle)

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

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

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

4.2.3 Recommended Dosage for Light Chain Amyloidosis

In Combination with Bortezomib, Cyclophosphamide and Dexamethasone (DARZALEX SC-VCd)

The recommended dose of DARZALEX SC is 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously over approximately 3-5 minutes.

Use the dosing schedule provided in Table 6 when DARZALEX SC is administered in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle).

Table 6: DARZALEX SC dosing schedule in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle)

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

[a] First dose of the every-2-week dosing schedule is given at Week 9
[b] First dose of the every-4-week dosing schedule is given at Week 25

When DARZALEX SC is administered as part of a combination therapy, *see Clinical Studies (5.1.3.2)* and the prescribing information for dosage recommendations for the other drugs.

4.2.4 Missed DARZALEX SC Doses

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

4.2.5 Recommended Concomitant Medications

Pre-medication

Administer the following pre-medications 1-3 hours before each dose of DARZALEX SC:

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

- Corticosteroid (long- or intermediate-acting)

  Monotherapy

  Administer methylprednisolone 100 mg (or equivalent) orally or intravenously. Consider reducing the dose of methylprednisolone to 60 mg (or equivalent) following the second dose of DARZALEX SC.

  In Combination

  Administer dexamethasone 20 mg (or equivalent) orally or intravenously prior to every DARZALEX SC administration.

  When dexamethasone is the background regimen-specific corticosteroid, the dexamethasone dose that is part of the background regimen will serve as pre-medication on DARZALEX SC administration days *[see Clinical Studies (5.1.3)]*.

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

Post-medication

Administer the following post-medications:

  Monotherapy

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

  In Combination

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

  If a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the administration of DARZALEX SC, additional corticosteroids may not be needed *[see Clinical Studies (5.1.3)]*.

If the patient does not experience a major systemic administration-related reaction after the first 3 doses of DARZALEX SC, consider discontinuing the administration of corticosteroids (excluding any background regimen-specific corticosteroid).

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

Prophylaxis for Herpes Zoster Reactivation

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting DARZALEX SC and continue for 3 months following the end of treatment *[see Undesirable effects (4.8.1)].*

4.2.6 Dosage Modifications for Adverse Reactions

No dose reductions of DARZALEX SC are recommended. Consider withholding DARZALEX SC to allow recovery of blood cell counts in the event of myelosuppression *[see Special Warnings and Precautions for Use (4.4.3, 4.4.4)]*.

4.2.7 Preparation and Administration

DARZALEX SC should be administered by a healthcare provider.

To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is DARZALEX SC for subcutaneous use. **Do not administer DARZALEX SC intravenously**.

DARZALEX SC is ready to use.

Preparation

- Remove the DARZALEX SC vial from refrigerated storage [2°C to 8°C (36°F to 46°F)] and equilibrate to ambient temperature [15°C to 30°C (59°F to 86°F)]. Store the unpunctured vial at ambient temperature and ambient light for a maximum of 24 hours. Keep out of direct sunlight. Do not shake.
- Withdraw 15 mL from the vial into a syringe.
- DARZALEX SC is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles. Use the product immediately.
- After the solution of DARZALEX SC is withdrawn into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe appropriately to include the route of administration per institutional standards. Label the syringe with the peel-off label.
- To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if opaque particles, discoloration or other foreign particles are present.

Storage

- If the syringe containing DARZALEX SC is not used immediately, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours and/or at room temperature at 15°C to 30°C (59°F to 86°F) for up to 7 hours under ambient light.
- Discard if storage time exceeds these limits.
- If stored in the refrigerator, allow the solution to come to room temperature before administration.

Administration

- **Inject 15 mL DARZALEX SC into the subcutaneous tissue of the abdomen approximately 3 inches [7.5 cm] to the right or left of the navel over approximately 3-5 minutes.** No data are available on performing the injection at other sites of the body.
- Rotate injection sites for successive injections.
- Never inject DARZALEX SC into areas where the skin is red, bruised, tender, hard or areas where there are scars.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by pausing or slowing down delivery rate, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- During treatment with DARZALEX SC, do not administer other medications for subcutaneous use at the same site as DARZALEX SC.

4.2.8 Use in Specific Populations

4.2.8.1 Pediatric Use

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

4.2.8.2 Geriatric Use

Of the 291 patients who received DARZALEX SC as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX SC have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

Of the 214 patients who received DARZALEX SC as combination therapy with pomalidomide and dexamethasone or DARZALEX SC as combination therapy with lenalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma, 43% were 65 to <75 years of age, and 18% were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=85). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 355 patients who were newly diagnosed with multiple myeloma and eligible for ASCT who received DARZALEX SC as combination therapy with bortezomib, lenalidomide and dexamethasone during induction and consolidation in the clinical trial, 74% were <65 years of age, and 26% were 65 to 70 years of age. The clinical trial did not enroll patients older

than 70 years of age *[see Clinical Studies (5.1.3.1)]*. No overall differences in effectiveness of DARZALEX SC in combination with bortezomib, lenalidomide and dexamethasone were observed between patients <65 years of age compared to patients 65 to 70 years of age. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients 65 to 70 years of age included constipation, hemorrhoids, nausea, injection site erythema, bronchitis, nasopharyngitis, back pain, myalgia, pain in extremity, dysgeusia, peripheral motor neuropathy, and insomnia. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients 65 to 70 years of age included febrile bone marrow aplasia, atrial fibrillation, pyrexia, and orthostatic hypotension.

Of the 193 patients who received DARZALEX SC as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX SC as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients *[see Pharmacokinetic Properties (5.2)]*

4.3 Contraindications

DARZALEX SC is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation *[see Special Warnings and Precautions for Use (4.4.1)* and *Undesirable effects (4.8.2)].*

4.4 Special Warnings and Precautions for Use

4.4.1 Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX SC. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX SC *[see Undesirable Effects (4.8.2)]*.

Systemic Reactions

In a pooled safety population of 1249 patients with multiple myeloma (N= 1056) or light chain (AL) amyloidosis (N=193) who received DARZALEX SC as monotherapy or as part of a combination therapy, 7% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 0.7%, Grade 4: 0.1%). Systemic administration-related reactions occurred in 7% of patients with the first injection, 0.2% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 2.9 hours (range:5 minutes to 3.5 days). Of the 165 systemic administration-related reactions that occurred in 93 patients, 144 (87%) occurred on the day of DARZALEX SC administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids *[see Posology and Method of Administration (4.2.5)]*. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX SC. Consider administering corticosteroids and other medications after the administration of DARZALEX SC depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions *[see Posology and Method of Administration (4.2.5)]*.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX SC and seek immediate ophthalmologic evaluation prior to restarting DARZALEX SC.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 7% of patients, including Grade 2 reactions in 0.8%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX SC. Monitor for local reactions and consider symptomatic management.

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

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX SC in combination with bortezomib, cyclophosphamide and dexamethasone *[see Undesirable Effects (4.8.1)]*. Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

4.4.3 Neutropenia

Daratumumab may increase neutropenia induced by background therapy *[see Undesirable effects (4.8.1)]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with

neutropenia for signs of infection. Consider withholding DARZALEX SC until recovery of neutrophils. In lower body weight patients receiving DARZALEX SC, higher rates of Grade 3-4 neutropenia were observed.

4.4.4 Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy *[see Undesirable effects (4.8.1)]*.

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

4.4.5 Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX SC can cause fetal harm when administered to a pregnant woman. DARZALEX SC may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX SC and for 3 months after the last dose *[see Pregnancy and Lactation (4.6.1, 4.6.3)]*.

The combination of DARZALEX SC with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

4.4.6 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 administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References (5.1.3.4)]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Interaction with other medicinal products and other forms of interactions (4.5.1)]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX SC. Type and screen patients prior to starting DARZALEX SC *[see Posology and Method of Administration (4.2.1)]*.

4.4.7 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 Interaction with other medicinal products and other forms of interactions (4.5.1)]*. This interference can impact the determination of complete response and of disease progression in some DARZALEX SC-treated patients with IgG kappa myeloma protein.

4.4.8 Hepatitis B Virus (HBV) reactivation

Hepatitis B virus (HBV) reactivation, in some cases fatal, has been reported in patients treated with daratumumab. HBV screening should be performed in all patients before initiation of treatment with DARZALEX SC.

For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of DARZALEX SC treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

In patients who develop reactivation of HBV while on DARZALEX SC, suspend treatment with DARZALEX SC and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of DARZALEX SC treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

4.5.1 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 (5.1.3.4)]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX SC-treated 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.

4.6 Pregnancy and Lactation

4.6.1 Pregnancy

Risk Summary

DARZALEX SC can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX SC in pregnant women to evaluate drug-

associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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% to 4% and 15% to 20%, respectively.

The combination of DARZALEX SC and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX SC may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab *in utero* until a hematology evaluation is completed.

Data

Animal Data

DARZALEX SC for subcutaneous injection contains daratumumab and hyaluronidase. 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. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

4.6.2 Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G 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. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX SC is administered with lenalidomide, thalidomide or pomalidomide, advise women not to

breastfeed during treatment with DARZALEX SC. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

4.6.3 Females and Males of Reproductive Potential

DARZALEX SC can cause fetal harm when administered to a pregnant woman *[see Pregnancy and Lactation (4.6.1)]*.

Pregnancy Testing

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

Contraception

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

4.7 Effects on Ability to Drive and Use Machine

DARZALEX SC has no or negligible influence on the ability to drive and use machines. However, fatigue has been reported in patients taking daratumumab and this should be taken into account when driving or using machines.

4.8 Undesirable Effects

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity and Other Administration Reactions *[see Special Warnings and Precautions for Use (4.4.1)]*.
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis [*see Special Warning and Precautions for Use (4.4.2)*].
- Neutropenia *[see Special Warnings and Precautions for Use (4.4.3)]*.
- Thrombocytopenia *[see Special Warnings and Precautions for Use (4.4.4)]*.

4.8.1 Clinical Trials Experience

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.

Newly Diagnosed Multiple Myeloma Eligible for Autologous Stem Cell Transplant
In Combination with Bortezomib, Lenalidomide and Dexamethasone

The safety of DARZALEX SC in combination with bortezomib, lenalidomide and dexamethasone (n=351) from the start of induction to the end of consolidation compared to bortezomib, lenalidomide and dexamethasone (VRd) (n=347) was evaluated in PERSEUS [*see Clinical Studies (5.1.3.1)*]. Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8 and once every 2 weeks from weeks 9 to 16 during induction in combination with VRd or VRd alone. After week 16, patients underwent stem cell mobilization, high dose chemotherapy, and ASCT. Within 12 weeks of ASCT, and when engraftment was complete, patients received DARZALEX SC once every 2 weeks from weeks 1 to 8 during consolidation in combination with VRd or VRd alone.

The median duration of treatment for induction and consolidation was 9.9 months (0.5 to 18.5 months) for DARZALEX SC-VRd.

Serious adverse reactions occurred in 37% of patients who received DARZALEX SC-VRd. The most frequent serious adverse reaction in >5% of patients who received DARZALEX SC-VRd was pneumonia (6%). Fatal adverse reactions occurred in 1.7% of patients who received DARZALEX SC-VRd.

Permanent treatment discontinuation due to an adverse reaction occurred in 2% of patients who received DARZALEX SC-VRd. An adverse reaction which resulted in permanent discontinuation of DARZALEX SC-VRd in more than 1 patient included sepsis.

The most common adverse reactions (≥20%) were peripheral neuropathy, fatigue, edema, pyrexia, upper respiratory infection, constipation, diarrhea, musculoskeletal pain, insomnia, and rash.

Table 7 summarizes the adverse reactions in patients who received DARZALEX SC in PERSEUS.

Table 7: Adverse Reactions (≥10%) in Patients with Newly Diagnosed Multiple Myeloma Eligible for ASCT Who Received DARZALEX SC-VRd through the End of Consolidation in PERSEUS

	DARZALEX SC-VRd (N=351)		VRd (N=347)	
Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Nervous system disorders				
Peripheral neuropathy[a]	52	5	54	4
Paraesthesia	11	<1[#]	11	<1[#]
General disorders and administration site conditions				

Fatigue[b]	35	3[#]	37	5[#]
Edema[b]	22	1	21	1[#]
Pyrexia	21	2[#]	22	3[#]
Infections				
Upper respiratory tract infection[c]	32	1[#]	26	2[#]
Pneumonia[d]	14	9	10	6[@]
Gastrointestinal disorders				
Constipation	31	2[#]	30	2[#]
Diarrhea	23	3[#]	25	5[#]
Nausea	16	1[#]	12	1[#]
Abdominal pain[b]	11	0	12	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[b]	26	1[#]	23	1[#]
Muscle spasm	12	0	9	<1[#]
Psychiatric disorders				
Insomnia	26	2[#]	16	2[#]
Skin and subcutaneous tissue disorders				
Rash[b]	25	3[#]	31	5
Hepatobiliary disorders				
Hepatotoxicity[e]	16	6[#]	16	5
Respiratory, thoracic and mediastinal disorders				
Cough[b]	12	<1[#]	8	0

Key: VRd=bortezomib-lenalidomide-dexamethasone
[a] Peripheral neuropathy includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.
[b] Includes other related terms.
[c] Upper respiratory tract infection includes fungal pharyngitis, h1n1 influenza, influenza, influenza like illness, laryngitis, nasopharyngitis, oral candidiasis, oropharyngeal candidiasis, parainfluenzae virus infection, pharyngitis, respiratory moniliasis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, upper respiratory tract infection, viral tonsillitis, and viral upper respiratory tract infection.
[d] Pneumonia includes bronchopulmonary aspergillosis, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia influenzal, pneumonia klebsiella, pneumonia legionella, and pneumonia streptococcal.
[e] Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic cytolysis, hepatic failure, hepatic function abnormal, hepatoxicity, hyperbilirubinemia, hypertransaminasemia, and liver disorder
[#] Only Grade 3 adverse reactions occurred.
[@] Fatal adverse reactions included Pneumonia: n=1 (0.3%) in the VRd arm.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX SC with bortezomib, lenalidomide and dexamethasone include:

- **Gastrointestinal disorders:** vomiting, hemorrhoids
- **Musculoskeletal and connective tissue disorders:** arthralgia
- **Infections:** bronchitis, sepsis, urinary tract infection, herpes zoster, Covid-19, cytomegalovirus infection
- **Respiratory, thoracic, and mediastinal disorders:** dyspnea, pulmonary edema
- **Metabolism and nutrition disorders:** hypocalcemia, decreased appetite, hyperglycemia, dehydration
- **Vascular disorders:** hypotension, hypertension, orthostatic hypotension
- **General disorders and administration site conditions:** infusion reactions, injection site reaction, chills
- **Nervous system disorders:** dizziness, headache, syncope
- **Cardiac disorders:** thrombosis, atrial fibrillation, tachycardia
- **Skin and subcutaneous tissue disorders:** pruritus

Table 8 summarizes the laboratory abnormalities in patients who received DARZALEX SC in PERSEUS.

Table 8: Select Laboratory Abnormalities (≥30%) That Worsened from Baseline in Patients with Newly Diagnosed Multiple Myeloma Eligible for ASCT Who Received DARZALEX SC-VRd through the End of Consolidation in PERSEUS

	DARZALEX SC-VRd[a]		VRd[a]	
Laboratory Abnormality	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology				
Decreased platelets	89	34	78	25
Decreased lymphocytes	87	69	69	43

Decreased leukocytes	78	47	56	22
Decreased neutrophils	67	52	47	34
Decreased hemoglobin	39	7	43	6
Chemistry				
Increased alanine aminotransferase (ALT)	52	7	48	5
Decreased sodium	40	5	25	5
Increased alkaline phosphatase	39	0	36	1
Decreased potassium	30	6	24	3

Key: VRd=bortezomib-lenalidomide-dexamethasone

[a] Denominator is based on number of subjects with a baseline and post-baseline laboratory value for each laboratory test: N=351 for DARZALEX SC-VRd and N=346 for VRd.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

In Combination with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX SC with bortezomib, melphalan and prednisone was evaluated in a single-arm cohort of PLEIADES *[see Clinical Studies (5.1.3.1)]*. Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 6 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 39% of patients who received DARZALEX SC. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fatal adverse reactions occurred in 3% of patients.

Permanent discontinuation of DARZALEX SC due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX SC in more than 1 patient was neutropenic sepsis.

Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX SC. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia.

The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

Table 9 summarizes the adverse reactions in patients who received DARZALEX SC in PLEIADES.

Table 9: Adverse Reactions (≥10%) in Patients Who Received DARZALEX SC with Bortezomib, Melphalan and Prednisone (DARZALEX SC-VMP) in PLEIADES

Adverse Reaction	DARZALEX SC with Bortezomib, Melphalan and Prednisone (N=67)	
	All Grades (%)	Grades ≥3 (%)
Infections		
Upper respiratory tract infection[a]	39	0
Bronchitis	16	0
Pneumonia[b]	15	7[#]
Gastrointestinal disorders		
Constipation	37	0
Nausea	36	0
Diarrhea	33	3[#]
Vomiting	21	0
Abdominal pain[c]	13	0
General disorders and administration site conditions		
Fatigue[d]	36	3
Pyrexia	34	0
Edema peripheral[e]	13	1[#]
Nervous system disorders		
Peripheral sensory neuropathy	34	1[#]
Dizziness	10	0
Respiratory, thoracic and mediastinal disorders		
Cough[f]	24	0
Psychiatric disorders		
Insomnia	22	3[#]
Musculoskeletal and connective tissue disorders		
Back pain	21	3[#]

Musculoskeletal chest pain	12	0
Metabolism and nutrition disorders		
Decreased appetite	15	1[#]
Skin and subcutaneous tissue disorders		
Rash	13	0
Pruritus	12	0
Vascular disorders		
Hypertension	13	6[#]
Hypotension	10	3[#]

[a] Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.
[b] Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, pneumonia, and pneumonia bacterial.
[c] Abdominal pain includes abdominal pain, and abdominal pain upper.
[d] Fatigue includes asthenia, and fatigue.
[e] Edema peripheral includes edema, edema peripheral, and peripheral swelling.
[f] Cough includes cough, and productive cough.
[#] Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX SC with bortezomib, melphalan and prednisone included:

- **General disorders and administration site conditions:** infusion reaction, injection site reaction, chills
- **Infections:** herpes zoster, urinary tract infection, influenza, sepsis
- **Musculoskeletal and connective tissue disorders:** arthralgia, muscle spasms
- **Nervous system disorders:** headache, paresthesia
- **Metabolism and nutrition disorders:** hypocalcemia, hyperglycemia
- **Respiratory, thoracic and mediastinal disorders:** dyspnea, pulmonary edema
- **Cardiac disorders:** atrial fibrillation

Table 10 summarizes the laboratory abnormalities in patients who received DARZALEX SC in PLEIADES.

Table 10: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX SC with Bortezomib, Melphalan and Prednisone (DARZALEX SC-VMP) in PLEIADES

	DARZALEX SC with Bortezomib, Melphalan and Prednisone [a]	
Laboratory Abnormality	**All Grades (%)**	**Grades 3-4 (%)**
Decreased leukocytes	96	52
Decreased lymphocytes	93	84
Decreased platelets	93	42

Decreased neutrophils	88	49
Decreased hemoglobin	48	19

[a] Denominator is based on the safety population treated with DARZALEX SC-VMP (N=67).

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX SC with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADES *[see Clinical Studies (5.1.3.2)].* Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX SC. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX SC due to an adverse reaction occurred in 11% of patients who received DARZALEX SC. Adverse reactions resulting in permanent discontinuation of DARZALEX SC in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX SC. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 11 summarizes the adverse reactions in patients who received DARZALEX SC in PLEIADES.

Table 11: Adverse Reactions (≥10%) in Patients Who Received DARZALEX SC with Lenalidomide and Dexamethasone (DARZALEX SC-Rd) in PLEIADES

	DARZALEX SC with Lenalidomide and Dexamethasone (N=65)	
Adverse Reaction	**All Grades (%)**	**Grades ≥3 (%)**
General disorders and administration site conditions		
Fatigue[a]	52	5[#]
Pyrexia	23	2[#]
Edema peripheral	18	3[#]

Gastrointestinal disorders		
Diarrhea	45	5[#]
Constipation	26	2[#]
Nausea	12	0
Vomiting	11	0
Infections		
Upper respiratory tract infection[b]	43	3[#]
Pneumonia[c]	23	17
Bronchitis[d]	14	2[#]
Urinary tract infection	11	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	31	2[#]
Back pain	14	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[e]	22	3
Cough[f]	14	0
Nervous system disorders		
Peripheral sensory neuropathy	17	2[#]
Psychiatric disorders		
Insomnia	17	5[#]
Metabolism and nutrition disorders		
Hyperglycemia	12	9[#]
Hypocalcemia	11	0

[a] Fatigue includes asthenia, and fatigue.
[b] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
[c] Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
[d] Bronchitis includes bronchitis, and bronchitis viral.
[e] Dyspnea includes dyspnea, and dyspnea exertional.
[f] Cough includes cough, and productive cough.
[#] Only Grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX SC with lenalidomide and dexamethasone included:

- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain

- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** influenza, sepsis, herpes zoster
- **Metabolism and nutrition disorders:** decreased appetite
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** chills, infusion reaction, injection site reaction
- **Vascular disorders:** hypotension, hypertension

Table 12 summarizes the laboratory abnormalities in patients who received DARZALEX SC in PLEIADES.

Table 12: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX SC with Lenalidomide and Dexamethasone (DARZALEX SC-Rd) in PLEIADES

	DARZALEX SC with Lenalidomide and Dexamethasone[a]	
Laboratory Abnormality	**All Grades (%)**	**Grades 3-4 (%)**
Decreased leukocytes	94	34
Decreased lymphocytes	82	58
Decreased platelets	86	9
Decreased neutrophils	89	52
Decreased hemoglobin	45	8

[a] Denominator is based on the safety population treated with DARZALEX SC-Rd (N=65).

In Combination with Pomalidomide and Dexamethasone

The safety of DARZALEX SC with pomalidomide and dexamethasone compared to pomalidomide and dexamethasone (Pd) in patients who had received at least one prior line of therapy with lenalidomide and a proteasome inhibitor (PI) was evaluated in APOLLO *[see Clinical Studies (5.1.3.2)]*. Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity in combination with pomalidomide and dexamethasone (n=149) or pomalidomide and dexamethasone (n=150). Among patients receiving DARZALEX SC-Pd, 71% were exposed for 6 months or longer and 50% were exposed for greater than one year.

Serious adverse reactions occurred in 50% of patients who received DARZALEX SC-Pd. The most frequent serious adverse reactions in >5% of patients who received DARZALEX SC-Pd were pneumonia (15%) and lower respiratory tract infection (12%). Fatal adverse reactions occurred in 7% of patients who received DARZALEX SC-Pd.

Permanent treatment discontinuation due to an adverse reaction occurred in 2% of patients who received DARZALEX SC-Pd.

The most common adverse reactions (≥20%) were fatigue, pneumonia, upper respiratory tract infection, and diarrhea.

Table 13 summarizes the adverse reactions in patients who received DARZALEX SC in APOLLO.

Table 13: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DARZALEX SC-Pd Arm in APOLLO

	DARZALEX SC-Pd (N=149)		Pd (N=150)	
Adverse Reaction	**All Grades (%)**	**Grades ≥3 (%)**	**All Grades (%)**	**Grades ≥3 (%)**
General disorders and administration site conditions				
Fatigue[a]	46	13	39	5[#]
Pyrexia	19	0	14	0
Edema peripheral[b]	15	0	9	0
Infections				
Pneumonia[c]	38	23[@]	27	17[@]
Upper respiratory infection[d]	36	1[#]	22	2[#]
Gastrointestinal disorders				
Diarrhea	22	5[#]	14	1[#]
Respiratory, thoracic and mediastinal disorders				
Cough[e]	13	0	8	0

Key: Pd=pomalidomide-dexamethasone

[a] Fatigue includes asthenia, and fatigue.

[b] Edema peripheral includes edema, edema peripheral and peripheral swelling.

[c] Pneumonia includes atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia respiratory syncytial viral.

[d] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection.

[e] Cough includes cough, and productive cough.

[#] Only Grade 3 adverse reactions occurred.

[@] Grade 5 adverse reactions occurred, n=3 (2.0%) in the DARZALEX SC-Pd arm and n=2 (1.3%) in the Pd arm.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX SC with pomalidomide and dexamethasone include:

- **Metabolism and nutrition disorders:** hypocalcemia, hypokalemia, decreased appetite, dehydration
- **Nervous system disorders:** peripheral sensory neuropathy, syncope, headache, paresthesia, dizziness

- **Musculoskeletal and connective tissue disorders:** muscle spasms, musculoskeletal chest pain, arthralgia
- **Psychiatric disorders:** insomnia
- **Gastrointestinal disorders:** nausea, abdominal pain, vomiting
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** infusion reactions, chills, injection site reaction
- **Infections:** urinary tract infection, influenza, hepatitis B reactivation, herpes zoster, sepsis
- **Vascular disorders:** hypertension, hypotension

Table 14 summarizes the laboratory abnormalities in patients who received DARZALEX SC in APOLLO.

Table 14: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX SC-Pd or Pd in APOLLO

	DARZALEX SC-Pd[a]		Pd[a]	
Laboratory Abnormality	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Decreased neutrophils	97	84	84	63
Decreased leukocytes	95	64	82	40
Decreased lymphocytes	93	59	79	33
Decreased platelets	75	19	60	19
Decreased hemoglobin	51	16	57	15

Key: Pd=pomalidomide-dexamethasone

[a] Denominator is based on number of subjects with a baseline and post-baseline laboratory value for each laboratory test: N=148 for DARZALEX SC-Pd and N=149 for Pd.

In Combination with Carfilzomib and Dexamethasone

The safety of DARZALEX SC with carfilzomib and dexamethasone was evaluated in a single-arm cohort of PLEIADES *[see Clinical Studies (5.1.3.2)].* Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from Weeks 1 to 8, once every 2 weeks from Weeks 9 to 24 and once every 4 weeks starting with Week 25 until disease progression or unacceptable toxicity (N=66) in combination with carfilzomib and dexamethasone. Among these patients, 77% were exposed for 6 months or longer and 27% were exposed for greater than one year.

Serious adverse reactions occurred in 27% of patients who received DARZALEX SC in combination with carfilzomib and dexamethasone. Fatal adverse reactions occurred in 3% of patients who received DARZALEX SC in combination with carfilzomib and dexamethasone.

Permanent discontinuation of DARZALEX SC due to an adverse reaction occurred in 6% of patients who received DARZALEX SC.

Dosage interruptions due to an adverse reaction occurred in 46% of patients who received DARZALEX SC.

The most common adverse reactions (≥20%) were upper respiratory tract infection, fatigue, insomnia, hypertension, diarrhea, cough, dyspnea, headache, pyrexia, nausea and edema peripheral.

Table 15 summarizes the adverse reactions in patients who received DARZALEX SC with carfilzomib and dexamethasone (DARZALEX SC-Kd) in PLEIADES.

Table 15: Adverse Reactions (≥10%) in Patients Who Received DARZALEX SC with Carfilzomib and Dexamethasone (DARZALEX SC-Kd) in PLEIADES

	DARZALEX SC-Kd (N=66)	
Adverse Reaction	**All Grades (%)**	**Grade ≥3 (%)**
Infections and infestations		
Upper respiratory tract infection[a]	52	0
Bronchitis[b]	12	2[#]
General disorders and administration site conditions		
Fatigue[c]	39	2[#]
Pyrexia	21	2[#]
Edema peripheral[d]	20	0
Psychiatric disorders		
Insomnia	33	6[#]
Vascular disorders		
Hypertension[e]	32	21[#]
Gastrointestinal disorders		
Diarrhea	29	0
Nausea	21	0
Vomiting	15	0

Respiratory, thoracic and mediastinal disorders		
Cough[f]	24	0
Dyspnea[g]	23	2[#]
Nervous system disorders		
Headache	23	0
Peripheral sensory neuropathy	11	0
Musculoskeletal and connective tissue disorders		
Back pain	17	2[#]
Musculoskeletal chest pain	11	0

[a] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, viral pharyngitis, and viral upper respiratory tract infection.
[b] Bronchitis includes bronchitis, and bronchitis viral.
[c] Fatigue includes asthenia, and fatigue.
[d] Edema peripheral includes generalized edema, edema peripheral, and peripheral swelling.
[e] Hypertension includes blood pressure increased, and hypertension.
[f] Cough includes cough, and productive cough.
[g] Dyspnea includes dyspnea, and dyspnea exertional.
[#] Only Grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX SC with carfilzomib and dexamethasone include:

- **Gastrointestinal disorders:** abdominal pain, constipation, pancreatitis
- **Infection and infestations:** pneumonia, influenza, urinary tract infection, herpes zoster, sepsis
- **Metabolism and nutrition disorders:** hyperglycemia, decreased appetite, hypocalcemia
- **Musculoskeletal and connective tissue disorders:** muscle spasms, arthralgia
- **Nervous system disorders:** paresthesia, dizziness, syncope
- **General disorders and administration site conditions:** injection site reaction, infusion reactions, chills
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Cardiac disorders:** cardiac failure
- **Vascular disorders:** hypotension

Table 16 summarizes the laboratory abnormalities in patients who received DARZALEX SC with carfilzomib and dexamethasone in PLEIADES.

Table 16: Select Laboratory Abnormalities (≥30%) Worsening from Baseline in Patients Who Received DARZALEX SC-Kd in PLEIADES

	DARZALEX SC-Kd[a]	
Laboratory Abnormality	**All Grades (%)**	**Grades 3-4 (%)**
Decreased platelets	88	18
Decreased lymphocytes	83	50

Decreased leukocytes	68	18
Decreased neutrophils	55	15
Decreased hemoglobin	47	6
Decreased corrected calcium	45	2
Increased alanine aminotransferase (ALT)	35	5

[a] Denominator is based on the safety population treated with DARZALEX SC-Kd (N=66).

Monotherapy

The safety of DARZALEX SC as monotherapy was evaluated in COLUMBA *[see Clinical Trials (5.1.3.2)].* Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX SC, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX SC. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX SC. Adverse reactions resulting in permanent discontinuation of DARZALEX SC in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX SC. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

The most common adverse reaction (≥20%) was upper respiratory tract infection.

Table 17 summarizes the adverse reactions in COLUMBA.

Table 17: Adverse Reactions (≥10%) in Patients Who Received DARZALEX SC or Intravenous Daratumumab in COLUMBA

	DARZALEX SC (N=260)		**Intravenous Daratumumab (N=258)**	
Adverse Reaction	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Infections				
Upper respiratory tract infection[a]	24	1[#]	22	1[#]
Pneumonia[b]	8	5	10	6[@]
Gastrointestinal disorders				

Table 17: Adverse Reactions (≥10%) in Patients Who Received DARZALEX SC or Intravenous Daratumumab in COLUMBA

Adverse Reaction	DARZALEX SC (N=260)		Intravenous Daratumumab (N=258)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Diarrhea	15	1#	11	0.4#
Nausea	8	0.4#	11	0.4#
General disorders and administration site conditions				
Fatigue[c]	15	1#	16	2#
Infusion reactions[d]	13	2#	34	5#
Pyrexia	13	0	13	1#
Chills	6	0.4#	12	1#
Musculoskeletal and connective tissue disorders				
Back pain	10	2#	12	3#
Respiratory, thoracic and mediastinal disorders				
Cough[e]	9	1#	14	0
Dyspnea[f]	6	1#	11	1#

[a] Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, and upper respiratory tract infection.
[b] Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, and pneumonia.
[c] Fatigue includes asthenia, and fatigue.
[d] Infusion reactions includes terms determined by investigators to be related to infusion.
[e] Cough includes cough, and productive cough.
[f] Dyspnea includes dyspnea, and dyspnea exertional.
[#] Only Grade 3 adverse reactions occurred.
[@] Grade 5 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX SC included:

- **General disorders and administration site conditions:** injection site reaction, peripheral edema
- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain, muscle spasms
- **Gastrointestinal disorders:** constipation, vomiting, abdominal pain
- **Metabolism and nutrition disorders:** decreased appetite, hyperglycemia, hypocalcemia, dehydration
- **Psychiatric disorders:** insomnia
- **Vascular disorders:** hypertension, hypotension

- **Nervous system disorders:** dizziness, peripheral sensory neuropathy, paresthesia
- **Infections:** bronchitis, influenza, urinary tract infection, herpes zoster, sepsis, hepatitis B virus reactivation
- **Skin and subcutaneous tissue disorders:** pruritus, rash
- **Cardiac disorders:** atrial fibrillation
- **Respiratory, thoracic and mediastinal disorders:** pulmonary edema

Table 18 summarizes the laboratory abnormalities in COLUMBA.

Table 18: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Receiving DARZALEX SC or Intravenous Daratumumab in COLUMBA

Laboratory Abnormality	DARZALEX SC[a]		Intravenous Daratumumab[a]	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	65	19	57	14
Decreased lymphocytes	59	36	56	36
Decreased neutrophils	55	19	43	11
Decreased platelets	43	16	45	14
Decreased hemoglobin	42	14	39	16

[a] Denominator is based on the safety population treated with DARZALEX SC (N=260) and Intravenous Daratumumab (N=258).

Light Chain Amyloidosis

In Combination with Bortezomib, Cyclophosphamide and Dexamethasone

The safety of DARZALEX SC with bortezomib, cyclophosphamide and dexamethasone (DARZALEX SC-VCd) was evaluated in ANDROMEDA *[see Clinical Studies (5.1.3.3)]*. Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity or a maximum of 2 years. Among patients who received DARZALEX SC-VCd, 74% were exposed for 6 months or longer and 32% were exposed for greater than one year.

Serious adverse reactions occurred in 43% of patients who received DARZALEX SC in combination with VCd. Serious adverse reactions that occurred in at least 5% of patients in the DARZALEX SC-VCd arm were pneumonia (9%), cardiac failure (8%), and sepsis (5%). Fatal adverse reactions occurred in 11% of patients. Fatal adverse reactions that occurred in more than one patient included cardiac arrest (4%), sudden death (3%), cardiac failure (3%), and sepsis (1%).

Permanent discontinuation of DARZALEX SC due to an adverse reaction occurred in 5% of patients. Adverse reactions resulting in permanent discontinuation of DARZALEX SC in more than one patient were pneumonia, sepsis, and cardiac failure.

Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 36% of patients who received DARZALEX SC. Adverse reactions which required a dosage interruption in ≥3% of patients included upper respiratory tract infection (9%),

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

The most common adverse reactions (≥20%) were upper respiratory tract infection, diarrhea, peripheral edema, constipation, fatigue, peripheral sensory neuropathy, nausea, insomnia, dyspnea, and cough.

Table 19 below summarizes the adverse reactions in patients who received DARZALEX SC in ANDROMEDA.

Table 19: Adverse Reactions (≥10%) in Patients with AL Amyloidosis Who Received DARZALEX SC with Bortezomib, Cyclophosphamide and Dexamethasone (DARZALEX SC-VCd) with a Difference Between Arms of >5% Compared to VCd in ANDROMEDA

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

[#] Only Grade 3 adverse reactions occurred.

[a] Upper respiratory tract infection includes laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection, upper respiratory tract infection bacterial, and viral upper respiratory tract infection.
[b] Pneumonia includes lower respiratory tract infection, pneumonia, pneumonia aspiration, and pneumonia pneumococcal.
[c] Dyspnea includes dyspnea, and dyspnea exertional.
[d] Cough includes cough, and productive cough.
[e] Arrhythmia includes atrial flutter, atrial fibrillation, supraventricular tachycardia, bradycardia, arrhythmia, bradyarrhythmia, cardiac flutter, extrasystoles, supraventricular extrasystoles, ventricular arrhythmia, ventricular extrasystoles, atrial tachycardia, ventricular tachycardia
[f] Injection site reactions includes terms determined by investigators to be related to daratumumab injection.

Clinically relevant adverse reactions not included in Table 19 and occurred in patients who received DARZALEX SC with bortezomib, cyclophosphamide and dexamethasone included:

- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Nervous system disorders:** paresthesia
- **General disorders and administration site conditions:** infusion reaction, chills
- **Cardiac disorders:** cardiac failure[a], cardiac arrest
- **Metabolism and nutrition disorders:** hyperglycemia, hypocalcemia, dehydration
- **Infections:** bronchitis, herpes zoster, sepsis, urinary tract infection, influenza
- **Vascular disorders:** hypertension
- **Musculoskeletal and connective tissue disorders:** musculoskeletal chest pain
- **Gastrointestinal disorders:** pancreatitis
- **Respiratory, thoracic and mediastinal disorders:** pulmonary edema

[a] Cardiac failure includes cardiac dysfunction, cardiac failure, cardiac failure congestive, cardiovascular insufficiency, diastolic dysfunction, pulmonary edema, and left ventricular dysfunction occurred in 11% of patients.

Table 20 summarizes the laboratory abnormalities in patients who received DARZALEX SC in ANDROMEDA.

Table 20: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX SC with Bortezomib, Cyclophosphamide and Dexamethasone (DARZALEX SC-VCd) in ANDROMEDA

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

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

Cardiac Adverse Reactions in Light Chain (AL) Amyloidosis
Among patients who received DARZALEX SC in combination with VCd, 72% of patients had baseline cardiac involvement with Mayo Cardiac Stage I (3%), Stage II (46%) and Stage III (51%). Serious cardiac disorders occurred in 16% of patients (8% of patients with Mayo Cardiac Stage I and II and 28% of patients with Stage III). Serious cardiac disorders in >2% of patients included cardiac failure (8%), cardiac arrest (4%) and arrhythmia (4%). Fatal cardiac disorders occurred in 10% of patients (5% of patients with Mayo Cardiac Stage I and II and 19% of patients with Stage III) who received DARZALEX SC in combination with VCd. Fatal cardiac disorders that occurred in more than one patient in the DARZALEX SC-VCd arm included cardiac arrest (4%), sudden death (3%), and cardiac failure (3%).

4.8.2 Postmarketing Experience

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

Immune System: Anaphylactic reaction, Systemic administration reactions (including death)

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

4.9 Overdose

No information in USPI.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

5.1.1 Mechanism of Action

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

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately

0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. In the doses administered, hyaluronidase in DARZALEX SC acts locally. The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

5.1.2 Pharmacodynamic Properties

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 SC treatment.

Cardiac Electrophysiology

DARZALEX SC 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 SC has the potential to delay ventricular repolarization.

Exposure-Response Relationship

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

5.1.3 Clinical Studies

5.1.3.1 Newly Diagnosed Multiple Myeloma

In Combination with Bortezomib, Lenalidomide and Dexamethasone in Patients Eligible for Autologous Stem Cell Transplant

The efficacy of DARZALEX SC with bortezomib, lenalidomide and dexamethasone (DARZALEX SC-VRd) during induction and consolidation was evaluated in PERSEUS (NCT03710603), an open-label, randomized, active-controlled trial in patients with newly diagnosed multiple myeloma eligible for ASCT. Enrollment was limited to patients 70 years of age and younger.

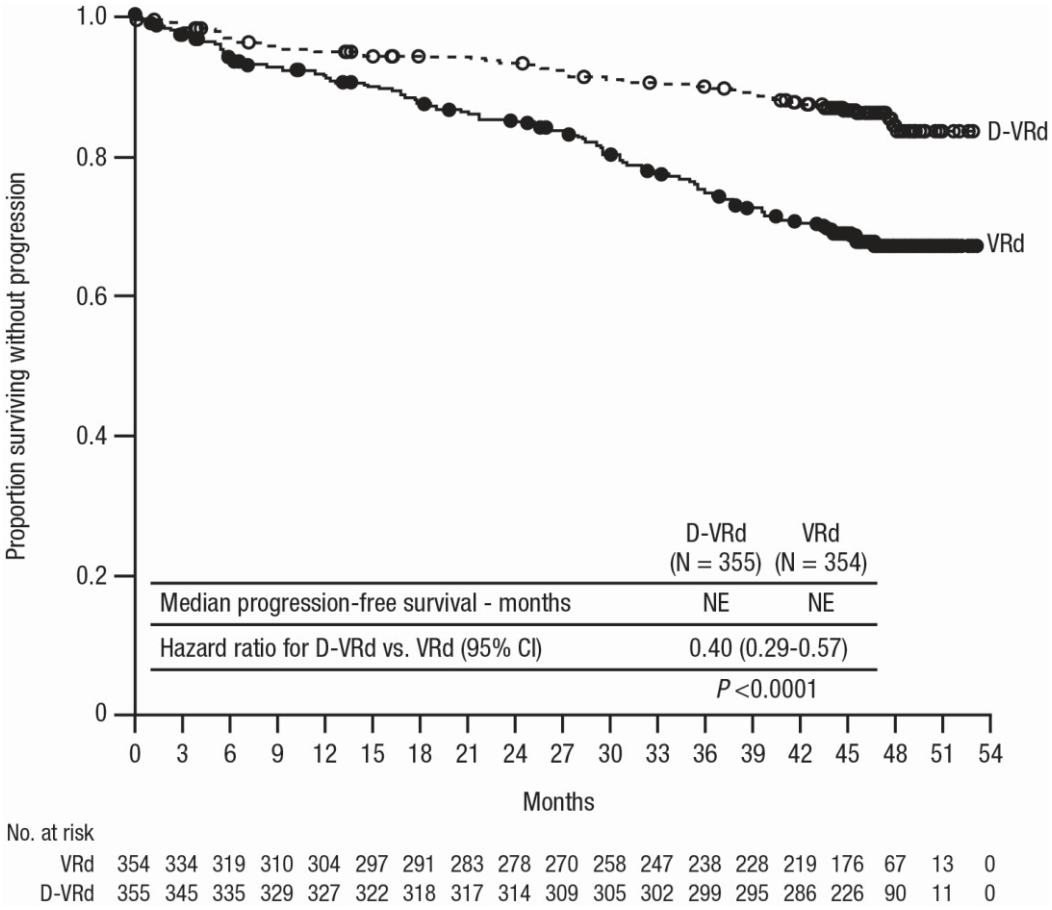
Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8 and once every 2 weeks from weeks 9 to 16 during induction. After week 16, patients underwent stem cell mobilization, high dose chemotherapy, and ASCT. Within 12 weeks of ASCT, and when engraftment was complete, patients received DARZALEX SC once every 2 weeks from weeks 1 to 8 during consolidation. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m2 body surface area twice weekly for two weeks (days 1, 4, 8, and 11) of each 28-day cycle for weeks 1-16 during induction and weeks 1-8 during consolidation. Lenalidomide was administered orally at 25 mg daily (days 1-21) during weeks 1-16 during induction and weeks 1-8 during consolidation. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1-4 and Days 9-12 during weeks 1-16 during induction and weeks 1-8 during consolidation. On the days of DARZALEX SC injection, the dexamethasone dose was administered orally or intravenously as a pre-injection medication. Following consolidation, patients received an investigational treatment regimen for maintenance that included DARZALEX SC in combination with lenalidomide or lenalidomide alone. The trial was not designed to isolate the effect of DARZALEX SC in the maintenance phase of treatment. The efficacy of DARZALEX SC in combination with lenalidomide for maintenance has not been established.

The major efficacy outcome measure was progression-free survival (PFS) by independent review committee (IRC) based on IMWG response criteria.

A total of 709 patients were randomized: 355 to the DARZALEX SC-VRd arm and 354 to the VRd arm. The median age was 60 years (range: 31 to 70); 59% were male, 92% were White, 1% were Black or African American, and 1% were Asian. Fifty-one percent had ISS Stage I, 34% had ISS Stage II, 15% had ISS Stage III disease. High-risk cytogenetics (presence of del(17p), t(4;14), t(14,16)) were present in 22% of patients.

PERSEUS demonstrated an improvement in PFS in the DARZALEX SC-VRd arm as compared to the VRd arm; the median PFS had not been reached in either arm. Treatment with DARZALEX SC-VRd resulted in a reduction in the risk of disease progression or death by 60% compared to VRd alone (HR [95% CI]: 0.40 [0.29, 0.57]; p value < 0.0001).

Figure 1: Kaplan-Meier Curve of PFS in PERSEUS



Additional efficacy results from PERSEUS are presented in Table 21.

Table 21: Efficacy Results through End of Consolidation from PERSEUS

	DARZALEX SC-VRd (n=355)	**VRd (n=354)**

Overall response (sCR+CR+VGPR+PR), n (%)[a]	338 (95.2%)	326 (92.1%)
Stringent complete response (sCR)	67 (18.9%)	46 (13.0%)
Complete response (CR)	91 (25.6%)	77 (21.8%)
Very good partial response (VGPR)	165 (46.5%)	168 (47.5%)
Partial response (PR)	15 (4.2%)	35 (9.9%)
CR or better (sCR+CR)[a], n (%)	158 (44.5%)	123 (34.7%)
95% CI (%)[b]	(39.3%, 49.9%)	(29.8%, 40.0%)
MRD negativity rate[a,c,d], n (%)	204 (57.5%)	115 (32.5%)
95% CI (%)[b]	(52.1%, 62.7%)	(27.6%, 37.6%)
MRD negativity rate in patients with CR or better[c,e]		
Number of patients with CR or better	n=158	n=123
MRD negativity rate n (%)	121 (76.6%)	72 (58.5%)
95% CI (%)[b]	(69.2%, 82.9%)	(49.3%, 67.3%)

VRd = bortezomib-lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval
a Based on intent-to-treat population
b Exact 95% confidence interval
c Based on threshold of 10-5 using a next-generation sequencing assay (clonoSEQ)
d Patients achieved both MRD negativity (threshold of 10-5) and response of CR or better
e Based on patients with CR or better response by the end of consolidation

<u>In Combination with Bortezomib, Melphalan and Prednisone in Patients Ineligible for Autologous Stem Cell Transplant</u>

The efficacy of DARZALEX SC with bortezomib, melphalan and prednisone was evaluated in a single-arm cohort of PLEIADES (NCT03412565), a multi-cohort, open-label trial. Eligible patients were required to have newly diagnosed multiple myeloma who are ineligible for transplant. Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity; bortezomib 1.3 mg/m^2 subcutaneously twice weekly on Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly on Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle); and melphalan 9 mg/m^2 and prednisone 60 mg/m^2 orally on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). The major efficacy outcome measure was overall response rate (ORR).

A total of 67 patients received DARZALEX SC with VMP. The median age was 75 years (range: 66 to 86 years); 46% were male; 69% were White, 8% Asian, and 2% Black or African American; and 33% had ISS Stage I, 45% had ISS Stage II, and 22% had ISS Stage III disease.

Efficacy results are summarized in Table 22. The median duration of follow-up for patients was 6.9 months.

Table 22: Efficacy Results from PLEIADES in Patients Who Received DARZALEX SC-VMP

	DARZALEX SC-VMP (N=67)
Overall response rate (sCR+CR+VGPR+PR), n (%)[a]	59 (88%)
95% CI (%)	(78%, 95%)
Stringent complete response (sCR)	5 (8%)
Complete response (CR)	7 (10%)
Very good partial response (VGPR)	31 (46%)
Partial response (PR)	16 (24%)

CI=confidence interval
[a] Based on treated patients

5.1.3.2 Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The efficacy of DARZALEX SC with lenalidomide and dexamethasone (DARZALEX SC-Rd) was evaluated in a single-arm cohort of PLEIADES (NCT03412565), a multi-cohort, open-label trial. Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity with lenalidomide 25 mg once daily orally on Days 1-21 of each 28-day cycle; and dexamethasone 40 mg per week (or a reduced dose of 20 mg per week for patients >75 years or BMI <18.5). The major efficacy outcome measure was ORR.

A total of 65 patients received DARZALEX SC with Rd. The median age was 69 years (range: 33 to 82 years); 69% were male; 69% were White, and 3% Black or African American; and 42% had ISS Stage I, 30% had ISS Stage II, and 28% had ISS Stage III disease. Patients had received a median of 1 prior line of therapy. A total of 52% of patients had a prior ASCT; 95% of patients received a prior PI; 59% received a prior immunomodulatory agent, including 22% who received prior lenalidomide; and 54% of patients received both a prior PI and immunomodulatory agent.

Efficacy results are summarized in Table 23. The median duration of follow-up for patients was 7.1 months.

Table 23: Efficacy Results from PLEIADES in Patients Who Received DARZALEX SC-Rd

	DARZALEX SC-Rd (N=65)
Overall response rate (sCR+CR+VGPR+PR), n (%)[a]	59 (91%)
95% CI (%)	(81%, 97%)
Stringent complete response (sCR)	4 (6%)
Complete response (CR)	8 (12%)
Very good partial response (VGPR)	30 (46%)
Partial response (PR)	17 (26%)

CI=confidence interval
[a] Based on treated patients

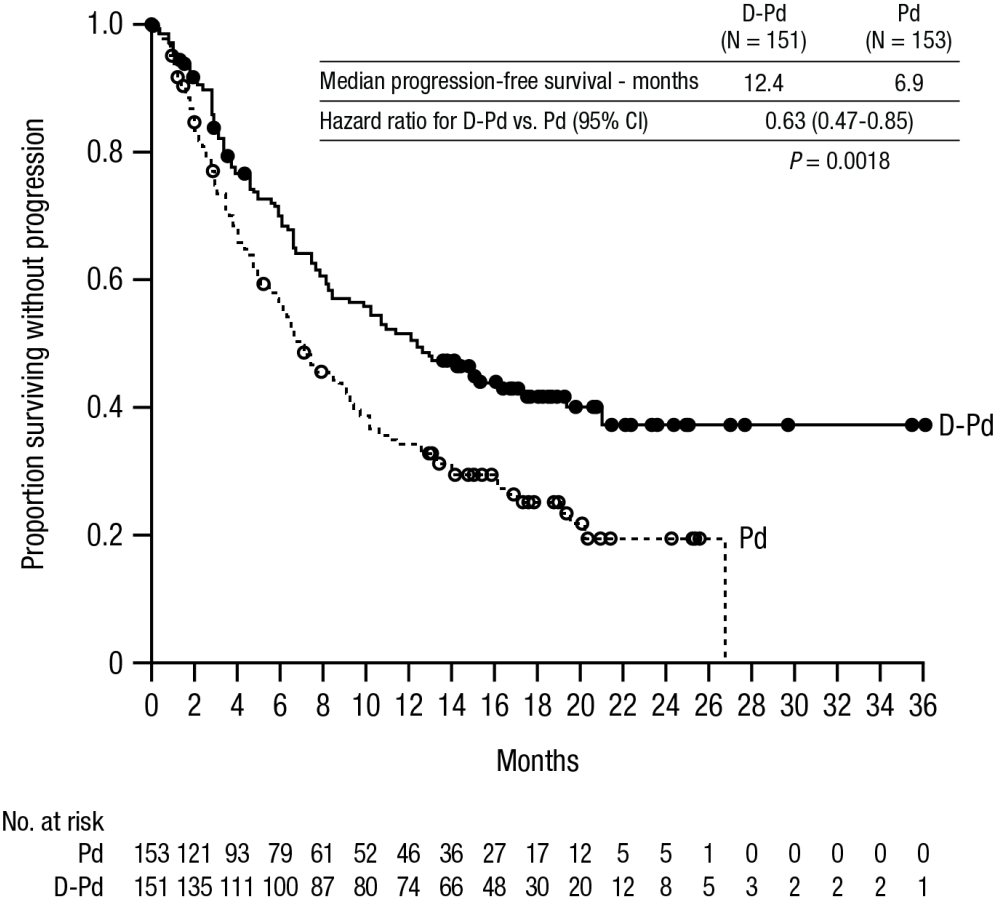
In Combination with Pomalidomide and Dexamethasone

The efficacy of DARZALEX SC with pomalidomide and dexamethasone (DARZALEX SC-Pd) versus pomalidomide and dexamethasone (Pd) alone was evaluated in APOLLO (NCT03180736), an open-label, randomized, active-controlled trial. Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity with pomalidomide 4 mg once daily orally on Days 1-21 of each 28-day cycle; and dexamethasone 40 mg per week (or a reduced dose of 20 mg per week for patients >75 years). The major efficacy outcome measure was progression-free survival (PFS).

A total of 304 patients were randomized: 151 to the DARZALEX SC-Pd arm and 153 to the Pd arm. The median age was 67 years (range: 35 to 90); 53% were male and 89% were White, <1% were Black or African American, and <1% were Asian, and 45% had ISS Stage I, 33% had ISS Stage II, and 22% had ISS Stage III disease. Patients had received a median of 2 prior lines of therapy (range 1-5), with 11% of patients having received 1 prior line of therapy and 75% of patients having received 2-3 prior lines of therapy. All patients received a prior treatment with a PI and lenalidomide, and 56% of patients received prior ASCT. The majority of patients were refractory to lenalidomide (80%), a PI (48%), or both an immunomodulatory agent and a PI (42%).

APOLLO demonstrated an improvement in PFS in the DARZALEX SC-Pd treatment group as compared to the Pd treatment group; the median PFS was 12.4 months in the DARZALEX SC-Pd treatment group and 6.9 months in the Pd treatment group (HR [95% CI]: 0.63 [0.47, 0.85]; p-value = 0.0018), representing a 37% reduction in the risk of disease progression or death for patients treated with DARZALEX SC-Pd versus Pd.

Figure 2: Kaplan-Meier Curve of PFS in APOLLO



Additional efficacy results from APOLLO are presented in Table 24.

Table 24: Efficacy results from APOLLO[a]

	DARZALEX SC-Pd (n=151)	**Pd (n=153)**
Overall response (sCR+CR+VGPR+PR) n (%)[a]	104 (68.9%)	71 (46.4%)
P-value[b]	<0.0001	
Stringent complete response (sCR)	14 (9.3%)	2 (1.3%)
Complete response (CR)	23 (15.2%)	4 (2.6%)
Very good partial response (VGPR)	40 (26.5%)	24 (15.7%)
Partial response (PR)	27 (17.9%)	41 (26.8%)
MRD negativity rate[c, e] n (%)	13 (8.6%)	3 (2.0%)
95% CI (%)	(4.7%, 14.3%)	(0.4%, 5.6%)
P-value[d]	0.0102	

MRD negativity rate in patients with CR or better[e]		
Number of patients with CR or better	**N=37**	**N=6**
MRD negativity rate n (%)	13 (35.1%)	3 (50.0%)
95% CI (%)	(20.2%, 52.5%)	(11.8%, 88.2%)

Pd=pomalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval
[a] Based on intent-to-treat population
[b] p-value from Cochran Mantel-Haenszel Chi-Squared test adjusted for stratification factors
[c] Based on the intent-to-treat population
[d] p-value from Fisher's exact test.
[e] Based on threshold of 10^{-5} using a next-generation sequencing assay (clonoSEQ).

In responders, the median time to response was 1 month (range: 0.9 to 9.1 months) in the DARZALEX SC-Pd group and 1.9 months (range: 0.9 to 17.3 months) in the Pd group. The median duration of response had not been reached in the DARZALEX SC-Pd group (range: 1 to 34.9+ months) and was 15.9 months (range: 1+ to 24.8 months) in the Pd group.

With a median follow-up of 16.9 months, 99 deaths were observed; 48 in the DARZALEX SC-Pd group and 51 in the Pd group. Median OS was not reached for either treatment group.

In Combination with Carfilzomib and Dexamethasone

The efficacy of DARZALEX SC with carfilzomib and dexamethasone (DARZALEX SC-Kd) was evaluated in a single-arm cohort of PLEIADES (NCT03412565), a multi-cohort, open-label trial. This cohort enrolled patients with relapsed or refractory multiple myeloma excluding patients with left ventricular ejection fraction (LVEF) less than 40%, myocardial infarction within 6 months, uncontrolled cardiac arrhythmia, or uncontrolled hypertension (systolic blood pressure >159 mmHg or diastolic >99 mmHg despite optimal treatment). Patients received DARZALEX SC 1,800 mg/30,000 units administered subcutaneously once weekly from Weeks 1 to 8, once every 2 weeks from Weeks 9 to 24 and once every 4 weeks starting with Week 25 until disease progression or unacceptable toxicity with carfilzomib administered by IV infusion at a dose of 20 mg/m^2 on Cycle 1 Day 1 and if a dose of 20 mg/m^2 was tolerated, carfilzomib was administered at a dose of 70 mg/m^2 as a 30-minute IV infusion, on Cycle 1 Day 8 and Day 15, and then Day 1, 8 and 15 of each cycle and dexamethasone 40 mg per week (or a reduced dose of 20 mg per week for patients ≥75 years or BMI <18.5). The major efficacy outcome measure was ORR.

A total of 66 patients received DARZALEX SC with Kd. The median age was 61 years (range: 42 to 84); 52% were male; 73% were White and 3% Black or African American; and 68% had ISS Stage I, 18% had ISS Stage II, and 14% had ISS Stage III disease. A total of 79% of patients had a prior ASCT; 91% of patients received a prior PI. All patients received 1 prior line of therapy with exposure to lenalidomide and 62% of patients were refractory to lenalidomide.

Efficacy results are summarized in Table 25. At a median follow-up of 9.2 months, the median duration of response had not been reached and an estimated 85.2% (95% CI: 72.5, 92.3) maintained response for at least 6 months and 82.5% (95% CI: 68.9, 90.6) maintained response for at least 9 months.

Table 25: Efficacy Results from PLEIADES in Patients Who Received DARZALEX SC-Kd

	DARZALEX SC-Kd (N=66)
Overall response rate (sCR+CR+VGPR+PR), n (%)[a]	56 (84.8%)
95% CI (%)	(73.9%, 92.5%)
Stringent complete response (sCR)	11 (16.7%)
Complete response (CR)	14 (21.2%)
Very good partial response (VGPR)	26 (39.4%)
Partial response (PR)	5 (7.6%)

CI=confidence interval

[a] Based on treated patients

Monotherapy

The efficacy of DARZALEX SC as monotherapy was evaluated in COLUMBA (NCT03277105), an open-label, randomized, non-inferiority study. Eligible patients were required to have 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. Patients were randomized to receive DARZALEX SC 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until unacceptable toxicity or disease progression. The major efficacy outcome measures were ORR by the IMWG response criteria and maximum C_{trough} at pre-dose Cycle 3 Day 1 *[see Pharmacokinetic Properties (5.2)]*. Randomization was stratified by body weight, myeloma type, and number of prior lines of therapy.

A total of 522 patients were randomized: 263 to the DARZALEX SC arm and 259 to the intravenous daratumumab arm. The median age was 67 years (range: 33 to 92 years); 55% were male; and 78% were White, 14% Asian, and 3% Black or African American. The median weight was 73 kg (range: 29 to 138). Patients had received a median of 4 prior lines of therapy. A total of 51% of patients had a prior ASCT; 100% of patients received both a PI and an immunomodulatory agent. Forty-nine percent of patients were refractory both a PI and an immunomodulatory agent. Eighty-two percent of patients were refractory to their last line of prior systemic therapy.

The results show that DARZALEX SC 1,800 mg/30,000 units administered subcutaneously is non-inferior to daratumumab 16 mg/kg administered intravenously in terms of ORR and maximum trough concentration *[see Pharmacokinetic Properties (5.2)]*. Median progression-free survival was 5.6 months in the DARZALEX SC arm and 6.1 months in the intravenous daratumumab arm. ORR results are provided in Table 26.

Table 26: Efficacy Results from COLUMBA

	DARZALEX SC (N=263)	Intravenous Daratumumab (N=259)
Overall response (sCR+CR+VGPR+PR), n (%)[a]	108 (41%)	96 (37%)
95% CI (%)	(35%, 47%)	(31%, 43%)
Ratio of response rates (95% CI)[b]		1.11 (0.89, 1.37)
CR or better, n (%)	5 (1.9%)	7 (2.7%)
Very good partial response (VGPR)	45 (17%)	37 (14%)
Partial response (PR)	58 (22%)	52 (20%)

[a] Based on intent-to-treat population.

5.1.3.3 Light Chain Amyloidosis

In Combination with Bortezomib, Cyclophosphamide and Dexamethasone

The efficacy of DARZALEX SC with VCd was evaluated in ANDROMEDA (NCT03201965), an open-label, randomized, active-controlled trial. Eligible patients were required to have newly diagnosed light chain (AL) amyloidosis with at least one affected organ, measurable hematologic disease, Cardiac Stage I-IIIA (based on European Modification of Mayo 2004 Cardiac Stage), and NYHA Class I-IIIA. Patients with NYHA Class IIIB and IV were excluded. Patients were randomized to receive bortezomib 1.3 mg/m^2 administered subcutaneously, cyclophosphamide 300 mg/m^2 (max dose 500 mg) administered orally or intravenously, and dexamethasone 40 mg (or a reduced dose of 20 mg for patients >70 years or body mass index <18.5 or who have hypervolemia, poorly controlled diabetes mellitus or prior intolerance to steroid therapy) administered orally or intravenously on Days 1, 8, 15, and 22 of each 28-day cycle with or without DARZALEX SC 1,800 mg/30,000 units subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or a maximum of two years. When DARZALEX SC and dexamethasone were administered on the same day, dexamethasone 20 mg was administered before DARZALEX SC with the remaining dose of dexamethasone administered after DARZALEX SC if applicable. The major efficacy outcome measure was confirmed hematologic complete response (HemCR) rate based on Consensus Criteria as determined by the Independent Review Committee (negative serum and urine immunofixation, involved free light chain level decrease to less than the upper limit of normal, and normal free light chain ratio). Randomization was stratified by Cardiac Stage (European Modification of Mayo 2004 Cardiac Stage) countries that typically offer autologous stem cell transplant (ASCT) for patients with light chain (AL) amyloidosis, and renal function.

A total of 388 patients were randomized: 195 to DARZALEX SC-VCd and 193 to VCd. The median patient age was 64 years (range: 34 to 87 years); 58% were male; 76% White, 17% Asian, and 3% Black or African American; 23% had light chain (AL) amyloidosis Cardiac Stage I, 40% had Stage II, and 37% had Stage IIIA. The median number of organs involved was 2 (range: 1-6) and 66% of patients had 2 or more organs involved. Vital organ involvement was: cardiac 71%, renal 59% and hepatic 8%. The majority (79%) of patients had lambda free light chain disease.

Efficacy results are summarized in Table 27.

Table 27: Efficacy results from ANDROMEDA[a]

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

VCd=bortezomib-cyclophosphamide-dexamethasone
[a] Based on intent-to-treat population
[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.
[c] Major organ deterioration-PFS defined as hematologic progression, major organ (cardiac or renal) deterioration or death

The median time to HemCR was 59 days (range: 8 to 299 days) in the DARZALEX SC-VCd arm and 59 days (range: 16 to 340 days) in the VCd arm. The median time to VGPR or better was 17 days (range: 5 to 336 days) in the DARZALEX SC-VCd arm and 25 days (range: 8 to 171 days) in the VCd arm. The median duration of HemCR had not been reached in either arm.

The median follow-up for the study is 11.4 months. Overall survival (OS) data were not mature. A total of 56 deaths were observed [N=27 (13.8%) DARZALEX SC-VCd vs. N=29 (15%) VCd group].

5.1.3.4 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).

5.2 Pharmacokinetic Properties

Following the recommended dose of DARZALEX SC 1,800 mg/30,000 units subcutaneously once weekly for 8 weeks, daratumumab peak concentration (C_{max}) increased 4.8-fold and area under the curve ($AUC_{0\text{-}7\ days}$) increased 5.4-fold from the 1st dose to the 8th dose as monotherapy. Maximum trough concentrations for DARZALEX SC are typically observed at the end of the weekly dosing regimens for both monotherapy and combination therapies. The mean ± standard deviation (SD) maximum trough serum concentration (C_{trough}) after the 8th dose was 593 ± 306 µg/mL when DARZALEX SC was administered as monotherapy and 537 ± 277 µg/mL, 526 ± 226 µg/mL, 756 ± 276 µg/mL, and 526 ± 209 µg/mL when DARZALEX SC was administered as combination with Pd, Rd, Kd, and VRd, respectively.

Table 28 lists the observed mean (±SD) maximum trough concentrations (C_{trough}) after the 8th dose, simulated median (5th-95th percentiles) maximum C_{trough} after the 8th dose, simulated median (5th-95th percentiles) C_{max} after the 8th dose, and simulated median (5th-95th percentiles) area under the curve ($AUC_{0\text{-}7day}$) after the 8th dose following DARZALEX SC 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously in patients with multiple myeloma or light chain (AL) amyloidosis. Daratumumab exposures were similar between patients treated with DARZALEX SC 1,800 mg/30,000 units monotherapy and combination therapies.

Table 28: Daratumumab Exposure for Patients with Multiple Myeloma or Light Chain (AL) Amyloidosis

Parameter	Intravenous Daratumumab 16 mg/kg Monotherapy in Patients with Multiple Myeloma	DARZALEX SC 1,800 mg/ 30,000 units Monotherapy in Patients with Multiple Myeloma	DARZALEX SC 1,800 mg/ 30,000 units in combination with VRd in Patients with Transplant Eligible Multiple Myeloma	DARZALEX SC 1,800 mg/ 30,000 units in combination with VCd in Patients with Light Chain (AL) Amyloidosis
Observed mean±SD max C_{trough} after 8th dose (µg/mL)	522±226[a]	593±306[a]	526±209	597±232
Simulated median (5th-95th percentiles) max C_{trough} after 8th dose (µg/mL)	472 (144-809)	563 (177-1063)	651 (413-915)	662 (315-1037)
Simulated median (5th-95th percentiles) C_{max} after 8th dose (µg/mL)	688 (369-1061)	592 (234-1114)	678 (431-958)	729 (390-1105)
Simulated median (5th-95th percentiles) $AUC_{0\text{-}7days}$ after 8th dose (µg/mL•day)	4019 (1740-6370)	4017 (1515-7564)	4637 (2941-6522)	4855 (2562-7522)

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

Absorption

At the recommended dose of DARZALEX SC 1,800 mg/30,000 units, the absolute bioavailability is 69%, with peak concentrations occurring around 3 days (T_{max}) in patients with multiple myeloma. Peak concentrations occurred around 4 days in patients with light chain (AL) amyloidosis.

Distribution

The estimated mean (coefficient of variation, CV) volume of distribution for the central compartment is 5.2 L (37%) and peripheral compartment was 3.8 L in patients with multiple myeloma. The estimated mean volume of distribution was 10.8 L (28%) in patients with light chain (AL) amyloidosis.

Elimination

Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. The estimated mean (CV%) linear clearance of daratumumab is 119 mL/day (59%) in patients with multiple myeloma and is 210 mL/day (42%) in patients with light chain (AL) amyloidosis. The estimated mean (CV%) elimination half-life associated with linear clearance is 20 days (22%) in patients with multiple myeloma and 28 days (74%) in patients with light chain (AL) amyloidosis.

Specific Populations

The following population characteristics have no clinically meaningful effect on the pharmacokinetics of daratumumab in patients administered DARZALEX SC as monotherapy or as combination therapy: sex, age (33 to 92 years), renal impairment [Creatinine clearance (CLcr) 15 to 89 mL/min as determined by the Cockcroft-Gault formula], and mild hepatic impairment (total bilirubin 1 to 1.5 times ULN and AST>ULN). The effect of moderate and severe hepatic impairment on daratumumab pharmacokinetics is unknown.

Racial or Ethnic Groups

Of 190 patients with light chain (AL) amyloidosis who received DARZALEX SC and had a maximum C_{trough} after the 8th dose, African-Americans (4%) had 24% higher daratumumab mean maximum C_{trough} after the 8th dose compared to that of Whites (83%) and Asians (10%) had 16% higher mean maximum C_{trough} after the 8th dose compared to that of Whites. The difference in exposure between that of Asians and Whites could be explained in part by differences in body size. The effect of African-American race on exposure and related safety and efficacy of daratumumab is unknown.

Body Weight

In patients with multiple myeloma who received DARZALEX SC 1,800 mg/30,000 units as monotherapy, the mean maximum C_{trough} after the 8th dose was 12% lower in the higher body weight (BW) group (>85 kg), while the mean maximum C_{trough} after the 8th dose was

81% higher in the lower BW group (≤50 kg) compared to the corresponding BW groups in the intravenous daratumumab arm.

In patients with light chain (AL) amyloidosis who received DARZALEX SC 1,800 mg/30,000 units in combination and had a maximum C_{trough} after the 8th dose, the mean maximum C_{trough} after the 8th dose was 22% lower in the higher BW group (>85 kg), while the mean maximum C_{trough} was 37% higher in the lower BW group (≤50 kg) compared to the patients with body weight of 51-85 kg.

Immunogenicity

The observed incidence of anti-drug antibody (ADA, including neutralizing antibody) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of daratumumab or of other daratumumab products.

With the median DARZALEX SC treatment ranging from 6.5 to 35.9 months across 7 clinical trials of patients with multiple myeloma and light chain (AL) amyloidosis treated with DARZALEX as monotherapy or as combination therapies, the incidence of anti-daratumumab antibody development was 0.6% (7/1,200) and 6 patients tested positive for neutralizing antibodies. Because of the low occurrence of anti-daratumumab antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of daratumumab products is unknown.

With the median DARZALEX SC treatment ranging from 6.5 to 35.9 months across 7 clinical trials of patients with multiple myeloma and light chain (AL) amyloidosis treated with DARZALEX as monotherapy or as combination therapies, the incidence of anti-rHuPH20 antibody development was 8.9% (106/1,193) and 1 patient tested positive for neutralizing antibodies. There was no identified clinically significant effect of anti-rHuPH20 antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of daratumumab products.

5.3 Preclinical Safety data

5.3.1 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.

No carcinogenicity, genotoxicity, or fertility studies were conducted for recombinant human hyaluronidase. There were no effects on reproductive tissues and function and no systemic exposure of hyaluronidase in monkeys given 22,000 U/kg/week subcutaneously (12 times higher than the human dose) for 39 weeks. As hyaluronidase is a recombinant form of the endogenous human hyaluronidase, no carcinogenicity, mutagenesis, or effects on fertility are expected.

6. Pharmaceutical Particulars

6.1 List of Excipients

Recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, and water for injection

6.2 Incompatibilities

No information in USPI.

6.3 Shelf-life

See expiry date on the outer pack.

6.4 Special Precautions for Storage

Store DARZALEX SC vials in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF) in the original carton to protect from light.

Do not freeze or shake.

Keep out of the sight and reach of children.

6.5 Nature and Contents of Container

DARZALEX SC (daratumumab and hyaluronidase) injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution for subcutaneous use supplied as individually packaged single-dose vials providing 1,800 mg of daratumumab and 30,000 units of hyaluronidase per 15 mL.

Patient Counseling Information

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

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing, and blurred vision *[see Special Warnings and Precautions for Use (4.4.1)]*.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions *[see Special Warnings and Precautions for Use (4.4.2)]*.

Neutropenia

- Advise patients to contact their healthcare provider if they have a fever *[see Special Warnings and Precautions for Use (4.4.3)]*.

Thrombocytopenia

- Advise patients to contact their healthcare provider if they have bruising or bleeding *[see Special Warnings and Precautions for Use (4.4.4)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Special Warnings and Precautions (4.4.5), Pregnancy and Lactation (4.6.1, 4.6.3)]*.

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX SC and for 3 months after the last dose *[see Pregnancy and Lactation (4.6.1, 4.6.3)]*.

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. *(see Pregnancy and Lactation* (*4.6.1, 4.6.3)]*.

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX SC, in the event of a planned transfusion *[see Special Warnings and Precautions for Use (4.4.6)]*.

Advise patients that DARZALEX SC 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 Special Warnings and Precautions for Use (4.4.7)]*.

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 SC could cause hepatitis B virus to become active again *[see Undesirable Effects (4.8.1)]*.

7. Marketing Authorization Holder

Janssen-Cilag Ltd.

8. Marketing Authorization Number and Date of Authorization

1C 15075/64 (NBC)

9.Date of first Authorization/ Renewal of Authorization

02 Jun 2021

10. Date of Revision of the Text

USPI version 30 Jul 2024 and CCDS Version Jun 2024 (Effect on ability to drive and use machine and administrative update

Manufactured by

Cilag AG, Schaffhausen, Switzerland

Imported by

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at *aepqcjacth@its.jnj.com*

For any product information, please contact us at *medinfosea@its.jnj.com*

Warning According to the Announcement of the Ministry of Public Health

This medicinal product may cause serious harm. It must be used only under physician's supervision.