PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

DARZALEX 20 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 20 mg daratumumab.

5 mL vial: Each single-use vial contains 100 mg of daratumumab.

20 mL vial: Each single-use vial contains 400 mg of daratumumab.

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

Contains sodium: 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.

Contains sugar: Each DARZALEX 100 mg and DARZALEX 400 mg vial contains 0,14 mg and 0,55 mg mannitol respectively.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

DARZALEX is a colourless to yellow preservative free liquid concentrate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DARZALEX is indicated for Multiple Myeloma:

- In combination with bortezomib, melphalan and prednisone in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).
- In combination with lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).
- In combination with bortezomib, thalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT).
- In combination with lenalidomide and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy.
- In combination with pomalidomide and dexamethasone in adult patients with multiple myeloma who have received at least two prior therapies.
- In combination with bortezomib and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an

immunomodulatory agent and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

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

Pre- and post-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below *Recommended concomitant medications*).

<u>Posology</u> - Adults (≥ 18 years)

The DARZALEX dosing schedule in Table 1 is for combination therapy with 4-week cycle regimens (e.g., lenalidomide, pomalidomide) and for monotherapy as follows:

- combination therapy with lenalidomide and low-dose dexamethasone for patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant (ASCT).
- combination therapy with lenalidomide or pomalidomide and low-dose dexamethasone for patients with relapsed/refractory multiple myeloma.
- monotherapy for patients with relapsed/refractory multiple myeloma.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Table 5):

Table 1: DARZALEX dosing schedule for monotherapy and in combination with 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 of medicines administered with DARZALEX, see manufacturer's prescribing information.

The DARZALEX dosing schedule in Table 2 is for combination therapy with bortezomib, melphalan and prednisone (6-week cycle regimen) for patients with newly diagnosed multiple myeloma ineligible for ASCT.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Table 5):

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

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

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

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

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles.

The DARZALEX dosing schedule in Table 3 is for combination therapy with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for ASCT.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Table 5):

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

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

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

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

For dosing instructions of medicines administered with DARZALEX, see manufacturer's prescribing information.

The DARZALEX dosing schedule in Table 4 is for combination therapy with 3-week cycle regimens (e.g., bortezomib) for patients with relapsed/refractory multiple myeloma.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Table 5):

Table 4: Dosing schedule for DARZALEX with 3-week cycle dosing regimens

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 medicines administered with DARZALEX see manufacturer's prescribing information.

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 medicines given in combination with DARZALEX, see manufacturer's prescribing information.

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:

- 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 (or equivalent) prior to every DARZALEX infusion. When dexamethasone is the background regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on DARZALEX infusion days.

  Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions. Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken

on DARZALEX infusion days when patients have received dexamethasone as a pre-medication.

- 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, prednisone) is administered the day after the DARZALEX infusion, additional post-infusion medications may not be needed.

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 medical practitioner.

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 dosage adjustment is necessary for patients with renal impairment.

Hepatic impairment

No dosage adjustments are necessary for patients with hepatic impairment.

Elderly

No dose adjustments are considered necessary (see section 4.8 and 5.2).

Paediatric population

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

Method of administration

DARZALEX is administered as an intravenous infusion following dilution with 0,9 % Sodium Chloride. For instructions on dilution of this medicine before administration, see section 6.6.

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

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

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

	Dilution Volume	**Initial Rate (first hour)**	**Rate Increment[a]**	**Maximum Rate**
Week 1 Infusion				
Option 1 (Single dose infusion)				
Week 1 Day 1 (16 mg/kg)	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Option 2 (Split dose infusion)				
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 2 (16 mg/kg) infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (Week 3 onwards, 16 mg/kg) infusions[c]	500 mL	50 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 for the 16 mg/kg dose should be used only if there were no infusion reactions the previous week. Otherwise, use a dilution volume of 1000 mL.
[c] Use a modified initial rate (100 mL/hour) for subsequent infusions (i.e., Week 3 onwards) only if there were no infusion reactions during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

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 a maximum rate of 200 mL/hour (Table 5).
- 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 (Table 5). 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.

4.3 Contraindications

Hypersensitivity to daratamumab or to any of the excipients of DARZALEX (see section 6.1).

Pregnancy and breastfeeding (see section 4.6).

Live attenuated vaccines should not be administered to patients receiving DARZALEX (see section 4.4).

4.4 Special warnings and precautions for use

Infusion-related reactions

DARZALEX can cause serious infusion related reactions (IRRs), 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 all patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, 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 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 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.

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 DARZALEX infusion. It should be recognised that DARZALEX 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 prior to starting DARZALEX.

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.

Hepatitis B virus (HBV) Reactivation

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

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

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

Use with vaccines

Currently, there are no data regarding a potential interaction between DARZALEX and vaccines. It is recommended that live viral or live bacterial vaccines should not be given concurrently with monoclonal antibodies.

Excipients:

Sodium

Each 5 mL and 20 mL vial of DARZALEX contains 0,4 mmol and 1,6 mmol (9,3 mg and 37,3 mg) sodium, respectively. This corresponds to 0,46 % and 1,86 % of the WHO recommended maximum daily intake of 2 g sodium for an adult, respectively.

Mannitol (sugar)

Patients with rare hereditary conditions of mannitol intolerance should not receive DARZALEX.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

To avoid exposure to the foetus, women of child bearing potential should use effective contraception during, and for 3 months after cessation of DARZALEX treatment.

Pregnancy

DARZALEX should not be used during pregnancy (see section 4.3).
IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy.

If the patient becomes pregnant while taking DARZALEX, the patient should be informed of the potential risk to the foetus.

Breastfeeding

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 woman receiving DARZALEX should not breastfeed her infant.

4.7 Effects on ability to drive and use machines

DARZALEX may be associated with fatigue and IRRs may impair the patient's ability to drive and use machines. Patients should determine their personal side effects profile.

4.8 Undesirable effects

Summary of the safety profile

The safety data described below reflect exposure to DARZALEX (16 mg/kg) in 2066 patients with multiple myeloma including 1910 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy.

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

Tabulated list of adverse reactions

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

System Organ Class	**Adverse Reaction**	**Frequency (all Grades)**
Infections and infestations	Pneumonia[+] Bronchitis[+] Upper respiratory tract infection[+]	Very Common
	Urinary tract infection Influenza Sepsis[+]	Common
Blood and lymphatic system disorders	Anaemia[+] Neutropenia[+] Thrombocytopenia[+] Lymphopenia[+] Leukopenia[+]	Very Common
Metabolism and nutrition disorders	Decreased appetite	Very Common
	Hyperglycaemia Hypocalcaemia Dehydration	Common

Nervous system disorders	Peripheral sensory neuropathy Paraesthesia Headache	Very Common
Cardiac disorders	Atrial fibrillation	Common
Vascular disorders	Hypertension[+]	Very Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea[+] Cough[+]	Very Common
	Pulmonary oedema[+]	Common
Gastrointestinal disorders	Nausea Diarrhoea Constipation Vomiting	Very Common
	Pancreatitis[+]	Common
Musculoskeletal and connective tissue disorders	Back pain Muscle spasms	Very Common
General disorders and administration site conditions	Fatigue Pyrexia Peripheral Oedema[+] Asthenia	Very Common
	Chills	Common
Injury, poisoning and procedural complications	Infusion-related reaction [#]	Very Common

[+] Indicates grouping of terms

* No grade 4

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

Postmarketing side effects

Immune System disorders

Anaphylactic reaction

Infections and Infestations

Hepatitis B virus reactivation

Infusion related reactions

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

The median time to onset of a reaction was 1,5 hours (range: 0 to 72,8 hours). The incidence of infusion modifications due to reactions was 36 %. Median durations of 16 mg/kg infusions for the 1st, 2nd and subsequent infusions were approximately 7, 4 and 3 hours respectively.

Severe infusion-related reactions included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse infusion-related reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea.

When DARZALEX dosing was interrupted in the setting of ASCT (Study MMY3006) for a median of 3,75 (range: 2,4; 6,9) months, upon re-initiation of DARZALEX the incidence of

IRRs was 11 % at first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption due to ASCT. IRRs occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3/4: < 1 %) with those reported in previous studies at Week 2 or subsequent infusions.

In study MMY1001, patients receiving daratumumab combination treatment (n = 97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e., 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 42 %, with 36 % of patients experiencing infusion-related reactions on Day 1 of Week 1, 4 % on Day 2 of Week 1, and 8 % with subsequent infusions. The median time to onset of a reaction was 1,8 hours (range: 0,1 to 5,4 hours). The incidence of infusion interruptions due to reactions was 30 %. Median durations of infusions were 4,2 h for Week 1-Day 1, 4,2 h for Week 1-Day 2, and 3,4 hours for the subsequent infusions.

Infections

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

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

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

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

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

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

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

Other Adverse Reactions

Other adverse reactions reported in patients treated with daratumumab: pancreatitis (1%). Pancreatitis includes the following reported terms: pancreatitis, acute pancreatitis, chronic pancreatitis, hyperamylasaemia, obstructive pancreatitis, and increased lipase.

Other special populations

Of the 2459 patients who received DARZALEX at the recommended dose, 38 % were 65 to 75 years of age, and 15 % were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients (see section 4.8). Among patients with relapsed and refractory multiple myeloma (n = 1213), the most common serious adverse reactions that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n = 710), the most common serious adverse reaction that occurred more frequently in elderly (≥ 75 years of age) was pneumonia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers

are asked to report any suspected adverse reactions via "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com)

4.9 Overdose

Symptoms and signs

Are expected to be an increase in the frequency and severity of the adverse events listed under section 4.8.

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

Pharmacological classification: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FC01

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 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 (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+Tregs) and B cells (CD38+Bregs) are susceptible to daratumumab mediated cell lysis.

In addition, daratumumab induced apoptosis *in vitro* after Fc mediated cross linking and 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.

T cells (CD3+, CD4+, and CD8+) also 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.

Immunogenicity

Anti-therapeutic antibody (ATA) responses to daratumumab have not been found in the 331 patients in clinical efficacy studies.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of daratumumab following intravenous administration were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0,1 mg/kg to 24 mg/kg.

In the 1 to 24 mg/kg cohorts, peak serum concentrations (C_{max}) after the first dose increased in approximate proportion to dose and volume of distribution was consistent with initial distribution into the plasma compartment. 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. 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 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, 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.

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.

<u>Special populations</u>

Age and gender

Based on population PK analysis, age (range: 31 - 84 years) had no clinically important effect on the PK of daratumumab.

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, 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 (CRCL < 30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. A population PK analysis was performed to evaluate the effect of hepatic impairment as defined using the National Cancer Institute (NCI) criteria of hepatic dysfunction on the clearance of daratumumab based on pre-existing hepatic function data in 223 patients. No clinically important differences in the exposure to daratumumab were observed between patients with mild hepatic impairment (TB 1,0 × to 1,5 × ULN or AST > ULN; n = 34) and those with normal hepatic function (TB and AST ≤ ULN; n = 189). Daratumumab has not been studied in patients with moderate (TB > 1,5 × to 3 × ULN and any AST) or severe (TB > 3 × ULN and any AST) hepatic impairment.

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 medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

24 months

See expiry date on the outer pack.

After dilution

Since DARZALEX solution does not contain a preservative, unless the method of opening / dilution precludes the risk of microbial contamination, the product should be used immediately. 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 ºC - 25 ºC) and room light.

Any unused portion of the medicine or waste material should be disposed of in accordance with local requirements.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

To protect from light, do not remove the vial from the outer container until required for use.

For storage conditions after reconstitution and dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

Clear Type 1 borosilicate single-use glass vials 5 mL and 20 mL (varying only in vial dimensions). The glass vial is colourless with clear clarity.

20 mm grey bromobutyl rubber stopper (same dimensions) with fluropolymer film and cross-linkable polymethylsiloxane coating.
20 mm aluminium seal with an aqua flip-off cap (5 mL vial) and purple flip-off cap (20 mL vial).

The DARZALEX vial is packed into an opaque paperboard carton. Each carton consists of vial and a package leaflet.

6.6 Special precautions for disposal and other handling

This medicine 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.
- Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. The diluted solution may develop very small, translucent to white proteinaceous particles, as DARZALEX 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 medicines.

- 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. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

51/26/0329

9 DATE OF FIRST AUTHORISATION

Date of registration: 23 June 2020

10 DATE OF REVISION OF TEXT

May 2022