เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

DARZALEX™

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 IgG1κ 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[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.

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[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 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[a]**	**Maximum infusion rate**
First infusion	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent 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 should be used only if there were no ≥ 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.

[c] A modified initial rate for subsequent infusions (i.e. third infusion onwards) should only be used only if there were no ≥ Grade 1 IRRs during a final infusion rate of ≥ 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 (≤ 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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
Infections and infestations	Pneumonia[+]	Very Common	16	10
	Upper respiratory tract infection[+]		52	5
	Influenza	Common	5	1*
Blood and lymphatic system disorders	Neutropenia	Very Common	44	37
	Thrombocytopenia		37	23
	Anaemia		31	16
	Lymphopenia		10	8
Nervous system disorders	Peripheral sensory neuropathy	Very Common	20	2*
	Headache	Very Common	13	< 1*
Cardiac disorders	Atrial fibrillation	Common	3	1
Respiratory, thoracic and mediastinal disorders	Cough[+]	Very Common	31	< 1*
	Dyspnoea[+]		22	3
Gastrointestinal disorders	Diarrhoea	Very Common	34	4
	Nausea		22	1*
	Vomiting		15	1*
Musculoskeletal and connective tissue disorders	Muscle spasms	Very Common	18	< 1*
General disorders and administration site conditions	Fatigue	Very Common	34	5
	Pyrexia		20	1*
	Oedema peripheral[+]		19	1*
Injury, poisoning and procedural complications	Infusion-related reaction[#]	Very common	48	6*

[+] 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 1st, 2nd 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, ≥ 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.

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_{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

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

Efficacy endpoint	**DARZALEX 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 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).

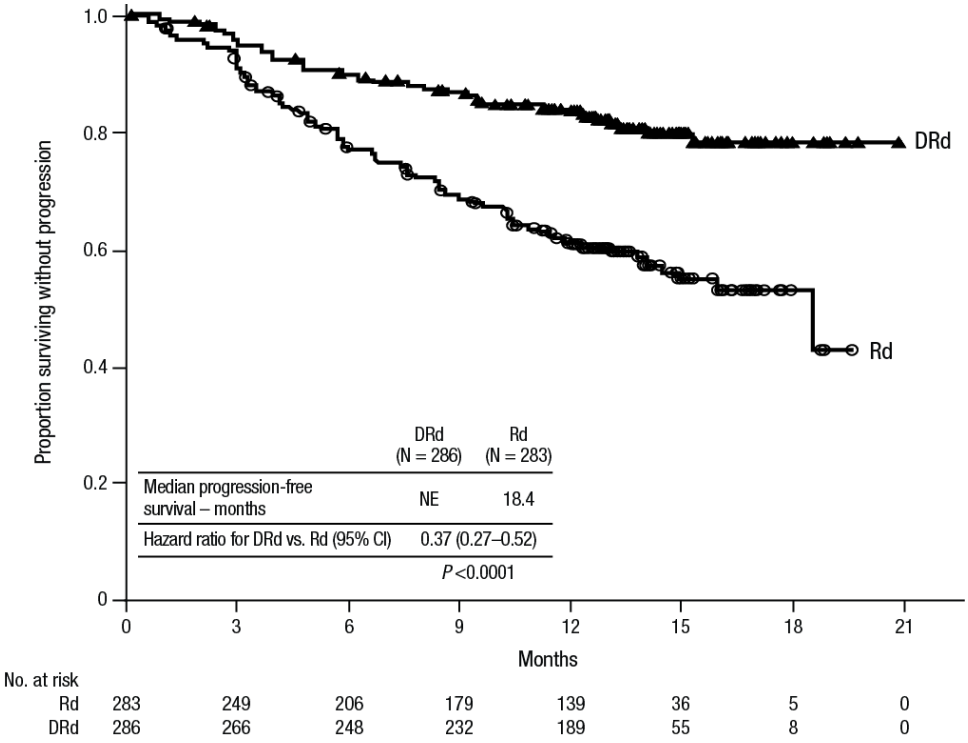
At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

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[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] (%)	29.0 (23.8, 34.7)	7.8 (4.9, 11.5)
Odds ratio with 95% CI[c]	4.85 (2.93, 8.03)	
P-value[d]	< 0.000001	

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^{-4}

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

[d] p-value is from a likelihood-ratio Chi-Squared test.

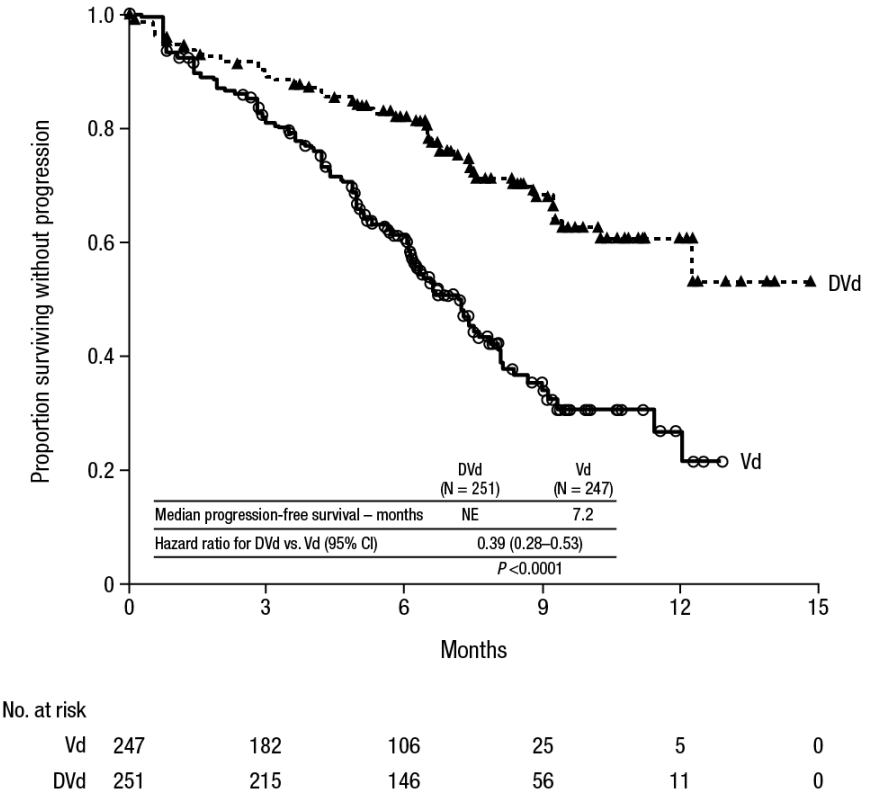
Median OS was not reached for either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; p = 0.0534).

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 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 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.

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



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[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]	13.5% (9.6%, 18.4%)	2.8% (1.1%, 5.8%)
Odds ratio with 95% CI[c]	5.37 (2.33, 12.37)	
P-value[d]	0.000006	

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^{-4}

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

[d] 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_{max}.

Paediatric population
No 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_{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.

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 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.

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 ≥ 75years, 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 xULN 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
See expiry date on the outer pack.

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.

MARKETING AUTHORISATION NUMBER AND DATE OF AUTHORISATION

Manufactured by	**Market Authorisation Number**	**Date of Authorisation**
Cilag AG, Schaffhausen, Switzerland	1C 30/60 (NBC)	3 August 2017
Vetter Pharma Fertigung GmbH & Co. KG, Ravensburg, Germany	1C 31/60 (NBC)	3 August 2017

DATE OF REVISION OF THE TEXT

28 April 2017

WARNING ACCORDING TO THE ANNOUNCEMENT FROM MINISTRY OF PUBLIC HEALTH

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

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