DARZALEX®

daratumumab

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

DARZALEX (daratumumab) 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:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent.

4.2 DOSE AND METHOD OF ADMINISTRATION

DARZALEX should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions (IRRs) if they occur.

Before DARZALEX therapy is commenced, clinicians should arrange for extended red cell phenotyping of patients (see 4.4 Special warnings and precautions for use – Effect on laboratory tests).

Pre- and post-infusion medications should be administered (see Recommended concomitant medications below).

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Dose

Adults (≥ 18 years)

Recommended dose

Monotherapy and Combination therapy with Lenalidomide and Low-Dose Dexamethasone (4-week cycle regimens)

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

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

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

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

For dosing instructions for medicinal products administered with DARZALEX, see section 5.1 Clinical efficacy and safety, and manufacturer's product information.

Combination therapy with VELCADE Bortezomib and Dexamethasone (3-week cycle regimens)

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

Table 2: Dosing schedule for DARZALEX 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 dosing instructions for medicinal products administered with DARZALEX see section 5.1 Clinical efficacy and safety, and manufacturer's product information.

Recommended concomitant medications

Pre-infusion medication

Administer the following pre-infusion medications to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of DARZALEX:

- Corticosteroid (long-acting or intermediate-acting)

  Monotherapy:

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

  Combination therapy:

  Administer 20 mg dexamethasone 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 500 to 1000 mg).

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

Post-infusion medication

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

Monotherapy:

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

Combination therapy:

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

However, if a background regimen-specific corticosteroid (e.g. dexamethasone) 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, consider the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids. 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.

Management of infusion-related reactions

Administer pre-infusion medications to reduce the risk of 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 also section 4.4).

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion 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 resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (see Method of Administration: Table 3).

- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate (Administration: Table 3). Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARZALEX upon the third occurrence of a Grade 3 or greater infusion reaction.

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

Missed dose(s)

If a planned dose of DARZALEX is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

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 manufacturer's product information.

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of DARZALEX in paediatric patients (17 years of age and younger) have not been established.

Elderly (65 years of age and older)

No overall differences in safety or effectiveness were observed between older (≥ 65 years) and younger patients.

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

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. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolized through hepatic pathways. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment) (see section 5.2).

Method of Administration

DARZALEX is administered as an intravenous infusion following dilution with 0.9% Sodium Chloride. For instructions on dilution of the medicinal product before administration, see section 6.6.

Following dilution the DARZALEX infusion should be intravenously administered at the appropriate 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	1000 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] Consider incremental escalation of the infusion rate only in the absence of infusion reactions
[b] Dilution volume of 500 mL should be used only if there were no infusion reactions 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] Use a modified initial rate for subsequent infusions (i.e. third infusion onwards) only if there were no infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.

4.3 CONTRAINDICATIONS

Patients with a history of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Before starting therapy, refer to the Data Sheet for medicinal products used in combination with DARZALEX.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before starting combination therapy, also refer to the Data Sheet for relevant other medicines (lenalidomide and dexamethasone, or bortezomib and dexamethasone). Patients receiving DARZALEX in combination with lenalidomide and dexamethasone should adhere to the pregnancy prevention programme of lenalidomide.

Infusion–related reactions

DARZALEX can cause serious infusion-related reactions, including anaphylactic reactions.

Monitor patients throughout the infusion and the post-infusion period.

In clinical trials, IRRs were reported in approximately half of all patients treated with DARZALEX.
The majority of IRRs occurred at the first infusion and were Grade 1-2. Four percent of patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, and hypertension, laryngeal oedema and pulmonary oedema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension (see section 4.8).

Pre-medicate patients with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with DARZALEX. Interrupt DARZALEX infusion for IRRs of any severity and institute medical management/supportive treatment as needed. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion. If an anaphylactic reaction or life-threatening (Grade 4) IRR occurs, permanently discontinue administration of DARZALEX and institute appropriate emergency care (see section 4.2).

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

Neutropenia/Thrombocytopenia

DARZALEX increases the incidence of neutropenia (including febrile neutropenia) and the incidence of thrombocytopenia.

Monitor complete blood cell counts periodically during treatment. This should be done as per clinical judgment but not less frequently than prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX dose 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.

Effect on laboratory tests

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 recognized 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.

Type and screen patients prior to starting DARZALEX.

In the event of a planned transfusion notify blood transfusion centres 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 affect the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Hepatitis B Virus (HBV) reactivation

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

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

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

Excipients

Each 5 mL and 20 mL vial of DARZALEX contains 0.4 mmol and 1.6 mmol (9.3 mg and 37.3 mg) sodium, respectively. This should be taken into consideration by patients on a controlled sodium diet.

Paediatric Use

The safety and efficacy of DARZALEX have not been established in paediatric patients.

Use in the Elderly

No overall differences in safety or effectiveness were observed between older (≥ 65 years) and younger patients.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-drug interaction studies have been performed.
Clinical pharmacokinetic assessments of pomalidomide, thalidomide, and bortezomib indicated no clinically-relevant drug-drug interaction between DARZALEX and these combination therapies.

Effects of DARZALEX on laboratory tests

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. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or genotyping. 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 (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

Pregnancy

Category C

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

To avoid exposure to the foetus, women of reproductive potential should use effective contraception during and for 3 months after cessation of DARZALEX treatment. However, when DARZALEX is used in combination with lenalidomide and dexamethasone, patients must also follow advice about use in pregnancy of those products – see below.

Use of DARZALEX with lenalidomide

Lenalidomide is associated with risk of foetal harm, including severe life-threatening human birth defects. Refer to the lenalidomide Data Sheet for additional information. Patients (both male and female) receiving DARZALEX in combination with lenalidomide and dexamethasone should adhere to the pregnancy prevention programme of lenalidomide.

Breast-feeding

It is not known whether daratumumab is excreted into human or animal milk or affects milk production. There are no studies to assess the effect of daratumumab on the breast-fed infant.

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. Because the risks of DARZALEX to the infant from oral ingestion are unknown, a decision should be made whether to discontinue breast-feeding, or 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.

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

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of daratumumab based on the comprehensive assessment of the available adverse event information. A causal relationship with daratumumab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Summary of the safety profile

The safety data described below reflect exposure to DARZALEX (16 mg/kg) in 820 patients with multiple myeloma including 526 patients from two phase 3 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; Study MMY1001), in combination with lenalidomide (n=35), or as monotherapy (n=156).

Tabulated list of adverse reactions

Combination treatment with lenalidomide

Adverse reactions described in Table 4 reflect exposure to DARZALEX (DRd arm) for a median treatment duration of 13.1 months (range: 0 to 20.7 months) and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide group (Rd) in Study MMY3003. The most frequent adverse reactions were infusion reactions, diarrhoea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnoea. Serious adverse reactions were pneumonia, upper respiratory tract infection, influenza and pyrexia. Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 4: Adverse reactions reported in Study MMY3003

System Organ Class Adverse Reaction	**DRd (N=283)**			**Rd (N=281)**		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**Any Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhoea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Influenza	7	3	0	5	1	0
Pneumonia[b]	19	10	2	15	7	2
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[b]	30	0	0	15	0	0
Dyspnoea	21	3	< 1	12	1	0

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

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

[b] Indicates grouping of preferred terms

Note: Adverse reactions that occurred in ≥ 10% of patients and with at least a 5% frequency greater in the DRd arm are listed. In addition, serious adverse events are listed if there was at least a 2% greater incidence in the DRd arm compared to the Rd arm.

Haematology laboratory related toxicities were excluded and reported separately in Table 5

Laboratory abnormalities worsening during treatment from baseline are listed in Table 5.

Table 5: Treatment-emergent haematology laboratory abnormalities

	Study MMY3003					
	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anaemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

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

Combination treatment with bortezomib

Adverse reactions described in Table 6 reflect exposure to DARZALEX (DVd arm) for a median treatment duration of 6.5 months (range: 0 to 14.8 months) and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in Study MMY3004. The most frequent adverse reactions (>20%) were infusion reactions, diarrhoea, peripheral oedema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnoea. Serious adverse reactions included diarrhoea, upper respiratory tract infection and atrial fibrillation. Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 6: Adverse reactions reported in Study MMY3004

System Organ Class Adverse Reaction	DVd (N=243)			Vd (N=237)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion reactions[a]	45	9	0	0	0	0
Cardiac disorders						
Atrial fibrillation	5	1	1	2	1	0
Gastrointestinal disorders						
Diarrhoea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Oedema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[b]	27	0	0	14	0	0
Dyspnoea[b]	21	4	0	11	1	0

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

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

[b] Indicates grouping of preferred terms

Note: Adverse reactions that occurred in ≥ 10% of patients and with at least a 5% frequency greater in the DVd arm are listed. In addition, serious adverse events are listed if there was at least a 2% greater incidence in the DVd arm compared to the Rd arm. Haematology laboratory related toxicities were excluded and reported separately in Table 7

Laboratory abnormalities worsening during treatment are listed in Table 7.

Table 7: Treatment-emergent haematology laboratory abnormalities

	Study MMY3004					
	DVd (N=243) %			**Vd (N=237) %**		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anaemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	<1
Lymphopenia	89	41	7	81	24	3

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

Monotherapy

The data described below reflect exposure to DARZALEX in three pooled open-label clinical studies that included 156 patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg. The median duration of DARZALEX treatment was 3.3 months, with the longest duration of treatment being 14.2 months. Adverse reactions occurring at a rate of ≥ 10% are presented in Table 8. The most frequently reported adverse reactions (≥ 20%) were IRRs, fatigue, nausea, back pain, anaemia, neutropenia and thrombocytopenia. Four percent of patients discontinued DARZALEX treatment due to adverse reactions, none of which were considered drug related.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000).

Table 8: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

System Organ Class	Adverse Reaction	Frequency (all Grades)	Incidence (%)	
			All Grades	Grade 3-4
Infections and infestations	Upper respiratory tract infection	Very Common	17	1*
	Nasopharyngitis		12	0
	Pneumonia**		10	6*
Blood and lymphatic system disorders	Anaemia	Very Common	25	17*
	Neutropenia		22	12
	Thrombocytopenia		20	14
Metabolism and nutrition disorders	Decreased appetite	Very Common	15	1*
Respiratory, thoracic and mediastinal disorders	Cough	Very Common	14	0
Gastrointestinal disorders	Nausea	Very Common	21	0
	Diarrhoea		15	0
	Constipation		14	0
Musculoskeletal and connective tissue disorders	Back pain	Very Common	20	2*
	Arthralgia		16	0
	Pain in extremity		15	1*
	Musculoskeletal chest pain		10	1*
General disorders and administration site conditions	Fatigue	Very Common	37	2*
	Pyrexia		17	1*
Injury, poisoning and procedural complications	Infusion-related reaction***	Very Common	51	4*

* No Grade 4

** Pneumonia also includes the terms pneumonia streptococcal and lobar pneumonia

*** Infusion-related reactions include but are not limited to, the following multiple adverse reaction terms: nasal congestion, cough, chills, allergic rhinitis, throat irritation, dyspnoea, nausea (all ≥ 5%), bronchospasm (2.6%), hypertension (1.9%) and hypoxia (1.3%).

Postmarketing data

Adverse reactions identified during postmarketing experience with DARZALEX are included in Table 9. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports
Not known	frequency cannot be estimated from the available data

In Table 9, adverse reactions are presented by frequency category based on spontaneous reporting rates, as well as frequency category based on precise incidence in a clinical trial, when known.

Table 9: Postmarketing Adverse Reactions

System Organ Class Adverse Reaction	Frequency Category based on Spontaneous Reporting Rate	Frequency Category based on Incidence in Clinical trial
Immune System disorders Anaphylactic reaction	Rare	Not known
Infections and Infestations Hepatitis B virus reactivation	Rare	Uncommon

Description of selected adverse reactions

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 reaction with second or subsequent infusions. No Grade 4 or 5 infusion reactions occurred.

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.

In combination studies, only 5 subjects (0.8%) discontinued DARZALEX treatment due to infusion-related reactions. In the monotherapy study, no subject treated with 16 mg/kg DARZALEX discontinued treatment due to an infusion-related reaction.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 without reaching the maximum tolerated dose.

Treatment

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 cells in a variety of haematological malignancies, including 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 inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilize multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) 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. 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 DARZALEX treatment in peripheral whole blood and bone marrow. T-cell receptor DNA sequencing verified that T-cell clonality was increased with DARZALEX 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 DARZALEX 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 (ATA) responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment. Following the start of DARZALEX 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.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

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}. The mean time-averaged QTcF interval increase was 10.1 ms (n=3) and 4.3 ms (n=42) in the 16 mg/kg cohorts from these analyses.

Clinical efficacy and safety

Combination treatment with lenalidomide
Study MMY3003, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy.

Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity. Patients refractory to lenalidomide were excluded from the study.

Table 10 Dosage regimen in combination treatment with lenalidomide

	Weeks 1-8	**Weeks 9-24**	**Weeks ≥ 25**
Daratumumab	16 mg/kg IV Weekly	16 mg/kg IV Every 2 weeks	16 mg/kg IV Every 4 weeks
Lenalidomide	25 mg oral, once daily Days 1-21 of each repeated 28 day [4 week] cycle		
Dexamethasone[a, b]	40 mg oral or IV Weekly		

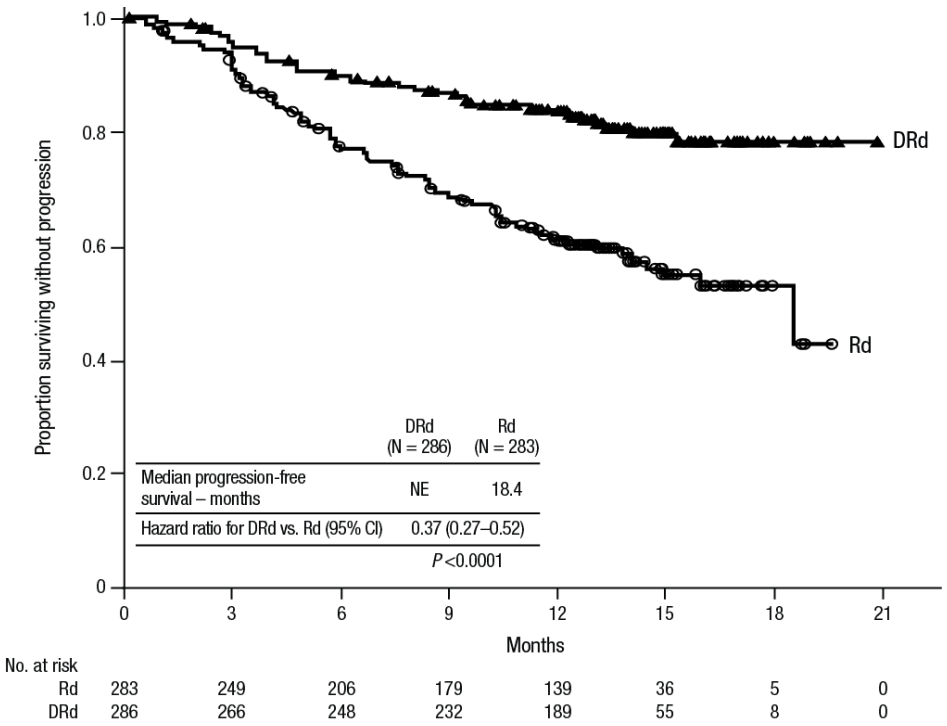
[a] Dexamethasone reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5

[b] On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.

A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 65 years (range 34 to 89 years), 11% were ≥ 75 years, 59% were male; 69% Caucasian, 18% Asian, and 3% African American. Patients had received a median of 1 prior line of therapy. Sixty -three percent (63%) of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior proteasome inhibitor (PI), 55% of patients had received a prior immunomodulatory agent (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. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

Study MMY3003 demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (hazard ratio [HR] = 0.37; 95% CI: 0.27, 0.52; p<0.0001) representing 63% reduction in the risk of disease progression or death in patients treated with DRd.

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



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

Table 11: Additional efficacy results from Study MMY3003

Response evaluable patient number	DRd (n=281)	Rd (n=276)
Overall response (sCR+CR+VGPR+PR) n (%) p-value[a]	261 (92.9) <0.0001	211 (76.4)
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 overall survival has not yet been reached in 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 VELCADE bortezomib

Study MMY3004, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV infusion at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of the 8 bortezomib cycles (80 mg/week for two out of three weeks of each 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 was continued until disease progression or unacceptable toxicity. Patients refractory to bortezomib were excluded from the study. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

Table 12 Dosage regimen in combination treatment with VELCADE bortezomib

	Weeks 1-9	**Weeks 10-24**	**Weeks ≥ 25**
Daratumumab	16 mg/kg IV Weekly	16 mg/kg IV Every 3 weeks	16 mg/kg IV Every 4 weeks
Bortezomib	1.3 mg/m^2 SC or IV Days 1,4,8,11 of each repeated 21 day [3 week] cycle		-
Dexamethasone[a, b]	20 mg oral or IV once daily Days 1, 2, 4, 5, 8, 9, 11, 12 of each repeated 21 day [3 week] cycle (ie 80 mg/week for two out of three weeks of each of the bortezomib cycle)		20 mg oral or IV (given as daratumumab pre-infusion medication)

[a] Dexamethasone reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy.

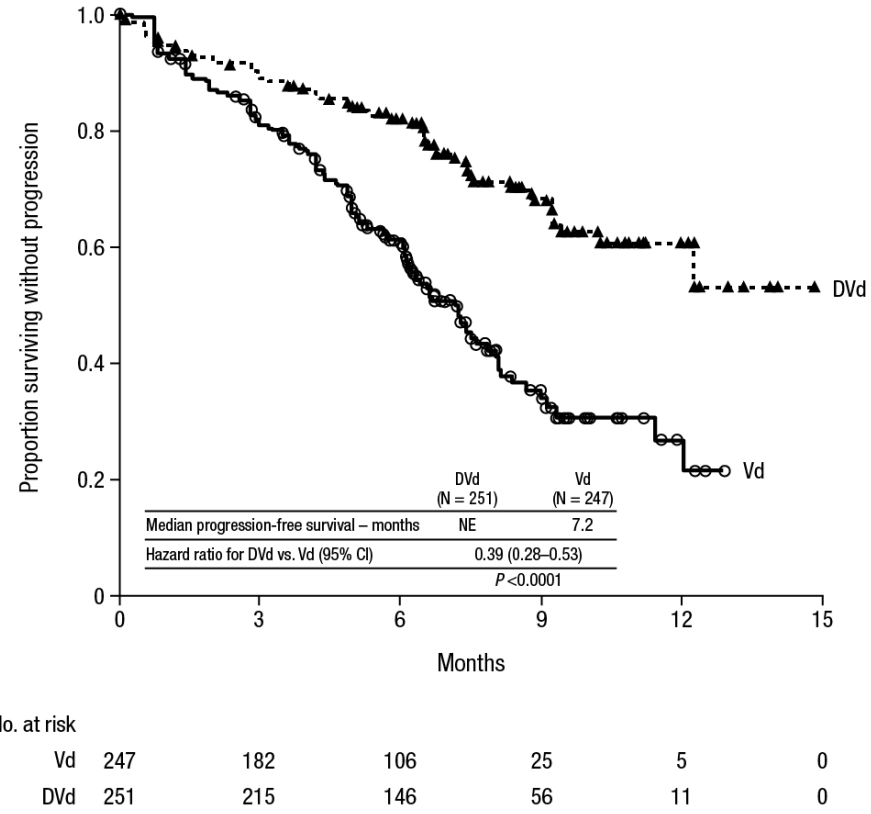
[b] On the days of DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.

A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years); 12% were ≥ 75 years, 57% were male; 87% Caucasian, 5% Asian and 4% African American. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior autologous stem cell transplantation (ASCT). Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an IMiD (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment and the proportions of patients refractory to any specific prior therapy were well balanced between the treatment groups. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were

refractory to lenalidomide. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

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.

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 Table 13 below.

Table 13: Additional efficacy results from Study MMY3004

Response evaluable patient number	DVd (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%) P-value[a] Stringent complete response (sCR) Complete response (CR) Very good partial response (VGPR) Partial response (PR)	199 (82.9) <0.0001 11 (4.6) 35 (14.6) 96 (40.0) 57 (23.8)	148 (63.2) 5 (2.1) 16 (6.8) 47 (20.1) 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).

Monotherapy

The clinical efficacy and safety of DARZALEX monotherapy for the treatment of patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent, 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), 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 PI and IMiD, 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results based on Independent Review Committee (IRC) assessment are presented in Table 14 below.

Table 14: 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.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of daratumumab following intravenous administration of DARZALEX 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. 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 minimized 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. 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 DARZALEX 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 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) 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 DARZALEX 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 DARZALEX in patients with hepatic impairment have been conducted. 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× to 1.5× 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× to 3.0× ULN), or severe (TB >3.0× 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

Carcinogenicity and mutagenicity

No animal studies have been performed to establish the carcinogenic potential of daratumumab. Routine genotoxicity and carcinogenicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Reproductive toxicology

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

Fertility

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

Unopened vials

24 months

After dilution

DARZALEX contains no antimicrobial preservative. To reduce microbiological hazard, use as soon as possible after dilution. If not used immediately, the solution may be stored in a refrigerator protected from light at 2°C–8°C for up to 24 hours prior to use, 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 an aqua flip-off button containing 100 mg of daratumumab.

20 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a purple flip-off button containing 400 mg of daratumumab.

DARZALEX is available in cartons containing 1 vial. Product is for single use in one patient only.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

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, discoloration 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 or freeze.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, 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 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland
NEW ZEALAND
Telephone: 0800 800 806
Fax: (09) 588 1398
Email: medinfo@janau.jnj.com

9 DATE OF FIRST APPROVAL

30 November 2017

10 DATE OF REVISION OF THE TEXT

22 February 2019

SUMMARY TABLE OF CHANGES

Section changes	**Summary of new information**
4.4	Addition of Hepatitis B Virus (HBV) reactivation
4.8	Addition of HBV reactivation to post-marketing adverse reactions