

**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 $\kappa$  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:

- 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.
- 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

### **4.2 Posology and method of administration**

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

#### Posology

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

#### *Dose*

Standard dosing for monotherapy and in combination with lenalidomide (4-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 1.

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

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

<sup>a</sup> First dose of the every-2-week dosing schedule is given at week 9

<sup>b</sup> 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.

Modified 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 2.

**Table 2: Modified 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 <sup>a</sup>	every three weeks (total of 5 doses)
Week 25 onwards until disease progression <sup>b</sup>	every four weeks

<sup>a</sup> First dose of the every-3-week dosing schedule is given at week 10

<sup>b</sup> 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 3 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

**Table 3: Infusion rates for DARZALEX administration**

	Dilution volume	Initial infusion rate (first hour)	Increments of infusion rate <sup>a</sup>	Maximum infusion rate
<b>First infusion</b>	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<b>Second infusion<sup>b</sup></b>	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<b>Subsequent infusions<sup>c</sup></b>	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

<sup>a</sup> Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

<sup>b</sup> A dilution volume of 500 mL should be used only if there were no  $\geq$  Grade 1 IRRs during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.

<sup>c</sup> A modified initial rate for subsequent infusions (i.e. third infusion onwards) should only be used only if there were no  $\geq$  Grade 1 IRRs during a final infusion rate of  $\geq$  100 mL/hr in the first two infusions. Otherwise, use instructions for the second infusion.

#### *Management of infusion-related reactions*

Pre-infusion medications 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 3).
- 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 3). 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 (s)*

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 medications

##### *Pre-infusion medication*

Pre-infusion medications 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, administered prior to every DARZALEX infusion (see section 5.1).  
Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions.
- Antipyretics (oral paracetamol 650 to 1,000 mg)
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

##### *Post-infusion medication*

Post-infusion medications should be administered to reduce the risk of delayed infusion-related reactions 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 ( $\leq 20$  mg) or equivalent the day after the DARZALEX infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone) is administered the day after the DARZALEX infusion, additional post-infusion medications may not be needed (see section 5.1).

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-infusion medications 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 medications 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(s) or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Infusion-related reactions

Infusion-related reactions (IRRs) were reported in approximately half of all patients treated with DARZALEX. Monitor such patients throughout the infusion and the post-infusion period.

The majority of IRRs occurred at the first infusion. 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. Medical management/supportive treatment for IRRs should be instituted as needed. The infusion rate should be reduced when re-starting the infusion (see section 4.2).

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following DARZALEX infusions. Additionally the use of post-infusion medications (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).

DARZALEX therapy should be permanently discontinued in the event of life-threatening IRRs.

#### Neutropenia/Thrombocytopenia

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

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

#### 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 should be taken into consideration by patients on a controlled sodium diet.

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

As an IgG1κ 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 pomalidomide, thalidomide, and bortezomib indicated no clinically-relevant drug-drug interaction between DARZALEX and these combination therapies.

#### 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, consider other methods to evaluate the depth of 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 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 safety data described below reflects exposure to DARZALEX (16 mg/kg) in 820 patients with multiple myeloma including 526 patients from two Phase III active-controlled trials who received DARZALEX in combination with either lenalidomide (DRd; n = 283; Study MMY3003) or bortezomib (DvD; n = 243; Study MMY3004) and five open-label, clinical trials in which patients received DARZALEX either in combination with pomalidomide (DPd; n = 103), in combination with lenalidomide (n = 35) or as monotherapy (n = 156).

The most frequent adverse reactions (> 20%) in individual randomised controlled studies were infusion reactions, fatigue, nausea, diarrhoea, muscle spasms, pyrexia, cough, dyspnoea, neutropenia, thrombocytopenia and upper respiratory tract infection. In addition, in combination with bortezomib, peripheral oedema and peripheral sensory neuropathy were frequently reported. Serious adverse reactions were pneumonia, upper respiratory tract infection, influenza, pyrexia, diarrhoea, atrial fibrillation.

#### Tabulated list of adverse reactions

Table 4 summarises the adverse drug reactions that occurred in patients receiving DARZALEX. 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 4: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg**

System Organ Class	Adverse reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
<b>Infections and infestations</b>	Pneumonia <sup>+</sup>	Very Common	16	10
	Upper respiratory tract infection <sup>+</sup>		52	5
	Influenza	Common	5	1*
<b>Blood and lymphatic system disorders</b>	Neutropenia	Very Common	44	37
	Thrombocytopenia		37	23
	Anaemia		31	16
	Lymphopenia		10	8
<b>Nervous system disorders</b>	Peripheral sensory neuropathy	Very Common	20	2*
	Headache	Very Common	13	< 1*
<b>Cardiac disorders</b>	Atrial fibrillation	Common	3	1
<b>Respiratory, thoracic and mediastinal disorders</b>	Cough <sup>+</sup>	Very Common	31	< 1*
	Dyspnoea <sup>+</sup>		22	3
<b>Gastrointestinal disorders</b>	Diarrhoea	Very Common	34	4
	Nausea		22	1*
	Vomiting		15	1*
<b>Musculoskeletal and connective tissue disorders</b>	Muscle spasms	Very Common	18	< 1*
<b>General disorders and administration site conditions</b>	Fatigue	Very Common	34	5
	Pyrexia		20	1*
	Oedema peripheral <sup>+</sup>		19	1*
<b>Injury, poisoning and procedural complications</b>	Infusion-related reaction <sup>#</sup>	Very common	48	6*

<sup>+</sup> Indicates grouping of terms

\* No grade 4

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

#### Infusion-related reactions

In clinical trials (monotherapy and combination treatments; N = 820) the incidence of any grade infusion-related reactions was 46% with the first infusion of DARZALEX, 2% with the second infusion, and 3% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion-related reaction with second or subsequent infusions.

The median time to onset of a reaction was 1.4 hours (range: 0.02 to 72.8 hours). The incidence of infusion interruptions due to reactions was 42%. Median durations of infusion for the 1<sup>st</sup>, 2<sup>nd</sup> and subsequent infusions were 7, 4.3 and 3.5 hours respectively.

Severe (Grade 3) infusion-related reactions included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse infusion-related reactions (any Grade,  $\geq 5\%$ ) were nasal congestion, cough, chills, throat irritation, vomiting and nausea.

#### Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported with DARZALEX combinations and background therapies (DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 2% to 5% of patients. Fatal infections were reported in 0.8% to 2% of patients across studies, primarily due to pneumonia and sepsis.



### 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.

### 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 overdosage 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 IgG1κ 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<sub>regs</sub>) and B cells (CD38+B<sub>regs</sub>) 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<sup>dim</sup>) 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

Patients treated with daratumumab monotherapy (n = 199) and combination therapy (n = 299) were evaluated for anti-therapeutic antibody responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment. Following the start of daratumumab treatment, none of the monotherapy patients and 2 (0.7%) of the combination therapy patients tested positive for anti-daratumumab antibodies; 1 of the combination therapy patients developed transient neutralizing antibodies against daratumumab.

However, the employed assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab. Therefore, the incidence of antibody development might not have been reliably determined.

### Clinical efficacy and safety

#### *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 5 below.

**Table 5: IRC assessed efficacy results for study MMY2002**

<b>Efficacy endpoint</b>	<b>DARZALEX 16 mg/kg N = 106</b>
Overall response rate <sup>†</sup> (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)

<sup>†</sup> 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.

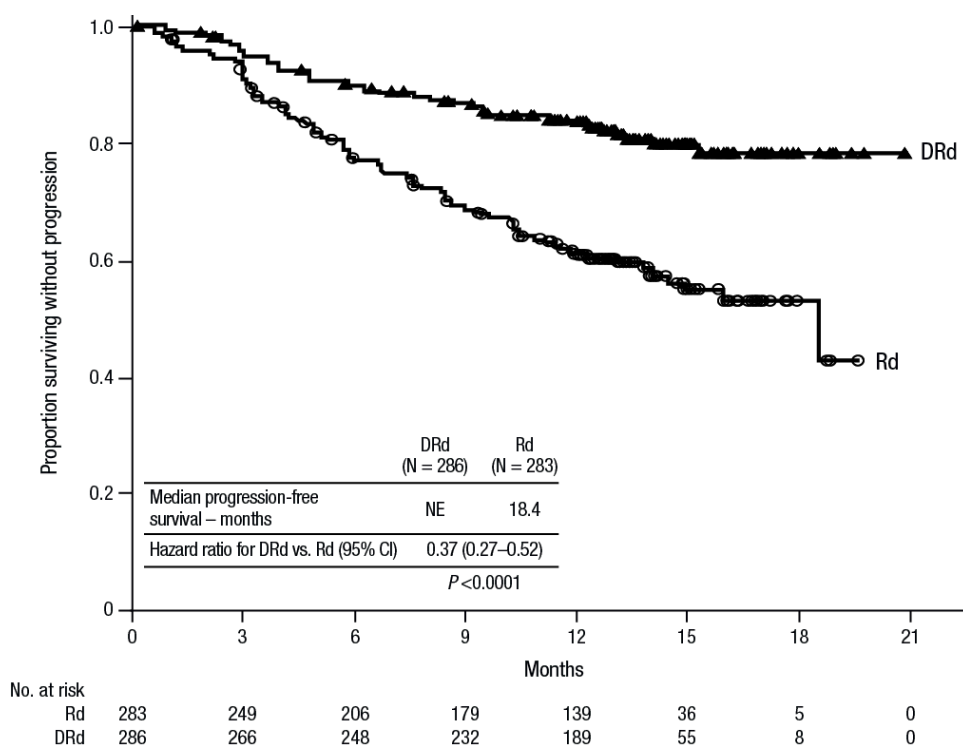
#### *Combination treatment with lenalidomide*

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 body mass index [BMI] < 18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. 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.

Study MMY3003 demonstrated 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 18.4 months in the Rd arm (hazard ratio [HR]=0.37; 95% CI: 0.27, 0.52;  $p < 0.0001$ ), representing 63% reduction in the risk of disease progression or death in patients treated with DRd (see Figure 1).

**Figure 1: Kaplan-Meier Curve of PFS in Study MMY3003**



Additional efficacy results from Study MMY3003 are presented in Table 6 below.

**Table 6: 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 <sup>a</sup>	< 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) <sup>b</sup> (%)	29.0 (23.8, 34.7)	7.8 (4.9, 11.5)
Odds ratio with 95% CI <sup>c</sup>	4.85 (2.93, 8.03)	
P-value <sup>d</sup>	< 0.000001	

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

<sup>a</sup> p-value from Cochran Mantel-Haenszel Chi-Squared test.

<sup>b</sup> Based on Intent-to-treat population and threshold of  $10^{-4}$

<sup>c</sup> A Chi-Squared estimate of the common odds ratio is used. An odds ratio > 1 indicates an advantage for DRd.

<sup>d</sup> p-value is from a likelihood-ratio Chi-Squared 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*

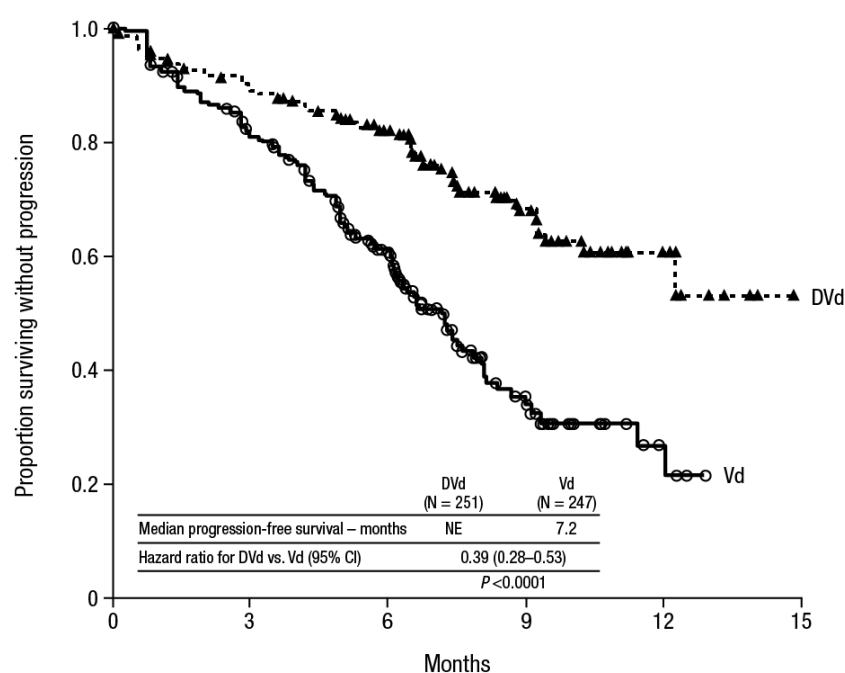
Study MMY3004, an open-label, randomised, active-controlled Phase III trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV infusion at a dose of  $1.3 \text{ mg/m}^2$  body surface area twice weekly for two weeks (Days 1, 4, 8, and 11)

of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients > 75 years, BMI < 18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years) 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.

Study MMY3004 demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd. (see Figure 2).

**Figure 2: Kaplan-Meier Curve of PFS in Study MMY3004**



No. at risk

Vd	247	182	106	25	5	0
DVd	251	215	146	56	11	0

Additional efficacy results from Study MMY3004 are presented in Table 7 below.

**Table 7: 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 <sup>a</sup>	< 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) <sup>b</sup>	13.5% (9.6%, 18.4%)	2.8% (1.1%, 5.8%)
Odds ratio with 95% CI <sup>c</sup>	5.37 (2.33, 12.37)	
P-value <sup>d</sup>	0.000006	

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

<sup>a</sup> p-value from Cochran Mantel-Haenszel Chi-Squared test.

<sup>b</sup> Based on Intent-to-treat population and threshold of 10<sup>-4</sup>

<sup>c</sup> A Chi-Squared estimate of the common odds ratio is used. An odds ratio > 1 indicates an advantage for DVd.

<sup>d</sup> p-value is from a likelihood-ratio chi-squared 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 20ms) at daratumumab C<sub>max</sub>.

### 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. A population PK model of daratumumab was developed to describe the PK characteristics of daratumumab and to evaluate the influence of covariates on the disposition of daratumumab in patients with multiple myeloma. The population PK analysis included 223 patients receiving DARZALEX monotherapy in two clinical trials (150 subjects received 16 mg/kg).

In the 1- to 24 mg/kg cohorts, peak serum concentrations (C<sub>max</sub>) 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<sub>max</sub> 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<sub>max</sub> 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.

Based on the population PK analysis of daratumumab monotherapy, daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period (by the 21<sup>st</sup> 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.

An additional population PK analysis was conducted in patients with multiple myeloma that received daratumumab in various combination therapies from four clinical trials (694 patients of which 684 received daratumumab at 16 mg/kg). Daratumumab concentration-time profiles were similar following the monotherapy and combination therapies. The mean (SD) estimated terminal half-life associated with linear clearance in combination therapy was approximately 23 (12) days.

Based on population PK analysis 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.

### Special populations

#### *Age and gender*

Based on population PK analysis in patients receiving daratumumab monotherapy, age (range: 31-84 years) had no clinically important effect on the PK of daratumumab, and the exposure of daratumumab was similar between younger (aged < 65 years, n = 127) and older (aged ≥ 65 years, n = 96; aged ≥ 75 years, n = 18; aged ≥ 85 years, n = 0) patients. Similar to monotherapy, no clinically important influence of age on the exposure to daratumumab was observed in the population PK analyses in patients receiving combination therapies. The difference in exposure was within 6% between younger (age < 65 years, n = 352; or age < 75 years, n = 630) and older subjects (age ≥ 65 years, n = 342; or age ≥ 75 years, n = 64).

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

#### *Renal impairment*

No formal studies of daratumumab in patients with renal impairment have been conducted. A population PK analysis was performed based on pre-existing renal function data in patients receiving daratumumab monotherapy, including 71 with normal renal function (creatinine clearance [CRCL] ≥ 90 mL/min), 78 with mild renal impairment (CRCL < 90 and ≥ 60 mL/min), 68 with moderate renal impairment (CRCL < 60 and ≥ 30 mL/min), and 6 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. Additional population PK analyses in patients receiving combination treatments also demonstrated no clinically important differences in exposure to daratumumab between patients with renal impairment (mild, n = 264; moderate, n = 166; severe, n = 12) and those with normal renal function (n = 251).

#### *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.

The population PK analysis of patients treated with daratumumab monotherapy included 189 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN]) and 34 with mild hepatic impairment (TB 1.0 x to 1.5 x ULN or AST > ULN). No clinically important differences in exposure to daratumumab were observed between patients with mild hepatic impairment and those with normal hepatic function. An additional population PK analysis of patients with multiple myeloma that received daratumumab in various combination therapies included 598 patients with normal hepatic function, 83 patients with mild hepatic impairment and 5 patients with moderate (TB > 1.5 x to 3.0 x ULN), or severe (TB > 3.0 x ULN) 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 the population PK analysis of daratumumab monotherapy, the exposure to daratumumab was similar between white (n=197) and non-white (n=26) subjects. In an additional population PK analysis in multiple myeloma patients that received daratumumab with various combination therapies, the exposure to daratumumab was also similar between white (n = 558) and non-white (n = 136) subjects.

### **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

18 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.

## 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

**9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 May 2016

**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 Biologics Ireland  
Barnahely  
Ringaskiddy, Co. Cork  
Ireland

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**

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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 (100 mg/400 mg)****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.

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
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<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
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Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
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EU/1/16/1101/001  
EU/1/16/1101/002

<b>13. BATCH NUMBER</b>
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Lot

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
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<b>15. INSTRUCTIONS ON USE</b>
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<b>16. INFORMATION IN BRAILLE</b>
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Justification for not including Braille accepted

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
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2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

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**

## **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. DARZALEX is used if your cancer has not responded to, or has come back after treatment.

#### **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.

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 fever or if you have signs of 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.

#### **Children and adolescents**

Do not give DARZALEX to children or young people 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 breastfeeding 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**

Each 5 mL vial of DARZALEX contains 0.4 mmol (9.3 mg) sodium. This should be taken into consideration if you are on a controlled sodium diet.

Each 20 mL vial of DARZALEX contains 1.6 mmol (37.3 mg) sodium. This should be taken into consideration if you are on a controlled sodium diet.

### **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 or with some medicines, 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

When DARZALEX may also be given with some medicines as follows:

- once a week for the first 9 weeks
- then once every 3 weeks for 15 weeks
- then once every 4 weeks after that

#### **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 are 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

Other common symptoms (affecting up to 1 in 10 people) are:

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

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
- flu
- diarrhoea
- headache
- nerve damage that may cause tingling, numbness, or pain
- muscle spasms
- swollen hands, ankles or feet
- lung infection (pneumonia)
- 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)
- 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)

### **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.

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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>.

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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.

#### **ANNEX IV**

### **CONCLUSIONS ON THE REQUEST FOR ONE-YEAR MARKETING PROTECTION PRESENTED BY THE EUROPEAN MEDICINES AGENCY**

**Conclusions presented by the European Medicines Agency on:**

- **one-year marketing protection**

The CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies as further explained in the European Public Assessment Report.