

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL vial contains 100 mg of daratumumab (20 mg daratumumab per mL).

Each 20 mL vial contains 400 mg of daratumumab (20 mg daratumumab per mL).

Daratumumab is a human monoclonal IgG1 κ antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Excipients with known effect

Each 5 mL and 20 mL vial of DARZALEX contains 0.4 mmol and 1.6 mmol (9.3 mg and 37.3 mg) sodium, respectively.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The solution is colourless to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

DARZALEX should be administered by a healthcare professional, in an environment where resuscitation facilities are available.

Pre- and post-infusion medicinal products should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below “Recommended concomitant medicinal products”, “Management of infusion-related reactions” and section 4.4.

Posology

Dosing schedule in combination with lenalidomide (4-week cycle regimen) and for monotherapy

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

Table 1: DARZALEX dosing schedule in combination with lenalidomide (4-week cycle dosing regimen) and monotherapy

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

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

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

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)

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

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

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

^a First dose of the every-3-week dosing schedule is given at Week 7

^b First dose of the every-4-week dosing schedule is given at Week 55

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. For information on the VMP dose and dosing schedule when administered with DARZALEX, see section 5.1.

Dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)

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

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

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

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

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

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib (3-week cycle regimen)

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 4.

Table 4: DARZALEX dosing schedule in combination with bortezomib (3-week cycle dosing regimen)

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

^a First dose of the every-3-week dosing schedule is given at Week 10

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

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Infusion rates

Following dilution the DARZALEX infusion should be intravenously administered at the initial infusion rate presented in Table 5 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively, see Table 5 below.

Table 5: Infusion rates for DARZALEX (16 mg/kg) administration

	Dilution volume	Initial rate (first hour)	Rate Increment ^a	Maximum rate
Week 1 Infusion				
<i>Option 1 (Single dose infusion)</i>				
Week 1 Day 1 (16 mg/kg)	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<i>Option 2 (Split dose infusion)</i>				
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 2 (16 mg/kg) infusion^b	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (Week 3 onwards, 16 mg/kg) infusions^c	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

^a Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

^b A dilution volume of 500 mL for the 16 mg/kg dose should be used only if there were no IRRs the previous week. Otherwise, use a dilution volume of 1,000 mL.

^c A modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) should only be used only if there were no IRRs during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

Management of infusion-related reactions

Pre-infusion medicinal products should be administered to reduce the risk of infusion-related reactions (IRRs) prior to treatment with DARZALEX.

For IRRs of any grade/severity, immediately interrupt the DARZALEX infusion and manage symptoms.

Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation of DARZALEX as outlined below (see section 4.4).

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, the infusion should be resumed at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 5).
- Grade 3 (severe): Once reaction symptoms resolve, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as

appropriate (Table 5). The procedure above should be repeated in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARZALEX upon the third occurrence of a Grade 3 or greater infusion reaction.

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

Missed dose

If a planned dose of DARZALEX is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications

No dose reductions of DARZALEX are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity (see section 4.4). For information concerning medicinal products given in combination with DARZALEX, see corresponding Summary of Product Characteristics.

Recommended concomitant medicinal products

Pre-infusion medicinal product

Pre-infusion medicinal products should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of DARZALEX as follows:

- Corticosteroid (long-acting or intermediate-acting)
 - Monotherapy:
Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg).
 - Combination therapy:
Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX infusion. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-infusion medicinal product on DARZALEX infusion days (see section 5.1).
Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions. Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX infusion days when patients have received dexamethasone as a pre-infusion medicinal product.
- Antipyretics (oral paracetamol 650 to 1,000 mg)
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-infusion medicinal product

Post-infusion medicinal products should be administered to reduce the risk of delayed IRRs as follows:

Monotherapy:

Oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) should be administered on each of the two days following all infusions (beginning the day after the infusion).

Combination therapy:

Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after the DARZALEX infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX infusion, additional post-infusion medicinal products may not be needed (see section 5.1).

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-infusion medicinal products including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion medicinal products may be discontinued at the discretion of the physician.

Prophylaxis for herpes zoster virus reactivation

Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Special populations

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment (see section 5.2).

Elderly

No dose adjustments are considered necessary (see section 5.2).

Paediatric population

The safety and efficacy of DARZALEX in children aged below 18 years of age have not been established.

No data are available (see section 5.1).

Method of administration

DARZALEX is for intravenous use. It is administered as an intravenous infusion following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

DARZALEX can cause serious IRRs, including anaphylactic reactions (see section 4.8).

All patients should be monitored throughout the infusion for IRRs. For patients that experience any Grade IRRs, continue monitoring post-infusion until symptoms resolve.

In clinical studies, IRRs were reported in approximately half of all patients treated with DARZALEX.

The majority of IRRs occurred at the first infusion and were Grade 1-2 (see section 4.8). Four percent of all patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema and pulmonary oedema. Symptoms predominantly included nasal congestion, cough, throat irritation, chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus and hypotension (see section 4.8).

Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with DARZALEX. DARZALEX infusion should be interrupted for IRRs of any severity and medical management/supportive treatment for IRRs should be instituted as needed. For patients with Grade 1, 2, or 3 IRRs, the infusion rate should be reduced when re-starting

the infusion. If an anaphylactic reaction or life-threatening (Grade 4) infusion reaction occurs, appropriate emergency resuscitation should be initiated immediately. DARZALEX therapy should be discontinued immediately and permanently (see sections 4.2 and 4.3).

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following DARZALEX infusions. Additionally the use of post-infusion medicinal products (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur (see section 4.2).

Neutropenia/Thrombocytopenia

DARZALEX may increase neutropenia and thrombocytopenia induced by background therapy (see section 4.8).

Complete blood cell counts should be monitored periodically during treatment according to manufacturer's prescribing information for background therapies. Patients with neutropenia should be monitored for signs of infection. DARZALEX delay may be required to allow recovery of blood cell counts. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions or growth factors.

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.

In the event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests (see section 4.5). If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

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 section 4.5). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Hepatitis B virus (HBV) reactivation

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

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 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, suspend treatment with DARZALEX and institute appropriate treatment. Resumption of DARZALEX treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Excipients

Each 5 mL and 20 mL vial of DARZALEX contains 0.4 mmol and 1.6 mmol (9.3 mg and 37.3 mg) sodium, respectively. This corresponds to 0.46% and 1.86% of the WHO recommended maximum daily intake of 2 g sodium for an adult, respectively.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

As an IgG1 κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes.

Clinical pharmacokinetic assessments of daratumumab in combination with lenalidomide, pomalidomide, thalidomide, bortezomib and dexamethasone indicated no clinically-relevant drug-drug interaction between daratumumab and these small molecule medicinal products.

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching (see section 4.4). Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered (see section 4.4).

Interference with serum protein electrophoresis and immunofixation tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a validated 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 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception

Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.

Pregnancy

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus.

Breast-feeding

It is not known whether daratumumab is excreted into human or animal milk. Maternal IgG is excreted in human milk, but does not enter the neonatal and newborn/infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed.

The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue DARZALEX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available to determine potential effects of daratumumab on fertility in males or females (see section 5.3).

4.7 Effects on ability to drive and use machines

DARZALEX 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

Summary of the safety profile

The most frequent adverse reactions of any grade $\geq 20\%$ were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, dyspnoea, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, asthenia, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were sepsis, pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

Tabulated list of adverse reactions

Table 6 summarises the adverse reactions that occurred in patients receiving DARZALEX. The data reflects exposure to DARZALEX (16 mg/kg) in 2066 patients with multiple myeloma including 1910 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. Post-marketing adverse reactions are also included.

In Study MMY3006, the number of CD34+ cell yield was numerically lower in the D-VTd arm compared with the VTd arm (Median: D-VTd: $6.3 \times 10^6/\text{kg}$; VTd $8.9 \times 10^6/\text{kg}$) and among those who completed mobilisation, more patients in the D-VTd group received plerixafor compared to those in the VTd arm (D-VTd: 21.7%; VTd: 7.9%). The rates of engraftment and haematopoietic reconstitution was similar among the transplanted subjects in the D-VTd and VTd arms (D-VTd: 99.8%; VTd: 99.6%; as measured by the recovery of neutrophils $> 0.5 \times 10^9/\text{L}$, leukocytes $> 1.0 \times 10^9/\text{L}$, and platelets $> 50 \times 10^9/\text{L}$ without transfusion).

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

System Organ Class	Adverse reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Pneumonia ^a	Very Common	16	10
	Bronchitis ^a		17	2
	Upper respiratory tract infection ^a		41	3
	Urinary tract infection	Common	8	1
	Influenza		5	1*
	Sepsis ^a		4	4
	Cytomegalovirus infection ^a		1	<1*
Hepatitis B Virus reactivation ^b	Uncommon	-	-	
Blood and lymphatic system disorders	Neutropenia ^a	Very Common	44	39
	Thrombocytopenia ^a		31	19
	Anaemia ^a		27	12
	Lymphopenia ^a		14	11
	Leukopenia ^a		12	6
Immune system disorders	Anaphylactic reaction ^b	Rare	-	-
Metabolism and nutrition disorders	Decreased appetite	Very Common	12	1
	Hyperglycemia	Common	7	3
	Hypocalcemia		6	1
	Dehydration		3	1*
Nervous system disorders	Peripheral sensory neuropathy	Very Common	32	3
	Paraesthesia		11	<1
	Headache		12	<1*
Cardiac disorders	Atrial fibrillation	Common	4	1
Vascular disorders	Hypertension ^a	Very Common	10	5
Respiratory, thoracic and mediastinal disorders	Cough ^a	Very Common	25	<1*
	Dyspnoea ^a		21	3
	Pulmonary oedema ^a	Common	1	<1
Gastrointestinal disorders	Diarrhoea	Very Common	32	4
	Constipation		33	1
	Nausea		26	2*
	Vomiting		16	1*
	Pancreatitis ^a	Common	1	1
Musculoskeletal and connective tissue disorders	Back pain	Very Common	18	2
	Muscle spasms		14	<1*
General disorders and administration site conditions	Fatigue	Very Common	26	4
	Oedema peripheral ^a		26	1
	Pyrexia		23	2
	Asthenia		21	2
	Chills	Common	9	<1*
Injury, poisoning and procedural complications	Infusion-related reaction ^c	Very Common	40	4

* No Grade 4

^a Indicates grouping of terms

^b Post-marketing adverse reaction

^c Infusion-related reaction includes terms determined by investigators to be related to infusion, see below

Description of selected adverse reactions

Infusion-related reactions (IRRs)

In clinical studies (monotherapy and combination treatments; N=2066) the incidence of any grade IRRs was 37% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 IRR with the Week 2 or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0 to 72.8 hours). The incidence of infusion modifications due to reactions was 36%. Median durations of 16 mg/kg infusions for the 1st Week, 2nd Week and subsequent infusions were approximately 7, 4 and 3 hours respectively. Severe IRRs included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse IRRs included nasal congestion, cough, chills, throat irritation, vomiting and nausea (see section 4.4).

When DARZALEX dosing was interrupted in the setting of ASCT (Study MMY3006) for a median of 3.75 (range: 2.4; 6.9) months, upon re-initiation of DARZALEX the incidence of IRRs was 11% at first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption due to ASCT. IRRs occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3/4: <1%) with those reported in previous studies at Week 2 or subsequent infusions.

In Study MMY1001, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade IRRs was 42%, with 36% of patients experiencing IRRs on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported as follows:

Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%

Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections were primarily due to pneumonia and sepsis.

In patients receiving DARZALEX combination therapy, fatal infections (Grade 5) were reported as follows:

Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%

Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone.

Haemolysis

There is a theoretical risk of haemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data.

Other special populations

In the Phase III study MMY3007, which compared treatment with D-VMP to treatment with VMP in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was consistent with the overall population (see section 5.1).

Elderly patients

Of the 2459 patients who received DARZALEX at the recommended dose, 38% were 65 to 75 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n=1213), the most common serious adverse reactions that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the most common serious adverse reaction that occurred more frequently in elderly (≥ 75 years of age) was pneumonia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms and signs

There has been no experience of overdose in clinical studies. Doses up to 24 mg/kg have been administered intravenously in a clinical study.

Treatment

There is no known specific antidote for daratumumab overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC24

Mechanism of action

Daratumumab is an IgG1 κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Daratumumab has been shown to potently inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. 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 mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.

Daratumumab induced apoptosis *in vitro* after Fc mediated cross-linking. In addition, daratumumab modulated CD38 enzymatic activity, inhibiting the cyclase enzyme activity and stimulating the hydrolase activity. The significance of these *in vitro* effects in a clinical setting, and the implications on tumour growth, are not well-understood.

Pharmacodynamic effects

Natural killer (NK) cell and T-cell count

NK cells are known to express high levels of 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 daratumumab treatment. However, baseline levels of NK cells did not show an association with clinical response.

Immunogenicity

In patients treated with intravenous daratumumab in clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

Clinical efficacy and safety

Newly diagnosed multiple myeloma

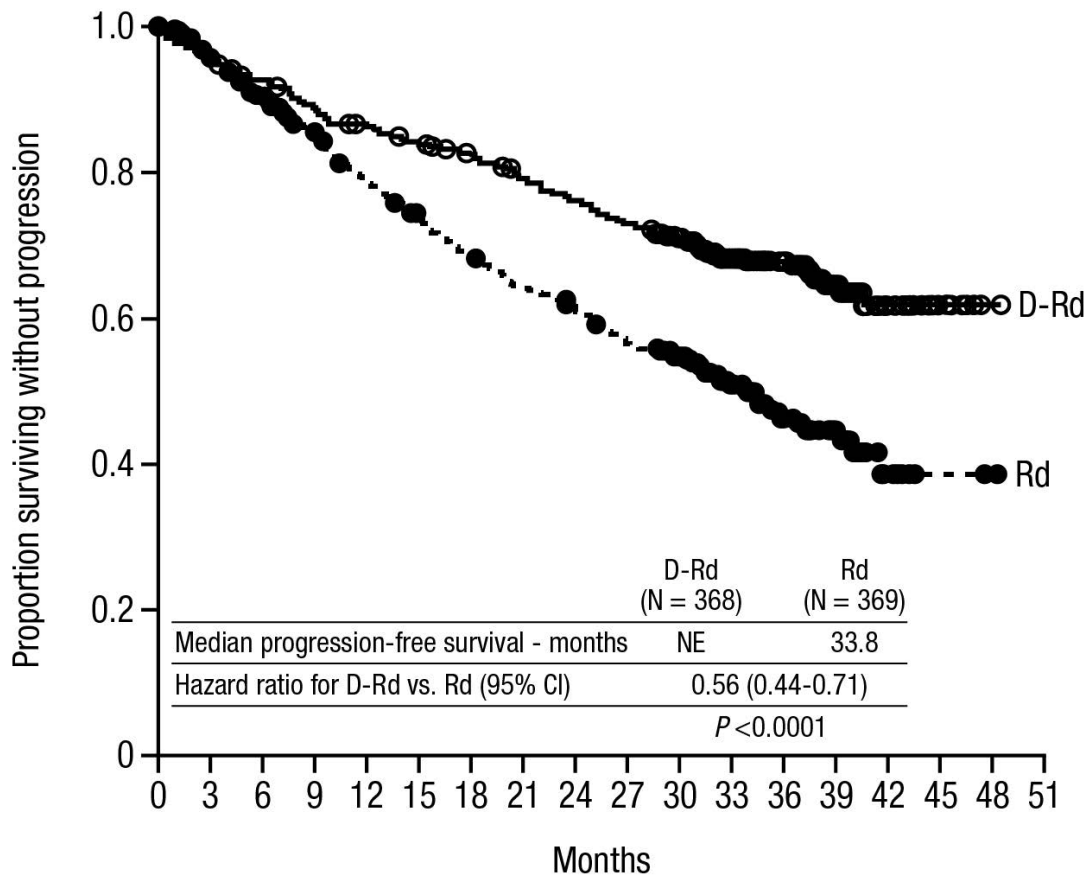
Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant:

Study MMY3008, an open-label, randomised, active-controlled Phase III study, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, the dexamethasone dose was given as a pre-infusion medicinal product. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 737 patients were randomised: 368 to the DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥75 years of age. The majority were white (92%), male (52%), 34% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 49.5% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥2. Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

Study MMY3008 showed an improvement in Progression Free Survival (PFS) in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; p<0.0001), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis approximately 9 months after the original clinical cutoff, continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and was 33.8 months in the Rd arm (HR=0.56; 95% CI: 0.44, 0.71; p<0.0001).

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3008



No. at risk

Rd	369	333	307	280	254	236	219	204	194	177	161	113	64	33	10	2	1	0
D-Rd	368	347	335	320	309	300	290	276	266	256	233	174	131	70	24	7	1	0

Additional efficacy results from Study MMY3008 are presented in Table 7 below.

Table 7: Additional efficacy results from Study MMY3008^a

	DRd (n=368)	Rd (n=369)
Overall response (sCR+CR+VGPR+PR) n(%) ^a	342 (92.9%)	300 (81.3%)
p-value ^b	<0.0001	
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)
Complete response (CR)	63 (17.1%)	46 (12.5%)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)
Partial response (PR)	50 (13.6%)	104 (28.2%)
CR or better (sCR + CR)	175 (47.6%)	92 (24.9%)
p-value ^b	<0.0001	
VGPR or better (sCR + CR + VGPR)	292 (79.3%)	196 (53.1%)
p-value ^b	<0.0001	
MRD negativity rate ^{a,c} n(%)	89 (24.2%)	27 (7.3%)
95% CI (%)	(19.9%, 28.9%)	(4.9%, 10.5%)
Odds ratio with 95% CI ^d	4.04 (2.55, 6.39)	
p-value ^e	<0.0001	

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

^c Based on threshold of 10⁻⁵

^d Mantel-Haenszel estimate of the odds ratio for un-stratified tables is used. An odds ratio >1 indicates an advantage for DRd.

^e p-value from Fisher's exact test.

In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the DRd group and 1.05 months (range: 0.3 to 15.3 months) in the Rd group. The median duration of response had not been reached in the DRd group and was 34.7 months (95% CI: 30.8, not estimable) in the Rd group.

Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant:

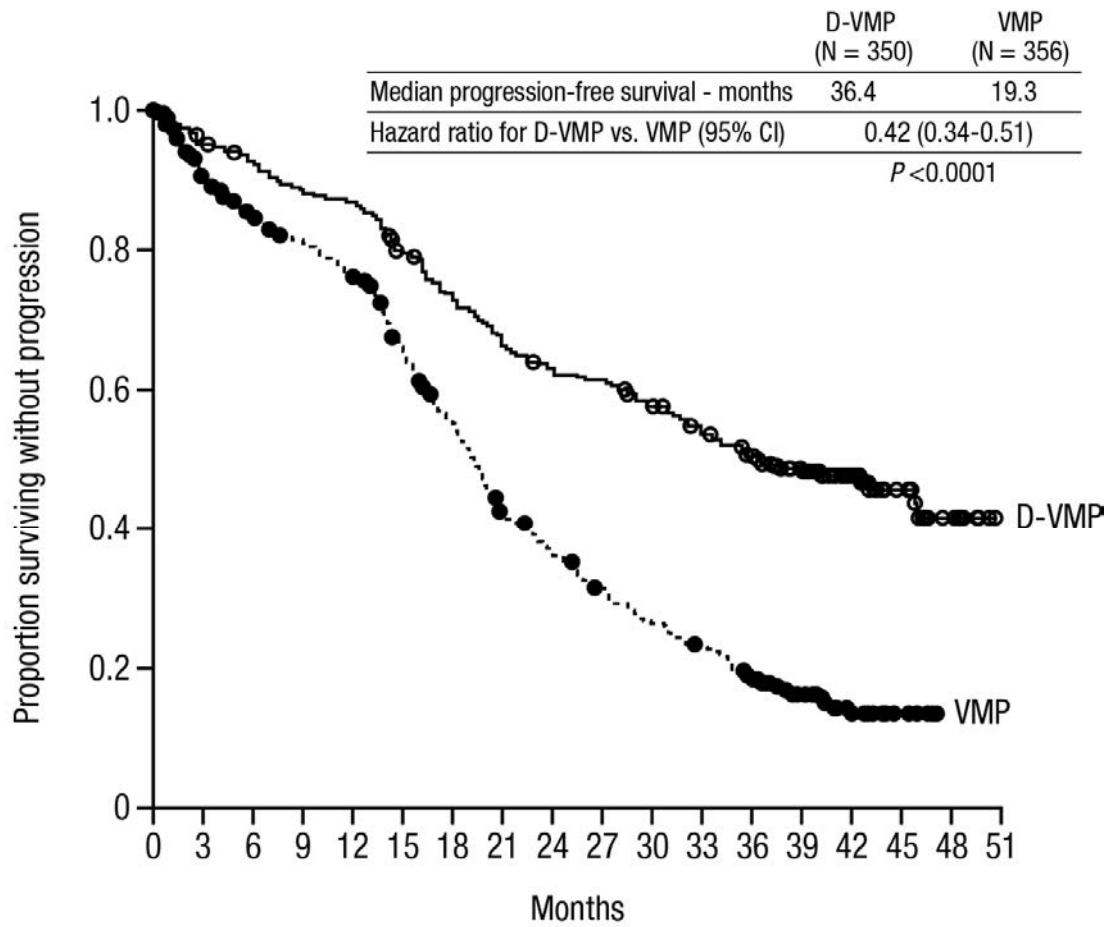
Study MMY3007, an open-label, randomised, active-controlled Phase III study, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m², and prednisone at 60 mg/m² were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomised: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%), female (54%), 25% had an ECOG performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Patients had IgG/IgA/Light chain myeloma in 64%/22%/10% of instances, 19% had ISS Stage I, 42% had ISS Stage II, 38% had ISS Stage III disease and 84% had standard risk cytogenetics. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

With a median follow-up of 16.5 months, the primary analysis of PFS in Study MMY3007 showed an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001). Results of an updated PFS analysis after a median follow-up of 40 months continued to show an improvement in PFS for patients in the D-VMP arm compared with the VMP arm. Median PFS was 36.4 months in the D-VMP arm and 19.3 months in the VMP arm (HR=0.42; 95% CI: 0.34, 0.51;

p<0.0001), representing a 58% reduction in the risk of disease progression or death in patients treated with D-VMP.

Figure 2: Kaplan-Meier Curve of PFS in Study MMY3007

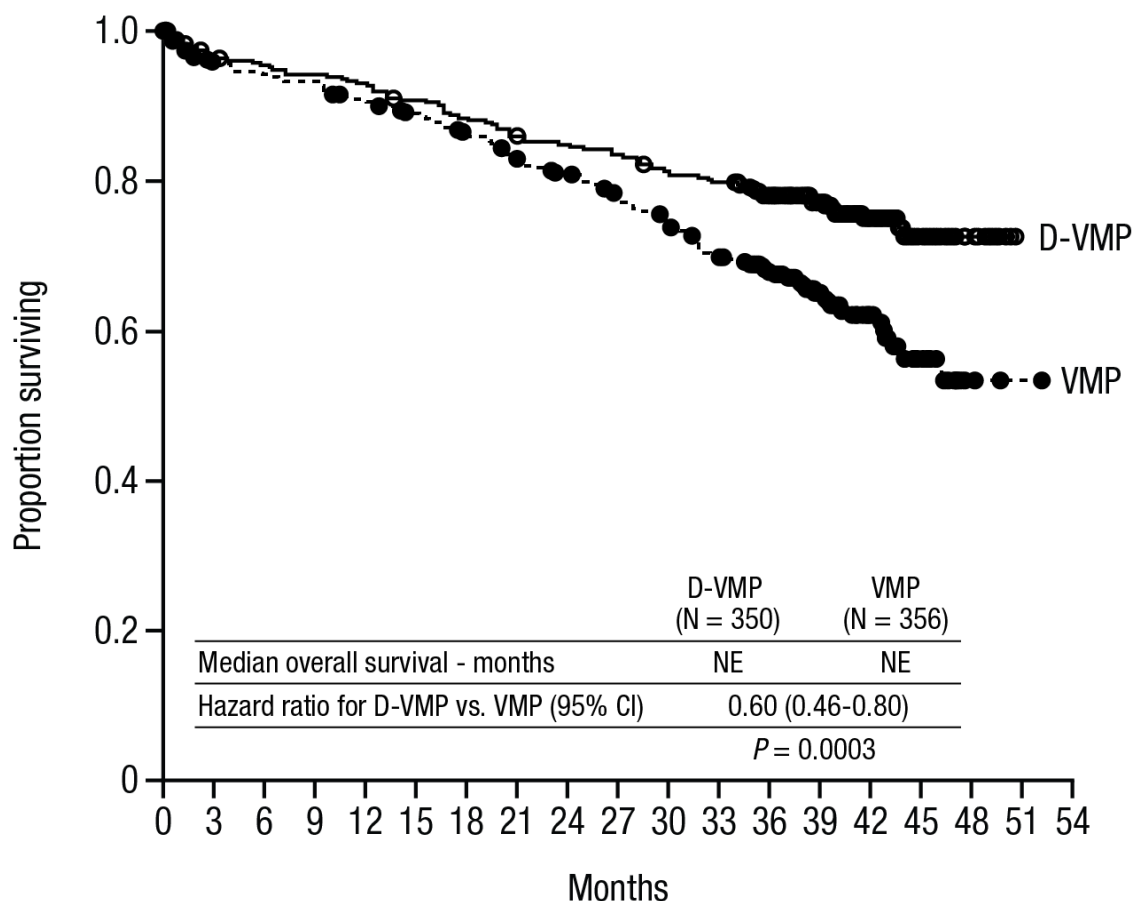


No. at risk

VMP	356	304	278	263	246	207	171	128	110	93	78	67	51	29	15	7	0	0
D-VMP	350	322	312	298	292	265	243	220	207	202	188	173	160	113	63	26	9	0

After a median follow-up of 40 months, D-VMP has shown an overall survival (OS) advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. Median OS was not reached for either arm.

Figure 3: Kaplan-Meier Curve of OS in Study MMY3007



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
VMP	356	331	325	322	312	302	292	278	269	257	242	226	198	132	73	27	3	1	0
D-VMP	350	330	327	322	318	309	301	292	288	283	275	270	248	171	97	40	12	0	0

Additional efficacy results from Study MMY3007 are presented in Table 8 below.

Table 8: Additional efficacy results from Study MMY3007^a

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) [n(%)]	318 (90.9)	263 (73.9)
p-value ^b	<0.0001	
Stringent complete response (sCR) [n(%)]	63 (18.0)	25 (7.0)
Complete response (CR) [n(%)]	86 (24.6)	62 (17.4)
Very good partial response (VGPR) [n(%)]	100 (28.6)	90 (25.3)
Partial response (PR) [n(%)]	69 (19.7)	86 (24.2)
MRD negativity rate (95% CI) ^c (%)	22.3 (18.0, 27.0)	6.2 (3.9, 9.2)
Odds ratio with 95% CI ^d	4.36 (2.64, 7.21)	
p-value ^e	<0.0001	

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

^a Based on intent-to-treat population

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

^c Based on threshold of 10⁻⁵

^d A Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio >1 indicates an advantage for D-VMP.

^e p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration

of response had not been reached in the D-VMP group and was 21.3 months (range: 18.4, not estimable) in the VMP group.

A subgroup analysis was performed on patients at least 70 years old, or those 65-69 years old with ECOG performance score of 2, or aged less than 65 years of age with significant comorbidity or ECOG performance score of 2 (D-VMP: n=273, VMP: n=270). The efficacy results in this subgroup were consistent with the overall population. In this subgroup, median PFS was not reached in the D-VMP group and was 17.9 months in the VMP group (HR=0.56; 95% CI: 0.42, 0.75); p<0.0001). The overall response rate was 90% in the D-VMP group and 74% in the VMP group (VGPR rate: 29% in D-VMP group and 26% in VMP group; CR: 22% in D-VMP group and 18% in VMP group; sCR rate: 20% in D-VMP group and 7% in VMP group). The safety results of this subgroup were consistent with the overall population. Furthermore, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was also consistent with the overall population.

Combination treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients eligible for autologous stem cell transplant (ASCT):

Study MMY3006 is a 2 Part, open-label, randomised, active-controlled Phase III study. Part 1 compared induction and consolidation treatment with DARZALEX 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (D-VTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete. In Part 2, subjects with at least a partial response (PR) by Day 100 post-transplant were re-randomised in a 1:1 ratio to daratumumab maintenance or observation only. Only results from Part 1 are described henceforth.

Bortezomib was administered by subcutaneous injection or intravenous injection at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 28 day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles (Cycles 5 and 6) following ASCT after Cycle 4. Thalidomide was administered orally at 100 mg daily during the six bortezomib cycles. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 of Cycles 1 and 2, and at 40 mg on Days 1-2 and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3-4. Dexamethasone 20 mg was administered on Days 1, 2, 8, 9, 15, 16 in Cycles 5 and 6. On the days of DARZALEX infusion, the dexamethasone dose was administered intravenously as a pre-infusion medicinal product. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 1085 patients were randomised: 543 to the D-VTd arm and 542 to the VTd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 (range: 22 to 65) years. All patients were ≤65 years: 43% were in the age group ≥60-65 years, 41% were in the age group ≥50-60 years and 16% below age of 50 years. The majority were male (59%), 48% had an ECOG performance score of 0, 42% had an ECOG performance score of 1 and 10% had an ECOG performance score of 2. Forty percent had International Staging System (ISS) Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by the stringent Complete Response (sCR) rate at Day 100 post-transplant and Progression free survival (PFS).

Table 9: Efficacy results from Study MMY3006^a

	D-VTd (n=543)	VTd (n=542)	P value ^b
Response assessment Day 100 post-transplant			
Stringent Complete Response (sCR)	157 (28.9%)	110 (20.3%)	0.0010
CR or better (sCR+CR)	211 (38.9%)	141 (26.0%)	<0.0001
Very Good Partial Response or better (sCR+CR+VGPR)	453 (83.4%)	423 (78.0%)	
MRD negativity ^{c, d} n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI ^e	2.27 (1.78, 2.90)		
MRD negativity in combination with CR or better ^c n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI ^e	2.06 (1.56, 2.72)		

D-VTd=daratumumab-bortezomib-thalidomide-dexamethasone; VTd=bortezomib-thalidomide-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.

^c Based on threshold of 10⁻⁵

^d Regardless of response per IMWG

^e Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

Results of a PFS analysis by censoring patients who were randomised to daratumumab maintenance in the second randomisation, at the date of the second randomisation showed HR=0.50; 95% CI: 0.34, 0.75; p=0.0005.

Relapsed/Refractory multiple myeloma

Monotherapy:

The clinical efficacy and safety of DARZALEX monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who had demonstrated disease progression on the last therapy, was demonstrated in two open-label studies.

In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 11% of patients were ≥75 years of age, 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent (IMiD), 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results of the pre-planned interim analysis based on Independent Review Committee (IRC) assessment are presented in Table 10 below.

Table 10: IRC assessed efficacy results for study MMY2002

Efficacy endpoint	DARZALEX 16 mg/kg N=106
Overall response rate ¹ (ORR: sCR+CR+VGPR+PR) [n (%)]	31 (29.2)
95% CI (%)	(20.8, 38.9)
Stringent complete response (sCR) [n (%)]	3 (2.8)
Complete response (CR) [n]	0
Very good partial response (VGPR) [n (%)]	10 (9.4)
Partial response (PR) [n (%)]	18 (17.0)
Clinical Benefit Rate (ORR+MR) [n (%)]	36 (34.0)

Median Duration of Response [months (95% CI)]	7.4 (5.5, NE)
Median Time to Response [months (range)]	1 (0.9; 5.6)

¹ Primary efficacy endpoint (International Myeloma Working Group criteria)
CI=confidence interval; NE=not estimable; MR=minimal response

Overall response rate (ORR) in MMY2002 was similar regardless of type of prior anti-myeloma therapy.

At a survival update with a median duration of follow-up of 14.7 months, median Overall Survival (OS) was 17.5 months (95% CI:13.7, not estimable).

In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX until disease progression. The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were Caucasian. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% were refractory to both a PI and IMiD, 60% were refractory to alkylating agents, 36% were refractory to pomalidomide and 17% were refractory to carfilzomib.

Pre-planned interim analysis showed that treatment with daratumumab at 16 mg/kg led to a 36% ORR with 5% CR and 5% VGPR. The median time to response was 1 (range: 0.5 to 3.2) month. The median duration of response was not reached (95% CI: 5.6 months, not estimable).

At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

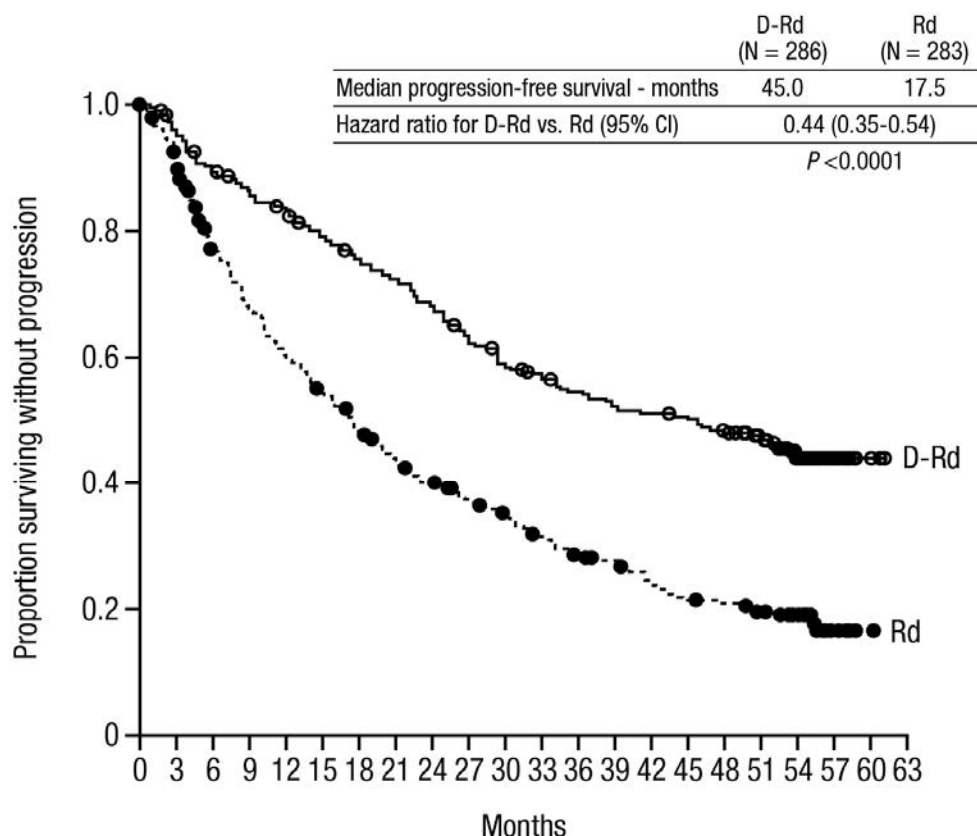
Combination treatment with lenalidomide:

Study MMY3003, an open-label, randomised, active-controlled Phase III trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose dexamethasone at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medicinal product and the remainder given the day after the infusion. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomised; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 65 years (range 34 to 89 years) and 11% were ≥75 years. The majority of patients (86%) received a prior PI, 55% of patients had received a prior IMiD, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and IMiD. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Patients refractory to lenalidomide were excluded from the study.

With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). Results of an updated PFS analysis after a median follow-up of 55 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 45.0 months in the DRd arm and 17.5 months in the Rd arm (HR=0.44; 95% CI: 0.35, 0.54; p<0.0001), representing a 56% reduction in the risk of disease progression or death in patients treated with DRd (see Figure 4).

Figure 4: Kaplan-Meier Curve of PFS in Study MMY3003



No. at risk

Rd	283	249	206	181	160	144	127	112	102	91	83	75	66	63	53	48	45	40	28	5	1	0
D-Rd	286	266	249	238	229	215	204	195	184	168	156	151	143	136	134	131	125	115	76	16	3	0

Additional efficacy results from Study MMY3003 are presented in Table 11 below.

Table 11: Additional efficacy results from Study MMY3003

Response evaluable patient number	DRd (n=281)	Rd (n=276)
Overall response (sCR+CR+VGPR+PR) n(%)	261 (92.9)	211 (76.4)
p-value ^a	<0.0001	
Stringent complete response (sCR)	51 (18.1)	20 (7.2)
Complete response (CR)	70 (24.9)	33 (12.0)
Very good partial response (VGPR)	92 (32.7)	69 (25.0)
Partial response (PR)	48 (17.1)	89 (32.2)
Median Time to Response [months (95% CI)]	1.0 (1.0, 1.1)	1.3 (1.1, 1.9)
Median Duration of Response [months (95% CI)]	NE (NE, NE)	17.4 (17.4, NE)
MRD negative rate (95% CI) ^b (%)	21.0 (16.4, 26.2)	2.8 (1.2, 5.5)
Odds ratio with 95% CI ^c	9.31 (4.31, 20.09)	
P-value ^d	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test.

^b Based on Intent-to-treat population and threshold of 10⁻⁵

^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DRd.

^d p-value is from a Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; p=0.0534).

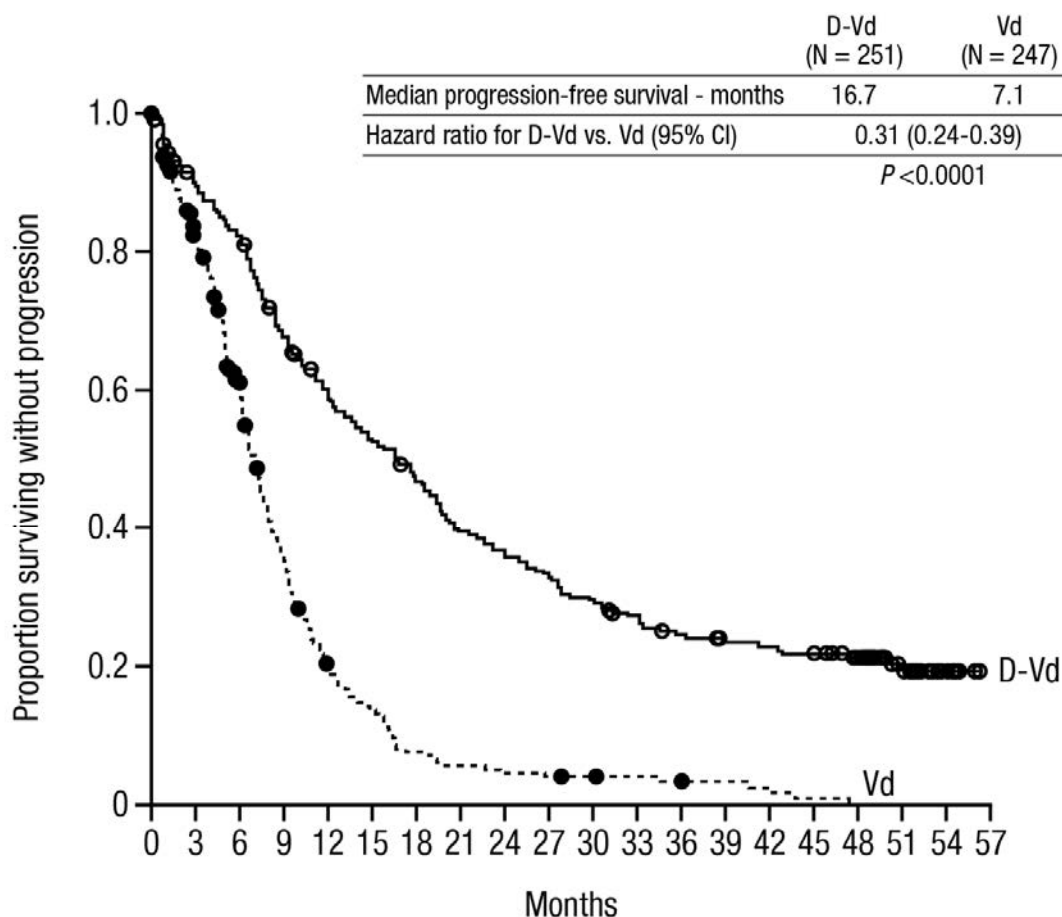
Combination treatment with bortezomib:

Study MMY3004, an open-label, randomised, active-controlled Phase III trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by subcutaneous injection or intravenous infusion at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medicinal product. DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 498 patients were randomised; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years) and 12% were ≥75 years. Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an IMiD (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were refractory to lenalidomide. Patients refractory to bortezomib were excluded from the study.

With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value<0.0001). Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the DVd arm compared with the Vd arm. Median PFS was 16.7 months in the DVd arm and 7.1 months in the Vd arm (HR [95% CI]: 0.31 [0.24, 0.39]; p-value<0.0001), representing a 69% reduction in the risk of disease progression or death in patients treated with DVd versus Vd (see Figure 5).

Figure 5: Kaplan-Meier Curve of PFS in Study MMY3004



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Vd	247	182	129	74	39	27	15	11	9	8	7	6	5	4	2	1	0	0	0	0
D-Vd	251	215	198	161	138	123	109	92	85	77	68	61	54	50	48	46	38	20	7	0

Additional efficacy results from Study MMY3004 are presented in Table 12 below.

Table 12: Additional efficacy results from Study MMY3004

Response evaluable patient number	DVd (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%)	199 (82.9)	148 (63.2)
P-value ^a	<0.0001	
Stringent complete response (sCR)	11 (4.6)	5 (2.1)
Complete response (CR)	35 (14.6)	16 (6.8)
Very good partial response (VGPR)	96 (40.0)	47 (20.1)
Partial response (PR)	57 (23.8)	80 (34.2)
Median Time to Response [months (range)]	0.9 (0.8, 1.4)	1.6 (1.5, 2.1)
Median Duration of Response [months (95% CI)]	NE (11.5, NE)	7.9 (6.7, 11.3)
MRD negative rate (95% CI) ^b	8.8% (5.6%, 13.0%)	1.2% (0.3%, 3.5%)
Odds ratio with 95% CI ^c	9.04 (2.53, 32.21)	
P-value ^d	0.0001	

DVd=daratumumab- bortezomib-dexamethasone; Vd=bortezomib-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test.

^b Based on Intent-to-treat population and threshold of 10⁻⁵

^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DVd.

^d p-value is from Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 7.4 months (95% CI: 0.0, 14.9), the hazard ratio for OS was 0.77 (95% CI: 0.47, 1.26; p=0.2975).

Cardiac electrophysiology

Daratumumab as a large protein has a low likelihood of direct ion channel interactions. The effect of daratumumab on the QTc interval was evaluated in an open-label study for 83 patients (Study GEN501) with relapsed and refractory multiple myeloma following daratumumab infusions (4 to 24 mg/kg). Linear mixed PK-PD analyses indicated no large increase in mean QTcF interval (i.e. greater than 20 ms) at daratumumab C_{max} .

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with DARZALEX in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of daratumumab following intravenous administration of daratumumab monotherapy were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg.

In the 1 to 24 mg/kg cohorts, peak serum concentrations (C_{max}) after the first dose increased in approximate proportion to dose and volume of distribution was consistent with initial distribution into the plasma compartment. Following the last weekly infusion, C_{max} increased in a greater than dose-proportional manner, consistent with target mediated drug disposition. Increases in AUC were more than dose-proportional and clearance (CL) decreased with increasing dose. These observations suggest CD38 may become saturated at higher doses, after which the impact of target binding clearance is minimised and the clearance of daratumumab approximates the linear clearance of endogenous IgG1. Clearance also decreased with multiple doses, which may be related to tumour burden decreases.

Terminal half-life increases with increasing dose and with repeated dosing. The mean (standard deviation [SD]) estimated terminal half-life of daratumumab following the first 16 mg/kg dose was 9 (4.3) days. The estimated terminal half-life of daratumumab following the last 16 mg/kg dose increased, but there are insufficient data for a reliable estimation. Based on population PK analysis, the mean (SD) half-life associated with non-specific linear elimination was approximately 18 (9) days; this is the terminal half-life that can be expected upon complete saturation of target mediated clearance and repeat dosing of daratumumab.

At the end of weekly dosing for the recommended monotherapy schedule and dose of 16 mg/kg, the mean (SD) serum C_{max} value was 915 (410.3) micrograms/mL, approximately 2.9-fold higher than following the first infusion. The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (331.5) micrograms/mL.

Four population PK analyses were performed to describe the PK characteristics of daratumumab and to evaluate the influence of covariates on the disposition of daratumumab in patients with multiple myeloma; Analysis 1 (n=223) in patients receiving DARZALEX monotherapy while Analysis 2 (n=694), Analysis 3 (n=352) and Analysis 4 (n=355) were conducted in patients with multiple myeloma that received daratumumab combination therapies. Analysis 2 included 694 patients (n=326 for lenalidomide-dexamethasone; n=246 for bortezomib-dexamethasone; n=99 for pomalidomide-dexamethasone; n=11 for bortezomib-melphalan-prednisone; and n=12 for bortezomib-thalidomide-dexamethasone), Analysis 3 included 352 patients (bortezomib-melphalan-prednisone) and Analysis 4 included 355 patients (lenalidomide-dexamethasone).

Based on the population PK analysis of daratumumab monotherapy (Analysis 1), daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean (SD) ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 (0.5). The mean (SD) central volume of distribution is 56.98 (18.07) mL/kg.

Three additional population PK analyses (Analysis 2, Analysis 3 and Analysis 4) were conducted in patients with multiple myeloma that received daratumumab combination therapies. Daratumumab concentration-time profiles were similar following the monotherapy and combination therapies. The mean estimated terminal half-life associated with linear clearance in combination therapy was approximately 15-23 days.

Based on the four population PK analyses (Analyses 1-4) body weight was identified as a statistically significant covariate for daratumumab clearance. Therefore, body weight based dosing is an appropriate dosing strategy for the multiple myeloma patients.

Simulation of daratumumab pharmacokinetics was conducted for all recommended dosing schedules in 1,309 patients with multiple myeloma. The simulation results confirmed that the split and single dosing for the first dose provide similar PK, with the exception of the PK profile in the first day of the treatment.

Special populations

Age and gender

Based on four individual population PK analyses (1-4) in patients receiving daratumumab monotherapy or various combination therapies (Analyses 1-4), age (range: 31-93 years) had no clinically important effect on the PK of daratumumab, and the exposure of daratumumab was similar between younger (aged <65 years, n=518) and older (aged ≥65 to <75 years n=761; aged ≥75 years, n=334) patients.

Gender did not affect exposure of daratumumab to a clinically relevant degree in the population PK analyses.

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Four individual population PK analyses were performed based on pre-existing renal function data in patients receiving daratumumab monotherapy, or various combination therapies (Analyses 1-4), and included a total of 441 patients with normal renal function (creatinine clearance [CRCL] ≥90 mL/min), 621 with mild renal impairment (CRCL <90 and ≥60 mL/min), 523 with moderate renal impairment (CRCL <60 and ≥30 mL/min), and 27 with severe renal impairment or end stage renal disease (CRCL <30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolised through hepatic pathways.

Four individual population PK analyses were performed in patients receiving daratumumab monotherapy or various combination therapies (Analyses 1-4), and included a total of 1404 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN]), 189 with mild hepatic impairment (TB 1.0 x to 1.5 x ULN or AST >ULN) and 8 patients with moderate (TB > 1.5 x to 3.0 x ULN; n=7), or severe (TB > 3.0 x ULN; n=1) hepatic impairment. No clinically important differences in the exposure to daratumumab were observed between patients with hepatic impairment and those with normal hepatic function.

Race

Based on four individual population PK analyses in patients receiving either daratumumab monotherapy or various combination therapies (Analyses 1-4), the exposure to daratumumab was similar between white (n=1371) and non-white subjects (n=242).

5.3 Preclinical safety data

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. No chronic toxicity testing has been conducted.

Carcinogenicity and mutagenicity

No animal studies have been performed to establish the carcinogenic potential of daratumumab.

Reproductive toxicology

No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development.

Fertility

No animal studies have been performed to determine potential effects on fertility in males or females.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
Mannitol (E421)
Polysorbate 20
Sodium acetate trihydrate
Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

24 months

After dilution

From a microbiological point of view, unless the method of opening/ dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should be no more than 24 hours at refrigerated conditions (2°C-8°C) protected from light, followed by 15 hours (including infusion time) at room temperature (15°C-25°C) and room light.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 100 mg of daratumumab. Pack size of 1 vial.

20 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 400 mg of daratumumab. Pack size of 1 vial.
DARZALEX is also supplied as an initiation pack containing 11 vials: (6 x 5 mL vials + 5 x 20 mL vials).

6.6 Special precautions for disposal and other handling

This medicinal product is for single-use only.

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient weight.
- Check that the DARZALEX solution is colourless to yellow. Do not use if opaque particles, discolouration or other foreign particles are present.
- Using aseptic technique, remove a volume of 0.9% Sodium Chloride from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to an infusion bag/container containing 0.9% Sodium Chloride (see section 4.2). Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Visually inspect parenteral medicinal products for particulate matter and discolouration prior to administration. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature (15°C-25°C) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions (2°C-8°C) and protected from light. Do not freeze.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/001
EU/1/16/1101/002
EU/1/16/1101/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2016

Date of latest renewal: 24 April 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 1,800 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mL vial of solution for injection contains 1,800 mg of daratumumab (120 mg daratumumab per mL).

Daratumumab is a human monoclonal IgG1 κ antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Excipients with known effect

Each 15 mL vial of solution for injection contains 735.1 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear to opalescent, colourless to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

DARZALEX subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified.

DARZALEX should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.

It is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being given to the patient as prescribed.

For patients currently receiving daratumumab intravenous formulation, DARZALEX solution for subcutaneous injection may be used as an alternative to the intravenous daratumumab formulation starting at the next scheduled dose.

Pre- and post-injection medicinal products should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below “Recommended concomitant medicinal products” and section 4.4.

Posology

Dosing schedule in combination with lenalidomide (4-week cycle regimen) and for monotherapy

The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide (4-week cycle dosing regimen) and monotherapy

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

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

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

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)

The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 2.

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

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

^a First dose of the every-3-week dosing schedule is given at Week 7

^b First dose of the every-4-week dosing schedule is given at Week 55

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. For information on the VMP dose and dosing schedule when administered with DARZALEX solution for subcutaneous injection, see section 5.1.

Dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)

The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 3.

Table 3: DARZALEX dosing schedule in combination with bortezomib, thalidomide and dexamethasone ([VTd]; 4-week cycle dosing regimen)

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

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

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

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib (3-week cycle regimen)

The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 4.

Table 4: DARZALEX dosing schedule in combination with bortezomib (3-week cycle dosing regimen)

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

^a First dose of the every-3-week dosing schedule is given at Week 10

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

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Missed dose

If a planned dose of DARZALEX is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications

No dose reductions of DARZALEX are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity (see section 4.4). For information concerning medicinal products given in combination with DARZALEX, see corresponding Summary of Product Characteristics.

In clinical studies, no modification to rate or dose of DARZALEX solution for subcutaneous injection was required to manage IRRs.

Recommended concomitant medicinal products

Pre-injection medicinal product

Pre-injection medicinal products (oral or intravenous) should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every administration of DARZALEX solution for subcutaneous injection as follows:

- Corticosteroid (long-acting or intermediate-acting)
 - Monotherapy:
 - Methylprednisolone 100 mg, or equivalent. Following the second injection, the dose of corticosteroid may be reduced to methylprednisolone 60 mg.
 - Combination therapy:
 - Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX solution for subcutaneous injection. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-injection

medicinal product on DARZALEX administration days (see section 5.1). Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX administration days when patients have received dexamethasone (or equivalent) as a pre-injection medicinal product.

- Antipyretics (paracetamol 650 to 1,000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-injection medicinal product

Post-injection medicinal products should be administered to reduce the risk of delayed IRRs as follows:

- **Monotherapy:**
Oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) should be administered on each of the two days following all injections (beginning the day after the injection).
- **Combination therapy:**
Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after the DARZALEX injection. However, if a background regimen specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX injection, additional post-injection medicinal products may not be needed (see section 5.1).

If the patient experiences no major IRRs after the first three injections, post-injection corticosteroids (excluding any background regimen corticosteroids) may be discontinued.

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection medicinal products may be discontinued at the discretion of the physician.

Prophylaxis for herpes zoster virus reactivation

Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Special populations

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. No dosage adjustments are necessary for patients with hepatic impairment (see section 5.2).

Elderly

No dose adjustments are considered necessary (see section 5.2).

Paediatric population

The safety and efficacy of DARZALEX in children aged below 18 years of age have not been established.

No data are available (see section 5.1).

Body weight (>120 kg)

Limited number of patients with body weight >120 kg have been studied using flat-dose (1,800 mg) DARZALEX solution for subcutaneous injection and efficacy in these patients has not been

established. No dose adjustment based on body weight can currently be recommended (see sections 4.4 and 5.2).

Method of administration

DARZALEX subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified. See section 6.6 for special precautions prior to administration.

To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

Inject 15 mL DARZALEX solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject DARZALEX solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections.

DARZALEX solution for subcutaneous injection should never be injected 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 slowing down the injection, 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 solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as DARZALEX.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

DARZALEX solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 11% (52/490) of patients experienced an IRR. Most IRRs occurred following the first injection and were Grade 1-2. IRRs occurring with subsequent injections were seen in less than 1% of patients (see section 4.8).

The median time to onset of IRRs following DARZALEX injection was 3.7 hours (range 0.15-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in less than 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia (see section 4.8).

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections. If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate

emergency care should be initiated immediately. DARZALEX therapy should be discontinued immediately and permanently (see sections 4.2 and 4.3).

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following DARZALEX injection (see section 4.2). Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease (see section 4.2).

Neutropenia/Thrombocytopenia

DARZALEX may increase neutropenia and thrombocytopenia induced by background therapy (see section 4.8).

Complete blood cell counts should be monitored periodically during treatment according to manufacturer's prescribing information for background therapies. Patients with neutropenia should be monitored for signs of infection. DARZALEX delay may be required to allow recovery of blood cell counts. In lower body weight patients receiving DARZALEX subcutaneous formulation, higher rates of neutropenia were observed; however, this was not associated with higher rates of serious infections. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions or growth factors.

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab administration. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.

In the event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests (see section 4.5). If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

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 section 4.5). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Hepatitis B virus (HBV) reactivation

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

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 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, suspend treatment with DARZALEX and institute appropriate treatment. Resumption of DARZALEX treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Body weight (>120 kg)

There is a potential for reduced efficacy with DARZALEX solution for subcutaneous injection in patients with body weight >120 kg (see sections 4.2 and 5.2).

Excipients

This medicinal product contains sorbitol (E420). Patients with rare hereditary fructose intolerance (HFI) should not take this medicinal product (see section 2).

This medicinal product also contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

As an IgG1 κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes.

Clinical pharmacokinetic assessments with daratumumab and lenalidomide, pomalidomide, thalidomide, bortezomib, melphalan, prednisone, carfilzomib and dexamethasone indicated no clinically-relevant drug-drug interaction between daratumumab and these small molecule medicinal products.

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching (see section 4.4). Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered (see section 4.4).

Interference with serum protein electrophoresis and immunofixation tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a validated 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 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception

Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.

Pregnancy

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus.

Breast-feeding

It is not known whether daratumumab is excreted into human or animal milk.

Maternal IgG is excreted in human milk, but does not enter the neonatal and newborn/infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed.

The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue DARZALEX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available to determine potential effects of daratumumab on fertility in males or females (see section 5.3).

4.7 Effects on ability to drive and use machines

DARZALEX 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

Summary of the safety profile

The most frequent adverse reactions of any grade ($\geq 20\%$ patients) with daratumumab (either intravenous or subcutaneous formulations) when administered either as monotherapy or combination treatment were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

With the exception of IRRs (see Table 5 below), the safety profile of DARZALEX subcutaneous formulation (evaluated in 260 and 258 patients treated with the subcutaneous and intravenous formulations respectively) from the Phase III study MMY3012 was similar to the known safety profile of the intravenous formulation. Neutropenia is the only adverse reaction reported at $\geq 5\%$ higher frequency for DARZALEX subcutaneous formulation compared to intravenous daratumumab (Grade 3 or 4: 13% vs 8%, respectively).

Tabulated list of adverse reactions

Table 5 summarises the adverse reactions that occurred in patients receiving DARZALEX subcutaneous formulation or intravenous formulation of daratumumab.

The data reflects exposure to DARZALEX subcutaneous formulation (1,800 mg) in 490 patients with multiple myeloma (MM) including 260 patients from a Phase III active-controlled trial (Study MMY3012) who received DARZALEX solution for subcutaneous injection as monotherapy and three open-label, clinical studies in which patients received DARZALEX solution for subcutaneous injection either as monotherapy (N=31, MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX solution for subcutaneous injection in combination with either bortezomib, melphalan and prednisone (D-VMP, n=67), lenalidomide and dexamethasone (D-Rd, n=65) or bortezomib, lenalidomide and dexamethasone (D-VRd, n=67).

The safety data also reflects exposure to intravenous daratumumab (16 mg/kg) in 2324 patients with multiple myeloma including 1910 patients who received intravenous daratumumab in combination with background regimens and 414 patients who received intravenous daratumumab as monotherapy. Post-marketing adverse reactions are also included.

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions in multiple myeloma patients treated with intravenous daratumumab or subcutaneous daratumumab

System Organ Class	Adverse reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Upper respiratory tract infection ^a	Very Common	38%	2%
	Bronchitis ^a	Very Common	14%	2%
	Pneumonia ^a	Very Common	14%	9%
	Urinary tract infection	Common	7%	1%
	Influenza	Common	4%	1% [#]
	Sepsis ^a	Common	4%	3%
	Cytomegalovirus infection ^a	Common	1%	<1% [#]
	Hepatitis B Virus reactivation ^a	Uncommon	<1%	<1%
Blood and lymphatic system disorders	Neutropenia ^a	Very Common	40%	33%
	Thrombocytopenia ^a	Very Common	30%	18%
	Anaemia ^a	Very Common	27%	12%
	Lymphopenia ^a	Very Common	13%	11%
	Leukopenia ^a	Very Common	11%	6%
Immune system disorders	Anaphylactic reaction ^b	Rare	-	-
Metabolism and nutrition disorders	Decreased appetite	Very Common	10%	1%
	Hyperglycaemia	Common	6%	3%
	Hypocalcaemia	Common	5%	1%
	Dehydration	Common	2%	1% [#]
Psychiatric disorders	Insomnia	Very Common	14%	1% [#]
Nervous system disorders	Peripheral sensory neuropathy	Very Common	26%	3%
	Headache	Very Common	11%	<1% [#]
	Dizziness	Common	9%	<1% [#]
	Paraesthesia	Common	9%	<1%
Cardiac disorders	Atrial fibrillation	Common	3%	1%
Vascular disorders	Hypertension ^a	Very Common	10%	5%
Respiratory, thoracic and mediastinal disorders	Cough ^a	Very Common	22%	<1% [#]
	Dyspnoea ^a	Very Common	18%	2%
	Pulmonary oedema ^a	Common	1%	<1%
Gastrointestinal disorders	Diarrhoea	Very Common	29%	3%
	Constipation	Very Common	28%	1%
	Nausea	Very Common	23%	1% [#]
	Vomiting	Very Common	14%	1% [#]
	Pancreatitis ^a	Common	1%	<1%
Skin and subcutaneous tissue disorders	Rash	Common	9%	<1% [#]
	Pruritus	Common	5%	<1% [#]
Musculoskeletal and connective tissue disorders	Back pain	Very Common	17%	2%
	Muscle spasms	Very Common	12%	<1% [#]
	Arthralgia	Very Common	10%	1% [#]
	Musculoskeletal chest pain	Common	6%	<1% [#]
General disorders and administration site conditions	Fatigue	Very Common	23%	3%
	Oedema peripheral ^a	Very Common	22%	1%
	Pyrexia	Very Common	22%	1%
	Asthenia	Very Common	18%	2%
	Chills	Common	9%	<1% [#]
	Injection site erythema ^c	Common	4%	0
	Injection site reactions ^{d,e}	Common	8%	0
Injury, poisoning and procedural complications	Infusion-related reactions ^c			
	Daratumumab intravenous ^f	Very Common	39%	5%
	Daratumumab subcutaneous ^e	Very Common	11%	1% [#]

-
- # No grade 4
- a Indicates a grouping of terms.
- b Based on post-marketing adverse reactions.
- c Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.
- d Injection site reactions includes terms determined by investigators as related to injection of daratumumab.
- e Frequency based on daratumumab subcutaneous studies only (N=490).
- f Frequency based on daratumumab intravenous studies only (N=2324).

Note: Based on 2814 multiple myeloma patients treated with daratumumab intravenous or daratumumab subcutaneous.

Description of selected adverse reactions

Infusion-related reactions (IRRs)

In clinical studies (monotherapy and combination treatments; N=490) with DARZALEX subcutaneous formulation, the incidence of any grade IRRs was 10.2% with the first injection of DARZALEX (1,800 mg, Week 1), 0.2% with the Week 2 injection, and 0.8% with subsequent injections. Grade 3 IRRs were seen in 1.4% of patients. No patients had Grade 4 IRRs.

Signs and symptoms of IRR may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia (see section 4.4).

Injection site reactions (ISRs)

In clinical studies (N=490) with DARZALEX subcutaneous formulation, the incidence of any grade injection site reaction was 8.2%. There were no Grade 3 or 4 ISRs. The most common ($\geq 1\%$) ISRs were erythema, injection site induration, pruritis.

Infections

In patients receiving DARZALEX subcutaneous formulation as monotherapy, incidence of infections was similar between DARZALEX subcutaneous formulation (52.9%) versus intravenous daratumumab groups (50.0%). Additionally, Grade 3 or 4 infections also occurred at similar frequencies between DARZALEX subcutaneous formulation (11.7%) and intravenous daratumumab (14.3%). Most infections were manageable and rarely led to treatment discontinuation. Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies.

In patients receiving intravenous daratumumab combination therapy, Grade 3 or 4 infections were reported as follows:

Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%

Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections were primarily due to pneumonia and sepsis.

In patients receiving intravenous daratumumab combination therapy, fatal infections (Grade 5) were reported as follows:

Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%

Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone.

Haemolysis

There is a theoretical risk of haemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data.

Other special populations

In the Phase III study MMY3007, which compared treatment with D-VMP to treatment with VMP in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was consistent with the overall population (see section 5.1).

Elderly patients

Of the 3207 patients who received daratumumab (n=490 subcutaneous; n=2717 intravenous) at the recommended dose, 38% were 65 to 75 years of age, and 17% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n=1827), the most common serious adverse reactions that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=777), the most common serious adverse reaction that occurred more frequently in elderly (≥ 75 years of age) was pneumonia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Symptoms and signs

There has been no experience of overdose in clinical studies.

Treatment

There is no known specific antidote for daratumumab overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC24

DARZALEX solution for subcutaneous injection contains recombinant human hyaluronidase (rHuPH20). rHuPH20 works locally and transiently to degrade hyaluronan ((HA), a naturally occurring glycoaminoglycan found throughout the body) in the extracellular matrix of the subcutaneous space by cleaving the linkage between the two sugars (N-acetylglucosamine and glucuronic acid) which comprise HA. rHuPH20 has a half-life in skin of less than 30 minutes. Hyaluronan levels in subcutaneous tissue return to normal within 24 to 48 hours because of the rapid biosynthesis of hyaluronan.

Mechanism of action

Daratumumab is an IgG1 κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Daratumumab has been shown to potently inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis

through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. 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 mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.

Daratumumab induced apoptosis *in vitro* after Fc mediated cross-linking. In addition, daratumumab modulated CD38 enzymatic activity, inhibiting the cyclase enzyme activity and stimulating the hydrolase activity. The significance of these *in vitro* effects in a clinical setting, and the implications on tumour growth, are not well-understood.

Pharmacodynamic effects

Natural killer (NK) cell and T-cell count

NK cells are known to express high levels of 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 daratumumab treatment. However, baseline levels of NK cells did not show an association with clinical response.

Immunogenicity

In patients treated with subcutaneous daratumumab in clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

The incidence of treatment-emergent non-neutralizing anti-rHuPH20 antibodies was 7.8% (35/447); with 7.5% (19/255) in the monotherapy DARZALEX subcutaneous formulation groups, and 8.3% (16/192) in the pooled combination DARZALEX subcutaneous formulation groups. The anti-rHuPH20 antibodies did not appear to impact daratumumab exposures. The clinical relevance of the development of anti-daratumumab or anti-rHuPH20 antibodies after treatment with DARZALEX subcutaneous formulation is not known.

Clinical experience of DARZALEX solution for subcutaneous injection (subcutaneous formulation)

Monotherapy – relapsed/refractory multiple myeloma

MMY3012, an open-label, randomised, Phase III non-inferiority study, compared efficacy and safety of treatment with DARZALEX solution for subcutaneous injection (1,800 mg) vs. intravenous (16 mg/kg) daratumumab in patients with relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD). Treatment continued until unacceptable toxicity or disease progression.

A total of 522 patients were randomised: 263 to the DARZALEX subcutaneous formulation arm and 259 to the intravenous daratumumab arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median patient age was 67 years (range: 33-92 years), 55% were male and 78% were Caucasian. The median patient weight was 73 kg (range: 29 – 138 kg). Patients had received a median of 4 prior lines of therapy. A total of 51% of patients had prior autologous stem cell transplant (ASCT), 100% of patients were previously treated with both PI(s) and IMiD(s) and most patients were refractory to a prior systemic therapy, including both PI and IMiD (49%).

The study met its co-primary endpoints of overall response rate (ORR) by the IMWG response criteria (Table 6) and maximum C_{trough} at pre-dose Cycle 3 Day 1, (see section 5.2).

Table 6: Key results from Study MMY3012

	Subcutaneous Daratumumab (N=263)	Intravenous Daratumumab (N=259)
Primary Endpoint		
Overall response (sCR+CR+VGPR+PR), n (%) ^a	108 (41.1%)	96 (37.1%)
95% CI (%)	(35.1%, 47.3%)	(31.2%, 43.3%)
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 (17.1%)	37 (14.3%)
Partial response (PR)	58 (22.1%)	52 (20.1%)
Secondary Endpoint		
Rate of Infusion-related Reaction, n (%) ^c	33 (12.7%)	89 (34.5%)
Progression-free Survival, months		
Median (95% CI)	5.59 (4.67, 7.56)	6.08 (4.67, 8.31)
Hazard ratio (95% CI)		0.99 (0.78, 1.26)

^a Based on intent-to-treat population.

^b p-value <0.0001 from Farrington-Manning test for non-inferiority hypothesis.

^c Based on safety population. P-value<0.0001 from Cochran-Mantel-Haenszel Chi-Squared test.

Safety and tolerability results, including in lower weight patients, were consistent with the known safety profile for DARZALEX subcutaneous formulation and intravenous daratumumab.

Results from the modified-CTSQ, a patient reported outcome questionnaire that assesses patient satisfaction with their therapy, demonstrated that patients receiving DARZALEX subcutaneous formulation had greater satisfaction with their therapy compared with patients receiving intravenous daratumumab. However, open-label studies are subject to bias.

Combination therapies in multiple myeloma

MMY2040 was an open-label trial evaluating the efficacy and safety of DARZALEX subcutaneous formulation 1,800 mg:

- in combination with bortezomib, melphalan, and prednisone (D-VMP) in patients with newly diagnosed multiple myeloma (MM) who are ineligible for transplant. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m², and prednisone at 60 mg/m² were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX subcutaneous formulation was continued until disease progression or unacceptable toxicity.
- in combination with lenalidomide and dexamethasone (D-Rd) in patients with relapsed or refractory MM. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI<18.5). DARZALEX subcutaneous formulation was continued until disease progression or unacceptable toxicity.
- in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd) in patients with newly diagnosed MM who are transplant eligible. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1 and 2. Lenalidomide was administered orally at 25 mg once daily on Days 1-14; low dose dexamethasone was administered 40 mg/week in 3-week cycles. Total treatment duration was 4 cycles.

A total of 199 patients (D-VMP: 67; D-Rd: 65; D-VRd: 67) were enrolled. Efficacy results were determined by computer algorithm using IMWG criteria. The study met its primary endpoint ORR for D-VMP and D-Rd and the primary endpoint VGPR or better for D-VRd (see Table 7).

Table 7: Efficacy results from Study MMY2040

	D-VMP (n=67)	D-Rd (n=65)	D-VRd (n=67)
Overall response (sCR+CR+VGPR+PR), n (%) ^a	60 (89.6%)	61 (93.8%)	65 (97.0%)
90% CI(%)	(81.3%, 95.0%)	(86.5%, 97.9%)	(90.9%, 99.5%)
Stringent complete response (sCR)	13 (19.4%)	12 (18.5%)	6 (9.0%)
Complete response (CR)	19 (28.4%)	13 (20.0%)	5 (7.5%)
Very good partial response (VGPR)	20 (29.9%)	26 (40.0%)	37 (55.2%)
Partial response (PR)	8 (11.9%)	10 (15.4%)	17 (25.4%)
VGPR or better (sCR + CR + VGPR)	52 (77.6%)	51 (78.5%)	48 (71.6%)
90% CI(%)	(67.6%, 85.7%)	(68.4%, 86.5%)	(61.2%, 80.6%)

D-VMP = Daratumumab-bortezomib-melphalan-prednisone; D-Rd = Daratumumab-lenalidomide-dexamethasone; D-VRd = Daratumumab-bortezomib-lenalidomide-dexamethasone; Daratumumab = DARAZALEX subcutaneous formulation; CI=confidence interval.

^a Based on treated subjects

Clinical experience with daratumumab concentrate for solution for infusion (intravenous formulation)

Newly diagnosed multiple myeloma

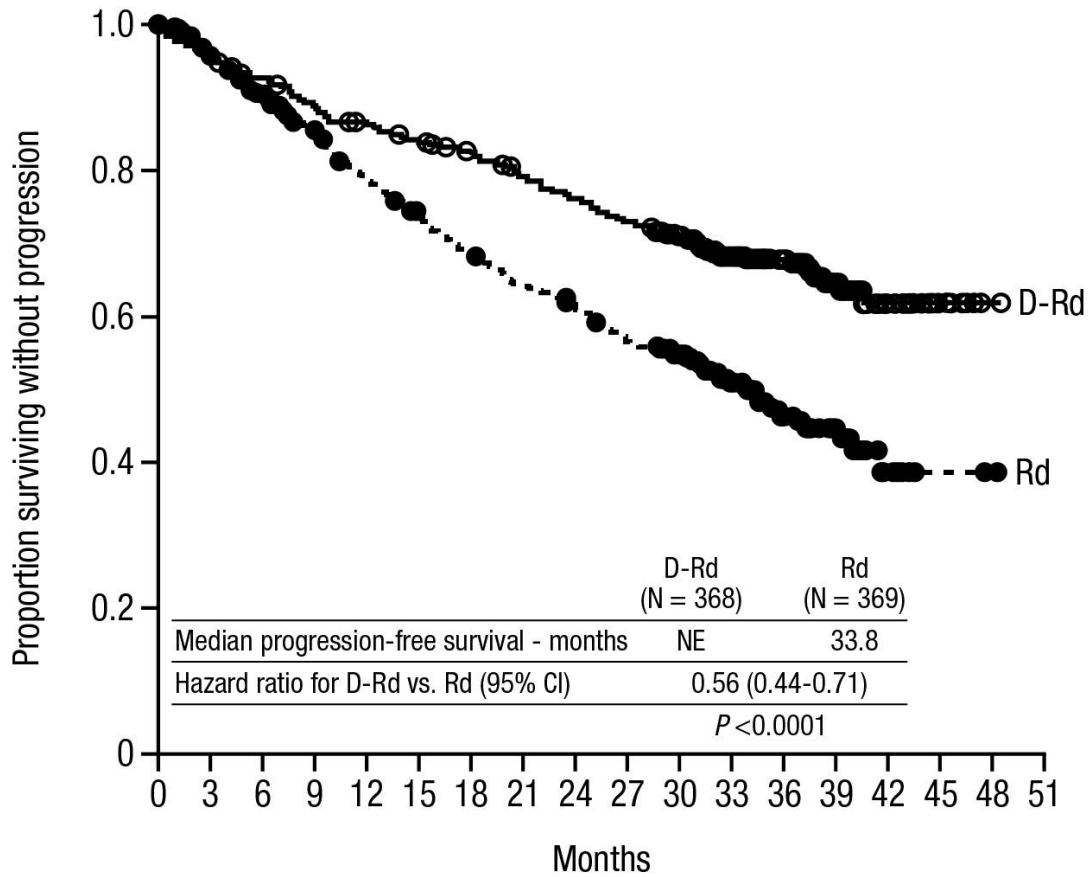
Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant:

Study MMY3008, an open-label, randomised, active-controlled Phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On intravenous daratumumab infusion days, the dexamethasone dose was given as a pre-infusion medicinal product. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 737 patients were randomised: 368 to the DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥75 years of age. The majority were white (92%), male (52%), 34% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 49.5% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥2. Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

Study MMY3008 showed an improvement in Progression Free Survival (PFS) in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; p<0.0001), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis approximately 9 months after the original clinical cutoff, continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and was 33.8 months in the Rd arm (HR=0.56; 95% CI: 0.44, 0.71; p<0.0001).

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3008



No. at risk

Rd	369	333	307	280	254	236	219	204	194	177	161	113	64	33	10	2	1	0
D-Rd	368	347	335	320	309	300	290	276	266	256	233	174	131	70	24	7	1	0

Additional efficacy results from Study MMY3008 are presented in Table 8 below.

Table 8: Additional efficacy results from Study MMY3008^a

	DRd (n=368)	Rd (n=369)
Overall response (sCR+CR+VGPR+PR) n(%) ^a	342 (92.9%)	300 (81.3%)
p-value ^b	<0.0001	
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)
Complete response (CR)	63 (17.1%)	46 (12.5%)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)
Partial response (PR)	50 (13.6%)	104 (28.2%)
CR or better (sCR + CR)	175 (47.6%)	92 (24.9%)
p-value ^b	<0.0001	
VGPR or better (sCR + CR + VGPR)	292 (79.3%)	196 (53.1%)
p-value ^b	<0.0001	
MRD negativity rate ^{a,c} n(%)	89 (24.2%)	27 (7.3%)
95% CI (%)	(19.9%, 28.9%)	(4.9%, 10.5%)
Odds ratio with 95% CI ^d	4.04 (2.55, 6.39)	
p-value ^e	<0.0001	

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

^c Based on threshold of 10⁻⁵

^d Mantel-Haenszel estimate of the odds ratio for un-stratified tables is used. An odds ratio >1 indicates an advantage for DRd.

^e p-value from Fisher's exact test.

In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the DRd group and 1.05 months (range: 0.3 to 15.3 months) in the Rd group. The median duration of response had not been reached in the DRd group and was 34.7 months (95% CI: 30.8, not estimable) in the Rd group.

Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant:

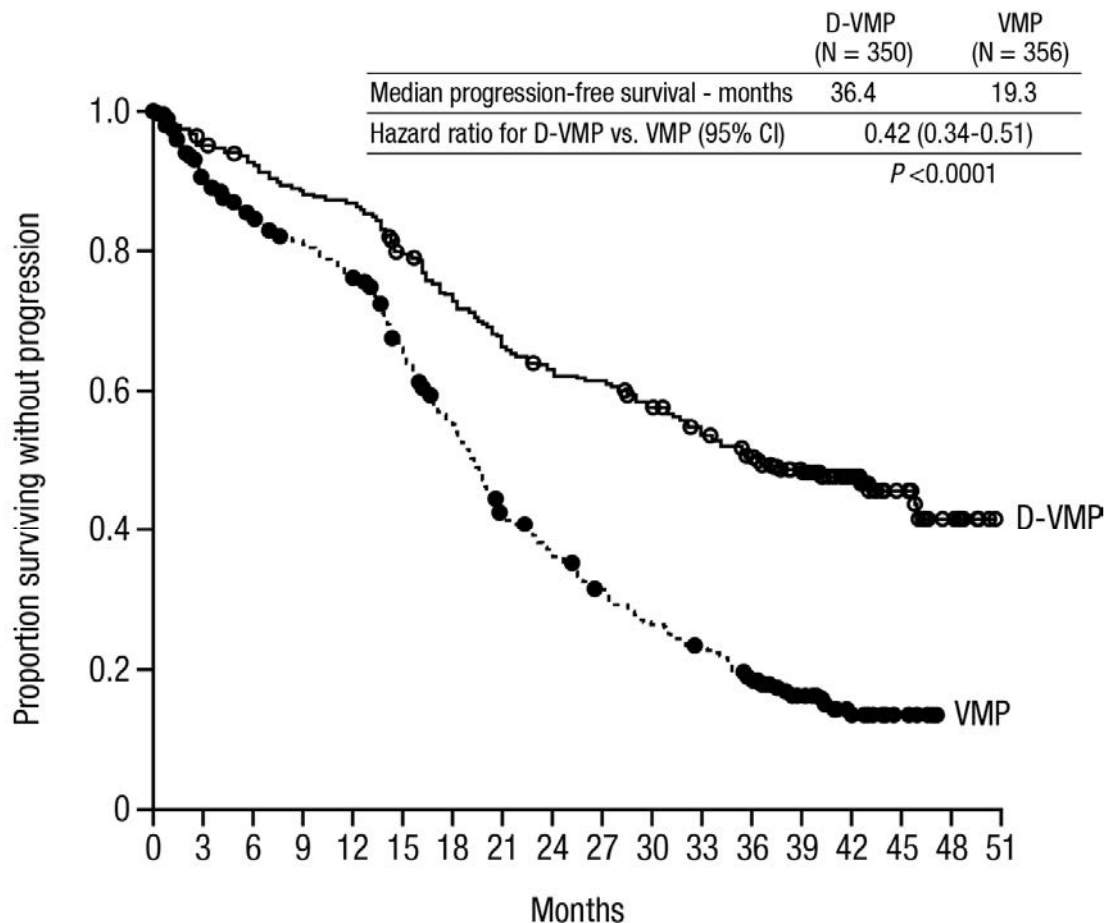
Study MMY3007, an open-label, randomised, active-controlled Phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m², and prednisone at 60 mg/m² were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). Intravenous daratumumab treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomised: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%), female (54%), 25% had an ECOG performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Patients had IgG/IgA/Light chain myeloma in 64%/22%/10% of instances, 19% had ISS Stage I, 42% had ISS Stage II, 38% had ISS Stage III disease and 84% had standard risk cytogenetics. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

With a median follow-up of 16.5 months, the primary analysis of PFS in Study MMY3007 showed an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001). Results of an updated PFS analysis after a median follow-up of 40 months continued to show an

improvement in PFS for patients in the D-VMP arm compared with the VMP arm. Median PFS was 36.4 months in the D-VMP arm and 19.3 months in the VMP arm (HR=0.42; 95% CI: 0.34, 0.51; $p < 0.0001$), representing a 58% reduction in the risk of disease progression or death in patients treated with D-VMP.

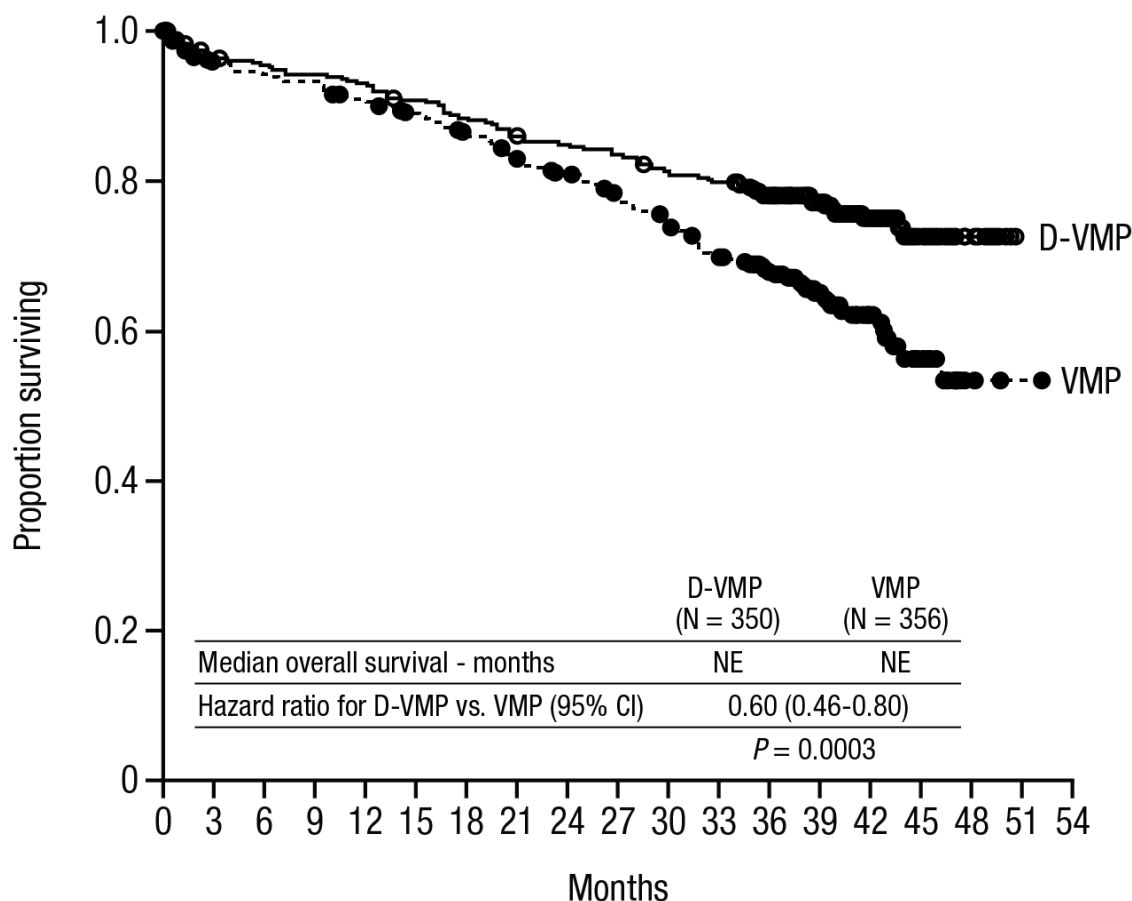
Figure 2: Kaplan-Meier Curve of PFS in Study MMY3007



No. at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
VMP		356	304	278	263	246	207	171	128	110	93	78	67	51	29	15	7	0	0
D-VMP		350	322	312	298	292	265	243	220	207	202	188	173	160	113	63	26	9	0

After a median follow-up of 40 months, D-VMP has shown an overall survival (OS) advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; $p = 0.0003$), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. Median OS was not reached for either arm.

Figure 3: Kaplan-Meier Curve of OS in Study MMY3007



No. at risk

VMP	356	331	325	322	312	302	292	278	269	257	242	226	198	132	73	27	3	1	0
D-VMP	350	330	327	322	318	309	301	292	288	283	275	270	248	171	97	40	12	0	0

Additional efficacy results from Study MMY3007 are presented in Table 9 below.

Table 9: Additional efficacy results from Study MMY3007^a

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) [n(%)]	318 (90.9)	263 (73.9)
p-value ^b	<0.0001	
Stringent complete response (sCR) [n(%)]	63 (18.0)	25 (7.0)
Complete response (CR) [n(%)]	86 (24.6)	62 (17.4)
Very good partial response (VGPR) [n(%)]	100 (28.6)	90 (25.3)
Partial response (PR) [n(%)]	69 (19.7)	86 (24.2)
MRD negativity rate (95% CI) ^c (%)	22.3 (18.0, 27.0)	6.2 (3.9, 9.2)
Odds ratio with 95% CI ^d	4.36 (2.64, 7.21)	
p-value ^e	<0.0001	

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

^a Based on intent-to-treat population

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

^c Based on threshold of 10⁻⁵

^d A Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio >1 indicates an advantage for D-VMP.

^e p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21.3 months (range: 18.4, not estimable) in the VMP group.

A subgroup analysis was performed on patients at least 70 years old, or those 65-69 years old with ECOG performance score of 2, or aged less than 65 years of age with significant comorbidity or ECOG performance score of 2 (D-VMP: n=273, VMP: n=270). The efficacy results in this subgroup were consistent with the overall population. In this subgroup, median PFS was not reached in the D-VMP group and was 17.9 months in the VMP group (HR=0.56; 95% CI: 0.42, 0.75); p<0.0001). The overall response rate was 90% in the D-VMP group and 74% in the VMP group (VGPR rate: 29% in D-VMP group and 26% in VMP group; CR: 22% in D-VMP group and 18% in VMP group; sCR rate: 20% in D-VMP group and 7% in VMP group). The safety results of this subgroup were consistent with the overall population. Furthermore, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was also consistent with the overall population.

Combination treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients eligible for autologous stem cell transplant (ASCT):

Study MMY3006 is a 2 Part, open-label, randomised, active-controlled Phase III study. Part 1 compared induction and consolidation treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (D-VTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete. In Part 2, subjects with at least a partial response (PR) by Day 100 post-transplant were re-randomised in a 1:1 ratio to daratumumab maintenance or observation only. Only results from Part 1 are described henceforth.

Bortezomib was administered by subcutaneous injection or intravenous injection at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 28 day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles (Cycles 5 and 6) following ASCT after Cycle 4. Thalidomide was administered orally at 100 mg daily during the six bortezomib cycles. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 of Cycles 1 and 2, and at 40 mg on Days 1-2 and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3-4. Dexamethasone 20 mg was administered on Days 1, 2, 8, 9, 15, 16 in Cycles 5 and 6. On the days of intravenous daratumumab infusion, the dexamethasone dose was administered intravenously as a pre-infusion medicinal product. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 1085 patients were randomised: 543 to the D-VTd arm and 542 to the VTd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 (range: 22 to 65) years. All patients were ≤65 years: 43% were in the age group ≥60-65 years, 41% were in the age group ≥50-60 years and 16% below age of 50 years. The majority were male (59%), 48% had an ECOG performance score of 0, 42% had an ECOG performance score of 1 and 10% had an ECOG performance score of 2. Forty percent had International Staging System (ISS) Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by the stringent Complete Response (sCR) rate at Day 100 post-transplant and Progression free survival (PFS).

Table 10: Efficacy results from Study MMY3006^a

	D-VTd (n=543)	VTd (n=542)	P value ^b
Response assessment Day 100 post-transplant			
Stringent Complete Response (sCR)	157 (28.9%)	110 (20.3%)	0.0010
CR or better (sCR+CR)	211 (38.9%)	141 (26.0%)	<0.0001
Very Good Partial Response or better (sCR+CR+VGPR)	453 (83.4%)	423 (78.0%)	
MRD negativity ^{c, d} n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI ^e	2.27 (1.78, 2.90)		
MRD negativity in combination with CR or better ^c n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI ^e	2.06 (1.56, 2.72)		

D-VTd=daratumumab-bortezomib-thalidomide-dexamethasone; VTd=bortezomib-thalidomide-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.

^c Based on threshold of 10⁻⁵

^d Regardless of response per IMWG

^e Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

Results of a PFS analysis by censoring patients who were randomised to daratumumab maintenance in the second randomisation, at the date of the second randomisation showed HR=0.50; 95% CI: 0.34, 0.75; p=0.0005.

Relapsed/Refractory multiple myeloma

Monotherapy:

The clinical efficacy and safety of intravenous daratumumab monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who had demonstrated disease progression on the last therapy, was demonstrated in two open-label studies.

In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg intravenous daratumumab until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 11% of patients were ≥75 years of age, 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent (IMiD), 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results of the pre-planned interim analysis based on Independent Review Committee (IRC) assessment are presented in Table 11 below.

Table 11: IRC assessed efficacy results for study MMY2002

Efficacy endpoint	Intravenous daratumumab 16 mg/kg N=106
Overall response rate ¹ (ORR: sCR+CR+VGPR+PR) [n (%)] 95% CI (%)	31 (29.2) (20.8, 38.9)
Stringent complete response (sCR) [n (%)]	3 (2.8)
Complete response (CR) [n]	0
Very good partial response (VGPR) [n (%)]	10 (9.4)
Partial response (PR) [n (%)]	18 (17.0)

Clinical Benefit Rate (ORR+MR) [n (%)]	36 (34.0)
Median Duration of Response [months (95% CI)]	7.4 (5.5, NE)
Median Time to Response [months (range)]	1 (0.9; 5.6)

¹ Primary efficacy endpoint (International Myeloma Working Group criteria)
CI=confidence interval; NE=not estimable; MR=minimal response

Overall response rate (ORR) in MMY2002 was similar regardless of type of prior anti-myeloma therapy.

At a survival update with a median duration of follow-up of 14.7 months, median Overall Survival (OS) was 17.5 months (95% CI:13.7, not estimable).

In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg intravenous daratumumab until disease progression. The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were Caucasian. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% were refractory to both a PI and IMiD, 60% were refractory to alkylating agents, 36% were refractory to pomalidomide and 17% were refractory to carfilzomib.

Pre-planned interim analysis showed that treatment with daratumumab at 16 mg/kg led to a 36% ORR with 5% CR and 5% VGPR. The median time to response was 1 (range: 0.5 to 3.2) month. The median duration of response was not reached (95% CI: 5.6 months, not estimable).

At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

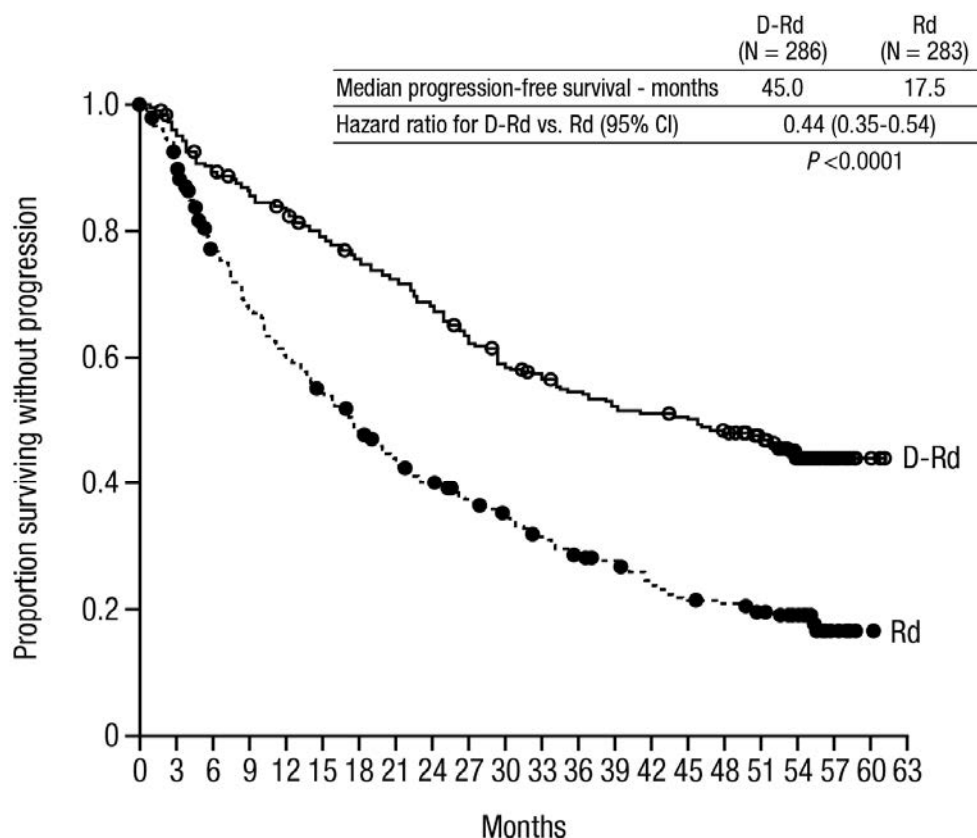
Combination treatment with lenalidomide:

Study MMY3003, an open-label, randomised, active-controlled Phase III trial, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose dexamethasone at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On intravenous daratumumab infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medicinal product and the remainder given the day after the infusion. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomised; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the intravenous daratumumab and the control arm. The median patient age was 65 years (range 34 to 89 years) and 11% were ≥75 years. The majority of patients (86%) received a prior PI, 55% of patients had received a prior IMiD, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and IMiD. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Patients refractory to lenalidomide were excluded from the study.

With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). Results of an updated PFS analysis after a median follow-up of 55 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 45.0 months in the DRd arm and 17.5 months in the Rd arm (HR=0.44; 95% CI: 0.35, 0.54; p<0.0001), representing a 56% reduction in the risk of disease progression or death in patients treated with DRd (see Figure 4).

Figure 4: Kaplan-Meier Curve of PFS in Study MMY3003



No. at risk

Rd	283	249	206	181	160	144	127	112	102	91	83	75	66	63	53	48	45	40	28	5	1	0
D-Rd	286	266	249	238	229	215	204	195	184	168	156	151	143	136	134	131	125	115	76	16	3	0

Additional efficacy results from Study MMY3003 are presented in Table 12 below.

Table 12: Additional efficacy results from Study MMY3003

Response evaluable patient number	DRd (n=281)	Rd (n=276)
Overall response (sCR+CR+VGPR+PR) n(%)	261 (92.9)	211 (76.4)
p-value ^a	<0.0001	
Stringent complete response (sCR)	51 (18.1)	20 (7.2)
Complete response (CR)	70 (24.9)	33 (12.0)
Very good partial response (VGPR)	92 (32.7)	69 (25.0)
Partial response (PR)	48 (17.1)	89 (32.2)
Median Time to Response [months (95% CI)]	1.0 (1.0, 1.1)	1.3 (1.1, 1.9)
Median Duration of Response [months (95% CI)]	NE (NE, NE)	17.4 (17.4, NE)
MRD negative rate (95% CI) ^b (%)	21.0 (16.4, 26.2)	2.8 (1.2, 5.5)
Odds ratio with 95% CI ^c	9.31 (4.31, 20.09)	
P-value ^d	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test.

^b Based on Intent-to-treat population and threshold of 10^{-5}

^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DRd.

^d p-value is from a Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; $p=0.0534$).

Combination treatment with bortezomib:

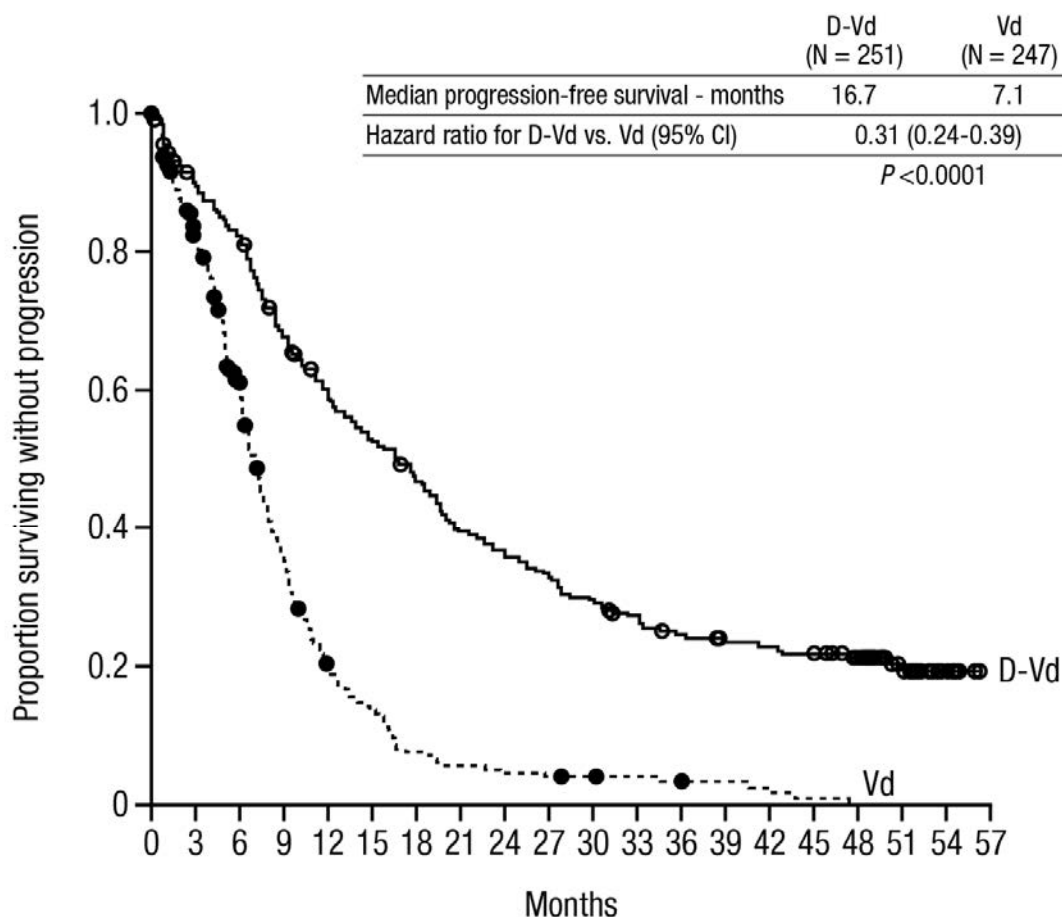
Study MMY3004, an open-label, randomised, active-controlled Phase III trial, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by subcutaneous injection or intravenous infusion at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles.

Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of intravenous daratumumab infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medicinal product. intravenous daratumumab treatment was continued until disease progression or unacceptable toxicity.

A total of 498 patients were randomised; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the intravenous daratumumab and the control arm. The median patient age was 64 years (range 30 to 88 years) and 12% were ≥75 years. Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an IMiD (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were refractory to lenalidomide. Patients refractory to bortezomib were excluded from the study.

With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value<0.0001). Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the DVd arm compared with the Vd arm. Median PFS was 16.7 months in the DVd arm and 7.1 months in the Vd arm (HR [95% CI]: 0.31 [0.24, 0.39]; p-value<0.0001), representing a 69% reduction in the risk of disease progression or death in patients treated with DVd versus Vd (see Figure 5).

Figure 5: Kaplan-Meier Curve of PFS in Study MMY3004



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Vd	247	182	129	74	39	27	15	11	9	8	7	6	5	4	2	1	0	0	0	0
D-Vd	251	215	198	161	138	123	109	92	85	77	68	61	54	50	48	46	38	20	7	0

Additional efficacy results from Study MMY3004 are presented in Table 13 below.

Table 13: Additional efficacy results from Study MMY3004

Response evaluable patient number	DVd (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%)	199 (82.9)	148 (63.2)
P-value ^a	<0.0001	
Stringent complete response (sCR)	11 (4.6)	5 (2.1)
Complete response (CR)	35 (14.6)	16 (6.8)
Very good partial response (VGPR)	96 (40.0)	47 (20.1)
Partial response (PR)	57 (23.8)	80 (34.2)
Median Time to Response [months (range)]	0.9 (0.8, 1.4)	1.6 (1.5, 2.1)
Median Duration of Response [months (95% CI)]	NE (11.5, NE)	7.9 (6.7, 11.3)
MRD negative rate (95% CI) ^b	8.8% (5.6%, 13.0%)	1.2% (0.3%, 3.5%)
Odds ratio with 95% CI ^c	9.04 (2.53, 32.21)	
P-value ^d	0.0001	

DVd=daratumumab- bortezomib-dexamethasone; Vd=bortezomib-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test.

^b Based on Intent-to-treat population and threshold of 10⁻⁵

^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DVd.

^d p-value is from Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 7.4 months (95% CI: 0.0, 14.9), the hazard ratio for OS was 0.77 (95% CI: 0.47, 1.26; p=0.2975).

Cardiac electrophysiology

Daratumumab as a large protein has a low likelihood of direct ion channel interactions. The effect of daratumumab on the QTc interval was evaluated in an open-label study for 83 patients (Study GEN501) with relapsed and refractory multiple myeloma following daratumumab infusions (4 to 24 mg/kg). Linear mixed PK-PD analyses indicated no large increase in mean QTcF interval (i.e. greater than 20 ms) at daratumumab C_{max} .

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with DARZALEX in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Daratumumab exposure in a monotherapy study following the recommended 1,800 mg administration of DARZALEX subcutaneous formulation (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter) as compared to 16 mg/kg intravenous daratumumab for the same dosing schedule, showed non-inferiority for the co-primary endpoint of maximum C_{trough} (Cycle 3 Day 1 pre-dose), with mean \pm SD of 593 ± 306 $\mu\text{g/mL}$ compared to 522 ± 226 $\mu\text{g/mL}$ for intravenous daratumumab, with a geometric mean ratio of 107.93% (90% CI: 95.74-121.67).

Following the recommended dose of 1,800 mg DARZALEX solution for subcutaneous injection, peak concentrations (C_{max}) increased 4.8-fold and total exposure ($AUC_{0-7 \text{ days}}$) increased 5.4-fold from first dose to last weekly dose (8th dose). Highest trough concentrations for DARZALEX solution for subcutaneous injection are typically observed at the end of the weekly dosing regimens for both monotherapy and combination therapy.

The simulated trough concentrations following 6 weekly doses of 1,800 mg DARZALEX solution for subcutaneous injection for combination therapy were similar to 1,800 mg DARZALEX solution for subcutaneous injection monotherapy.

Absorption and distribution

At the recommended dose of 1,800 mg, the absolute bioavailability of DARZALEX solution for subcutaneous injection is 69%, with an absorption rate of 0.012 hour^{-1} , with peak concentrations occurring at 70 to 72 h (T_{max}).

The model predicted mean estimate of the volume of distribution for the central compartment was 5.25 L (36.9% CV) and peripheral compartment was 3.78 L, suggesting that daratumumab is primarily localised to the vascular system with limited extravascular tissue distribution.

Metabolism and elimination

Daratumumab exhibits both concentration and time-dependent pharmacokinetics with parallel linear and nonlinear (saturable) elimination that is characteristic of target-mediated clearance. The population PK model estimated mean clearance value of daratumumab is 4.96 mL/h (58.7% CV). The model-based geometric mean for half-life associated with linear elimination is 20.4 days (22.4% CV). For the monotherapy regimen, the steady state is achieved at approximately 5 months into every 4 weeks dosage at the recommended dose and schedule (1,800 mg; once weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter).

A population PK analysis was conducted using data from DARZALEX solution for subcutaneous injection monotherapy and combination therapy, and the predicted PK exposures are summarised in Table 14.

Table 14: Daratumumab exposure following administration of DARZALEX subcutaneous formulation (1,800 mg) or intravenous daratumumab (16 mg/kg) monotherapy

PK parameters	Cycles	subcutaneous daratumumab Median (5 th ; 95 th percentile)	intravenous daratumumab Median (5 th ; 95 th percentile)
C _{trough} (µg/mL)	Cycle 1, 1 st weekly dose	123 (36; 220)	112 (43; 168)
	Cycle 2, last weekly dose (Cycle 3 Day 1 C _{trough})	563 (177; 1063)	472 (144; 809)
C _{max} (µg/mL)	Cycle 1, 1 st weekly dose	132 (54; 228)	256 (173; 327)
	Cycle 2, last weekly dose	592 (234; 1114)	688 (369; 1061)
AUC _{0-7 days} (µg/mL•day)	Cycle 1, 1 st weekly dose	720 (293; 1274)	1187 (773; 1619)
	Cycle 2, last weekly dose	4017 (1515; 7564)	4019 (1740; 6370)

Special populations

Age and gender

Based on population PK analyses in patients (33-92 years) receiving monotherapy or various combination therapies, age had no statistically significant effect on the PK of daratumumab. No individualisation is necessary for patients on the basis of age.

Gender had a statistically significant effect on PK, with slightly higher exposure in females than males, but the difference in exposure is not considered clinically meaningful. No individualisation is necessary for patients on the basis of gender.

Renal impairment

No formal studies of DARZALEX subcutaneous formulation in patients with renal impairment have been conducted. Population PK analyses were performed based on pre-existing renal function data in patients receiving DARZALEX subcutaneous formulation monotherapy or various combination therapies, including 220 patients with normal renal function (creatinine clearance [CRCL] ≥ 90 mL/min), 273 with mild renal impairment (CRCL < 90 and ≥ 60 mL/min), 215 with moderate renal impairment (CRCL < 60 and ≥ 30 mL/min), and 33 with severe renal impairment or end stage renal disease (CRCL < 30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment

No formal studies of DARZALEX subcutaneous formulation in patients with hepatic impairment have been conducted.

Population PK analyses were performed in patients receiving DARZALEX subcutaneous formulation monotherapy or various combination therapies, including 655 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] \leq upper limit of normal [ULN]), 82 with mild hepatic impairment [(total bilirubin \leq ULN and AST $>$ ULN) or (ULN $<$ total bilirubin $\leq 1.5 \times$ ULN)] and 5 patients with moderate ($1.5 \times$ ULN $<$ total bilirubin $\leq 3 \times$ ULN) hepatic impairment. No clinically important differences in the exposure to daratumumab were observed between patients with normal hepatic function and mild hepatic impairment. There were very few patients with moderate hepatic impairment and no patients with severe hepatic impairment to make meaningful conclusions for these populations.

Race

Based on the population PK analyses in patients receiving either DARZALEX subcutaneous formulation monotherapy or various combination therapies, the daratumumab exposure was similar across races.

Body weight

The flat-dose administration of DARZALEX subcutaneous formulation 1,800 mg as monotherapy achieved adequate exposure for all body-weight subgroups. The mean Cycle 3 Day 1 C_{trough} in the lower body-weight subgroup (≤ 65 kg) was 60% higher and in the higher body weight (> 85 kg)

subgroup, 12% lower than the intravenous daratumumab subgroup. In some patients with body weight >120 kg, lower exposure was observed which may result in reduced efficacy. However, this observation is based on limited number of patients.

5.3 Preclinical safety data

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. No chronic toxicity testing has been conducted.

No animal studies have been performed to establish the carcinogenic potential of 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 (E420)

Water for injections

6.2 Incompatibilities

This medicinal product must not be used with other materials except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

1 year

During the shelf-life, the product in unpunctured vials may be stored at room temperature ($\leq 30^{\circ}\text{C}$) for a single period of up to 24 hours. Once the product has been taken out of the refrigerator, it must not be returned to the refrigerator (see section 6.6).

Prepared syringe

Chemical and physical in-use stability in syringe has been demonstrated for 4 hours at ambient temperature up to 30°C (86°F) and ambient light. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions of the opened medicinal product (see section 6.3).

6.5 Nature and contents of container

15 mL solution in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 1,800 mg of daratumumab. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

DARZALEX solution for subcutaneous injection is for single use only and is ready to use.

DARZALEX solution for subcutaneous injection should be a clear to opalescent and colourless to yellow solution. Do not use if opaque particles, discolouration or other foreign particles are present.

DARZALEX solution for subcutaneous injection is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles.

Remove the DARZALEX solution for subcutaneous injection vial from refrigerated storage (2°C-8°C) and equilibrate to ambient temperature (15°C-30°C). The unpunctured vial may be stored at ambient temperature and ambient light for a maximum of 24 hours in the original carton to protect from light. Keep out of direct sunlight. Do not shake.

Prepare the dosing syringe in controlled and validated aseptic conditions. Once transferred from the vial into the syringe, store DARZALEX solution for subcutaneous injection for up to 4 hours at ambient temperature and ambient light (see section 6.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2016

Date of latest renewal: 24 April 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURE RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Biogen Inc.
5000 Davis Drive
Research Triangle Park
North Carolina
27709
United States

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy, Co. Cork
Ireland

Samsung Biologics Co, LTD
300, Songdo bio-daero,
Yeonsu-gu, Incheon, 21987,
Republic of Korea

Biogen (Denmark) Manufacturing ApS
Biogen Alle 1
Hillerod, 3400
Denmark (DNK)

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• Additional risk minimisation measures

Prior to the launch of DARZALEX (daratumumab) in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, aiming at increasing awareness about the Important Identified Risk of “Interference for blood typing (minor antigen) (Positive Indirect Coombs’ test)” and providing guidance on how to manage it.

The MAH shall ensure that in each MS where DARZALEX (daratumumab) is marketed, all HCPs and patients who are expected to prescribe, dispense and receive this product have access to/are provided with the below.

The HCPs and Blood Banks educational materials, shall contain the following key elements:

- The guide for HCPs and Blood Banks, to advice about the risk of interference for blood typing and how to minimise it;
- The Patient Alert Card.

The Guide for HCP and Blood Banks shall contain the following key elements:

- All patients should be typed and screened prior to start treatment with daratumumab; alternatively, phenotyping may also be considered;
- Daratumumab-mediated positive indirect Coombs test (interfering with cross-matching of blood) may persist for up to 6 months after the last product’s infusion, therefore, the HCP should advise the patient to carry the Patient Alert Card until 6 months after the treatment has ended;
- Daratumumab bound to Red Blood Cells (RBCs) may mask the detection of antibodies to minor antigens in the patient’s serum;
- The determination of a patient’s ABO and Rh blood type are not impacted;
- The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, genotyping may also be considered;
- In case of urgent need for transfusion, non-cross matched ABO/RhD compatible RBC units can be administered as per local bank practices;
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the interference with indirect antiglobulin tests;
- Reference to the need to consult the Summary of Product Characteristics (SmPC);
- Reference to the need of giving the Patient Alert Card to the patients and to advise them to consult the Package Leaflet (PL).

The Patient Alert Card, shall contain the following key elements:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using DARZALEX (daratumumab), and that this treatment is associated with the Important Identified Risk of Interference for blood typing (minor antigen) (Positive Indirect Coombs' test), which might persist for up to 6 months after the last product's infusion, and a clear reference that the patient should continue to carry this card until 6 months after the treatment has ended;
- Contact details of the DARZALEX (daratumumab) prescriber;
- Reference to the need to consult the Package Leaflet (PL).

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR INITIATION PACK COMPRISING 11 PACKS (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
Initiation pack: 11 vials (6 x 5 mL vials + 5 x 20 mL vials)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (100 mg/400 mg) FOR 1 VIAL COMPONENT AS INTERMEDIATE PACK/COMPONENT OF AN INITIATION PACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial, 100 mg/5 mL
1 vial, 400 mg/20 mL
Component of an initiation pack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (100 mg/400 mg) (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial, 100 mg/5 mL
1 vial, 400 mg/20 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/001
EU/1/16/1101/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab
For intravenous use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/5 mL
400 mg/20 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 1,800 mg solution for injection
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 15 mL vial contains 1,800 mg of daratumumab (120 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For subcutaneous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

DARZALEX 1,800 mg solution for injection
daratumumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

DARZALEX 20 mg/mL concentrate for solution for infusion daratumumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DARZALEX is and what it is used for
2. What you need to know before you are given DARZALEX
3. How DARZALEX is given
4. Possible side effects
5. How to store DARZALEX
6. Contents of the pack and other information

1. What DARZALEX is and what it is used for

What DARZALEX is

DARZALEX is a cancer medicine that contains the active substance daratumumab. It belongs to a group of medicines called “monoclonal antibodies”. Monoclonal antibodies are proteins that have been designed to recognise and attach to specific targets in the body. Daratumumab has been designed to attach to specific cancer cells in your body, so that your immune system can destroy the cancer cells.

What DARZALEX is used for

DARZALEX is used in adults 18 years or older, who have a type of cancer called “multiple myeloma”. This is a cancer of your bone marrow.

2. What you need to know before you are given DARZALEX

You must not be given DARZALEX

- if you are allergic to daratumumab or any of the other ingredients of this medicine (listed in section 6).

Do not use DARZALEX if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given DARZALEX.

Warnings and precautions

Talk to your doctor or nurse before you are given DARZALEX:

Infusion-related reactions

DARZALEX is given as an infusion (drip) into a vein. Before and after each infusion of DARZALEX, you will be given medicines which help to lower the chance of infusion-related reactions (see “Medicines given during treatment with DARZALEX” in section 3). These reactions can happen during the infusion or in the 3 days after the infusion.

In some cases you may have a severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives).

Tell your doctor or nurse straight away if you get any of the infusion-related reactions listed at the top of section 4.

If you get infusion-related reactions, you may need other medicines, or the infusion may need to be slowed down or stopped. When these reactions go away, or get better, the infusion can be started again.

These reactions are most likely to happen with the first infusion. If you have had an infusion-related reaction once it is less likely to happen again. Your doctor may decide not to use DARZALEX if you have a strong infusion reaction.

Decreased blood cell counts

DARZALEX can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop any symptoms of infection such as fever or any symptoms of decreased platelet counts such as bruising or bleeding.

Blood transfusions

If you need a blood transfusion, you will have a blood test first to match your blood type.

DARZALEX can affect the results of this blood test. Tell the person doing the test that you are using DARZALEX.

Hepatitis B

Tell your doctor if you have ever had or might now have a hepatitis B infection. This is because DARZALEX could cause hepatitis B virus to become active again. Your doctor will check you for signs of this infection before, during and for some time after treatment with DARZALEX. Tell your doctor right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes.

Children and adolescents

Do not give DARZALEX to children or adolescents below 18 years of age. This is because it is not known how the medicine will affect them.

Other medicines and DARZALEX

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines you can get without a prescription, and herbal medicines.

Pregnancy

Talk to your doctor or nurse before you are given DARZALEX if you are pregnant, think you might be pregnant or are planning to have a baby.

If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

Contraception

Women who are being given DARZALEX should use effective contraception during treatment and for 3 months after treatment.

Breast-feeding

You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known how it will affect the baby.

Driving and using machines

You may feel tired after taking DARZALEX which may affect your ability to drive or use machines.

DARZALEX contains sodium

This medicine contains 9.3 mg sodium (main component of cooking/table salt) in each 5 mL vial. This is equivalent to 0.46% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 37.3 mg sodium (main component of cooking/table salt) in each 20 mL vial. This is equivalent to 1.86% of the recommended maximum daily dietary intake of sodium for an adult.

3. How DARZALEX is given

How much is given

Your doctor will work out your dose and schedule of DARZALEX. The dose of DARZALEX will depend on your body weight.

The usual starting dose of DARZALEX is 16 mg per kg of body weight. DARZALEX may be given alone or together with other medicines used to treat multiple myeloma.

When given alone, DARZALEX is given as follows:

- once a week for the first 8 weeks
- then once every 2 weeks for 16 weeks
- then once every 4 weeks after that as long as your condition does not worsen.

When DARZALEX is given together with other medicines your doctor may change the time between doses as well as how many treatments you will receive.

In the first week your doctor may give you the DARZALEX dose split over two consecutive days.

How the medicine is given

DARZALEX will be given to you by a doctor or nurse. It is given as a drip into a vein (“intravenous infusion”) over several hours.

Medicines given during treatment with DARZALEX

You may be given medicines to lower the chance of getting shingles.

Before each infusion of DARZALEX you will be given medicines which help to lower the chance of infusion-related reactions. These may include:

- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol).

After each infusion of DARZALEX you will be given medicines (such as corticosteroids) to lower the chance of infusion-related reactions.

People with breathing problems

If you have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease (COPD), you will be given medicines to inhale which help your breathing problems:

- medicines to help the airways in your lungs stay open (bronchodilators)
- medicines to lower swelling and irritation in your lungs (corticosteroids)

If you are given more DARZALEX than you should

This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you for side effects.

If you forget your appointment to have DARZALEX

It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion-related reactions

Tell your doctor or nurse straight away if you get any of the following signs of an infusion-related reaction during or in the 3 days after the infusion. You may need other medicines, or the infusion may need to be slowed down or stopped.

These reactions include the following symptoms:

Very common (may affect more than 1 in 10 people):

- chills
- sore throat, cough
- feeling sick (nausea)
- vomiting
- itchy, runny or blocked nose
- feeling short of breath or other breathing problems.

Common (may affect up to 1 in 10 people):

- chest discomfort
- dizziness or lightheadedness (hypotension)
- itching
- wheezing.

Rare (may affect up to 1 in 1,000 people):

- Severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 2.

If you get any of the infusion-related reactions above, tell your doctor or nurse straight away.

Other side effects

Very common (may affect more than 1 in 10 people):

- fever
- feeling very tired
- diarrhoea
- constipation
- decreased appetite
- headache
- nerve damage that may cause tingling, numbness, or pain
- high blood pressure
- muscle spasms
- swollen hands, ankles or feet
- feeling weak
- back pain
- chills
- lung infection (pneumonia)
- bronchitis
- infections of the airways – such as nose, sinuses or throat
- low number of red blood cells which carry oxygen in the blood (anaemia)
- low number of white blood cells which help fight infections (neutropenia, lymphopenia, leukopenia)
- low number of a type of blood cell called platelets which help to clot blood (thrombocytopenia)
- unusual feeling in the skin (such as a tingling or crawling feeling).

Common (may affect up to 1 in 10 people):

- irregular heart beat (atrial fibrillation)
- build up of fluid in the lungs making you short of breath
- flu
- urinary tract infection
- severe infection throughout the body (sepsis)
- dehydration
- high level of sugar in the blood
- low level of calcium in the blood
- inflamed pancreas
- type of herpes virus infection (cytomegalovirus infection)

Uncommon (may affect up to 1 in 100 people)

- inflamed liver (hepatitis)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DARZALEX

DARZALEX will be stored at the hospital or clinic.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What DARZALEX contains

- The active substance is daratumumab. One mL of concentrate contains 20 mg daratumumab. Each vial of 5 mL concentrate contains 100 mg of daratumumab. Each vial of 20 mL concentrate contains 400 mg of daratumumab.
- The other ingredients are glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride and water for injections (see “DARZALEX contains sodium” in section 2).

What DARZALEX looks like and contents of the pack

DARZALEX is a concentrate for solution for infusion and is a colourless to yellow liquid.

DARZALEX is supplied as a carton pack containing 1 glass vial.

DARZALEX is also supplied as an initiation pack containing 11 vials: (6 x 5 mL vials + 5 x 20 mL vials).

Marketing Authorisation Holder

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

This medicinal product is for single-use only.

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient weight.
- Check that the DARZALEX solution is colourless to yellow. Do not use if opaque particles, discolouration or other foreign particles are present.
- Using aseptic technique, remove a volume of 0.9% Sodium Chloride from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to an infusion bag/container containing 0.9% Sodium Chloride. Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene

(PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.

- Gently invert the bag/container to mix the solution. Do not shake.
- Visually inspect parenteral medicinal products for particulate matter and discolouration prior to administration. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature (15°C-25°C) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions (2°C-8°C) and protected from light. Do not freeze.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Package leaflet: Information for the patient

DARZALEX 1,800 mg solution for injection daratumumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DARZALEX is and what it is used for
2. What you need to know before you are given DARZALEX
3. How DARZALEX is given
4. Possible side effects
5. How to store DARZALEX
6. Contents of the pack and other information

1. What DARZALEX is and what it is used for

What DARZALEX is

DARZALEX is a cancer medicine that contains the active substance daratumumab. It belongs to a group of medicines called “monoclonal antibodies”. Monoclonal antibodies are proteins that have been designed to recognise and attach to specific targets in the body. Daratumumab has been designed to attach to specific cancer cells in your body, so that your immune system can destroy the cancer cells.

What DARZALEX is used for

DARZALEX is used in adults 18 years or older, who have a type of cancer called “multiple myeloma”. This is a cancer of your bone marrow.

2. What you need to know before you are given DARZALEX

You must not be given DARZALEX

- if you are allergic to daratumumab or any of the other ingredients of this medicine (listed in section 6).

Do not use DARZALEX if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given DARZALEX.

Warnings and precautions

Talk to your doctor or nurse before you are given DARZALEX:

Infusion-related reactions

DARZALEX is given as a subcutaneous injection using a small needle to inject the medicine under your skin. Before and after each injection, you will be given medicines which help to lower the chance of infusion-related reactions (see “Medicines given during treatment with DARZALEX” in section 3). These reactions are most likely to happen with the first injection and most reactions occur on the day of injection. If you have had an infusion-related reaction once it is less likely to happen again.

However, delayed reactions can happen up to 3-4 days after the injection. Your doctor may decide not to use DARZALEX if you have a strong reaction after the injection.

In some cases you may have a severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 4.

Tell your doctor or nurse straight away if you get any of the infusion-related reactions listed at the top of section 4. If you get infusion-related reactions, you may need other medicines to treat your symptoms, or the injections may need to be stopped. When these reactions go away, or get better, the injection can be started again.

Decreased blood cell counts

DARZALEX can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop any symptoms of infection such as fever or any symptoms of decreased platelet counts such as bruising or bleeding.

Blood transfusions

If you need a blood transfusion, you will have a blood test first to match your blood type. DARZALEX can affect the results of this blood test. Tell the person doing the test that you are using DARZALEX.

Hepatitis B

Tell your doctor if you have ever had or might now have a hepatitis B infection. This is because DARZALEX could cause hepatitis B virus to become active again. Your doctor will check you for signs of this infection before, during and for some time after treatment with DARZALEX. Tell your doctor right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes.

Children and adolescents

Do not give DARZALEX to children or adolescents below 18 years of age. This is because it is not known how the medicine will affect them.

Other medicines and DARZALEX

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines you can get without a prescription, and herbal medicines.

Pregnancy

Talk to your doctor or nurse before you are given DARZALEX if you are pregnant, think you might be pregnant or are planning to have a baby.

If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

Contraception

Women who are being given DARZALEX should use effective contraception during treatment and for 3 months after treatment.

Breast-feeding

You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known how it will affect the baby.

Driving and using machines

You may feel tired after taking DARZALEX which may affect your ability to drive or use machines.

DARZALEX solution for subcutaneous injection contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 15 mL, that is to say essentially 'sodium-free'.

DARZALEX solution for subcutaneous injection contains sorbitol

Sorbitol is a source of fructose. If your doctor has told you that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you take this medicine.

3. How DARZALEX is given

How much is given

The dose of DARZALEX solution for subcutaneous injection is 1,800 mg.

DARZALEX may be given alone or together with other medicines used to treat multiple myeloma.

When given alone, DARZALEX is given as follows:

- once a week for the first 8 weeks
- then once every 2 weeks for 16 weeks
- then once every 4 weeks after that as long as your condition does not worsen.

When DARZALEX is given together with other medicines your doctor may change the time between doses as well as how many treatments you will receive.

How the medicine is given

DARZALEX will be given to you by a doctor or nurse as an injection under your skin (subcutaneous injection) over approximately 3 to 5 minutes. It is given in the stomach area (abdomen), not in other sites of the body, and not into areas of the abdomen where the skin is red, bruised, tender, hard or where there are scars.

If you experience pain during the injection, the doctor or nurse may interrupt the injection and give you the remaining injection in another area of your abdomen.

Medicines given during treatment with DARZALEX

You may be given medicines to lower the chance of getting shingles.

Before each injection of DARZALEX you will be given medicines which help to lower the chance of infusion-related reactions. These may include:

- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol).

After each injection of DARZALEX you will be given medicines (such as corticosteroids) to lower the chance of infusion-related reactions.

People with breathing problems

If you have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease (COPD), you will be given medicines to inhale which help your breathing problems:

- medicines to help the airways in your lungs stay open (bronchodilators)
- medicines to lower swelling and irritation in your lungs (corticosteroids)

If you are given more DARZALEX than you should

This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you for side effects.

If you forget your appointment to have DARZALEX

It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion-related reactions

Tell your doctor or nurse straight away if you get any of the following symptoms within 3-4 days after the injection. You may need other medicines, or the injection may need to be interrupted or stopped.

These reactions include the following symptoms:

Very common (may affect more than 1 in 10 people):

- chills
- sore throat, cough
- feeling sick (nausea)
- vomiting
- itchy, runny or blocked nose
- feeling short of breath or other breathing problems.

Common (may affect up to 1 in 10 people):

- chest discomfort
- dizziness or lightheadedness (hypotension)
- itching
- wheezing.

Rare (may affect up to 1 in 1,000 people):

- Severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 2.

If you get any of the infusion-related reactions above, tell your doctor or nurse straight away.

Injection site reactions

Skin reactions at or near the injection site (local), including injection site reactions, can happen with DARZALEX solution for subcutaneous injection. These reactions are common (may affect up to 1 in 10 people) and symptoms may include:

- redness of the skin
- itching
- swelling

Other side effects

Very common (may affect more than 1 in 10 people):

- fever
- feeling very tired
- diarrhoea
- constipation
- decreased appetite
- difficulty sleeping
- headache
- nerve damage that may cause tingling, numbness, or pain
- muscle spasms
- joint pain
- high blood pressure
- swollen hands, ankles or feet
- feeling weak
- back pain

- lung infection (pneumonia)
- bronchitis
- infections of the airways – such as nose, sinuses or throat
- low number of red blood cells which carry oxygen in the blood (anaemia)
- low number of white blood cells which help fight infections (neutropenia, lymphopenia, leukopenia)
- low number of a type of blood cell called platelets which help to clot blood (thrombocytopenia)

Common (may affect up to 1 in 10 people):

- irregular heart beat (atrial fibrillation)
- build up of fluid in the lungs making you short of breath
- urinary tract infection
- severe infection throughout the body (sepsis)
- dehydration
- high level of sugar in the blood
- low level of calcium in the blood
- feeling dizzy
- chest muscle pain
- flu
- chills
- rash
- itching
- unusual feeling in the skin (such as a tingling or crawling feeling)
- inflamed pancreas
- type of herpes virus infection (cytomegalovirus infection)

Uncommon (may affect up to 1 in 100 people)

- inflamed liver (hepatitis)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DARZALEX

DARZALEX solution for subcutaneous injection will be stored at the hospital or clinic.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What DARZALEX contains

- The active substance is daratumumab. One mL of solution contains 120 mg daratumumab. One vial of 15 mL solution for injection contains 1,800 mg of daratumumab.
- The other ingredients are recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol (E420), and water for injections (see “DARZALEX contains sodium and sorbitol” in section 2).

What DARZALEX looks like and contents of the pack

DARZALEX solution for subcutaneous injection is a colourless to yellow liquid.

DARZALEX solution for subcutaneous injection is supplied as a carton pack containing 1 single-dose glass vial.

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Manufacturer

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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

DARZALEX solution for subcutaneous injection should be administered by a healthcare professional.

To prevent medication errors, it is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being given to the patient as prescribed. DARZALEX solution for injection should be given by subcutaneous injection only, using the dose specified. DARZALEX subcutaneous formulation is not intended for intravenous administration.

DARZALEX solution for subcutaneous injection is for single use only and is ready to use.

- DARZALEX solution for subcutaneous injection is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles.
- DARZALEX solution for subcutaneous injection should be a clear to opalescent and colourless to yellow solution. Do not use if opaque particles, discolouration or other foreign particles are present.
- Remove the DARZALEX solution for subcutaneous injection vial from refrigerated storage (2°C – 8°C) and equilibrate to ambient temperature (15°C–30°C). The unpunctured vial may be stored at ambient temperature and ambient light for a maximum of 24 hours in the original carton to protect from light. Keep out of direct sunlight. Do not shake.
- Prepare the dosing syringe in controlled and validated aseptic conditions.
- To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

Storage of prepared syringe

- If the syringe containing DARZALEX is not used immediately, store the solution of DARZALEX for up to 4 hours at ambient temperature and ambient light.

Administration

- Inject 15 mL DARZALEX solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject DARZALEX solution for subcutaneous injection at other sites of the body as no data are available.
- Injection sites should be rotated for successive injections.
- DARZALEX solution for subcutaneous injection should never be injected 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 slowing down the injection, 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 solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as DARZALEX.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.