

Daratumumab Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
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	C90	00426a	ODMS (01/04/2018)

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment with daratumumab is administered as an intravenous infusion according to the dosing schedule in Table 1 below until disease progression or unacceptable toxicity develops.

The first dose of daratumumab may be administered as a single dose infusion of 16mg/kg on day 1 or split over two consecutive days i.e. 8mg/kg on day 1 and day 2 at the discretion of the prescribing Consultant and as detailed in Table 3 below.

Facilities to treat anaphylaxis MUST be present when daratumumab is administered.

Table 1: Dosing schedule of daratumumab

Schedule	Weeks
Weekly	Weeks 1 to 8
Every two weeks	Weeks 9 to 24
Every four weeks	Week 25 onwards until disease progression

Table 2: Treatment table for daratumumab

Day	Drug	Dose	Route	Diluent and Rate
1	Daratumumab	16mg/kg	IV infusion	0.9% NaCl (Ref Table 3 for volume and infusion rates)
If a planned dose of daratumumab is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.				
Following dilution the daratumumab infusion should be intravenously administered at the appropriate initial infusion rate, as presented in Table 3 below. 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.				

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Table 3: Infusion rates for daratumumab 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)	1,000ml	50ml/hour	50ml/hour every hour	200ml/hour
Option 2 (Split dose infusion)				
• Week 1 Day 1 (8 mg/kg)	500ml	50ml/hour	50ml/hour every hour	200ml/hour
• Week 1 Day 2 (8 mg/kg)	500ml	50ml/hour	50ml/hour every hour	200ml/hour
Week 2 (16mg/kg) infusion^b	500ml	50ml/hour	50ml/hour every hour	200 ml/hour
Subsequent (Week 3 onwards, 16mg/kg infusion)^c	500ml	100ml/hour	50ml/hour every hour	200ml/hour

^a Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.
^b A dilution volume of 500 mL for the 16 mg/kg dose should be used only if there were no IRRs the previous week. Otherwise, use a dilution volume of 1,000 mL.
^c A modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) should only be used only if there were no IRRs during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

ELIGIBILITY:

- Indication as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to daratumumab or any of the excipients
- Pregnancy
- Breast Feeding
- Severe uncontrolled asthma/obstructive airways disease

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Uric acid
- Urine pregnancy testing for pre-menopausal women < 55 years
- Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that patient is due to commence daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of daratumumab to red cells.
- Virology Screen: EBV, CMV, Hep B, Hep C and HIV
- *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

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Regular tests:

- FBC, renal and liver profile monthly.

Disease monitoring:

Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- No dose reductions of daratumumab are recommended.
- Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity
- Consider supportive care with transfusions or growth factors.

Renal and Hepatic Impairment:

Table 4: Recommended starting dose modification for daratumumab in patients with renal or hepatic impairment

Renal impairment	Hepatic impairment
<p>No formal studies of daratumumab in patients with renal impairment have been conducted.</p> <p>Based on a population pharmacokinetic (PK) analysis no dosage adjustment is necessary for patients with renal impairment</p>	<p>No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment</p>

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Management of infusion related reactions (IRRs):

Table 5: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Infusion Related Reactions (IRRs) Grade 1-2	<ul style="list-style-type: none"> Interrupt infusion immediately and manage symptoms. Once the patient's condition is stable, the infusion should be resumed at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as clinically appropriate up to the maximum rate of 200ml/hour (Table 3).
Grade 3 First occurrence	<ul style="list-style-type: none"> Interrupt infusion immediately and manage symptoms. Once reaction symptoms resolve, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate (Table 3).
Second occurrence	The procedure above should be repeated in the event of recurrence of Grade 3 symptoms.
Third occurrence	Discontinue treatment
Grade 4	Discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**Refer to local policy**).

PREMEDICATIONS:

Pre-infusion medications consisting of corticosteroid, anti-pyretic and anti-histamines should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of daratumumab as follows:

- IV corticosteroid (long-acting or intermediate-acting)(e.g. methylprednisolone 100 mg or equivalent . Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg).
- oral antipyretics (e.g. paracetamol 1,000 mg)
- oral or intravenous antihistamine (e.g. diphenhydramine 25 to 50 mg or equivalent)

See other supportive care for recommended post-infusion medications

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OTHER SUPPORTIVE CARE:

- Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation. **(Refer to local policy).**
- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- Tumour lysis syndrome prophylaxis **(Refer to local policy).**
- H2 antagonist or proton pump inhibitor **(Refer to local policy).**
- Consider PJP prophylaxis **(Refer to local policy).**
- Influenza vaccination in appropriate patients
- **Recommended post-infusion medications**
 - For the prevention of delayed IRRs, oral corticosteroid (20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local policy) should be administered on each of the two days following all infusions (beginning the day after the infusion).
 - Additionally, for patients with a history of obstructive pulmonary disorder, the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered.
 - Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

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

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Daratumumab is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Infusion related reactions:** Infusion-related reactions (IRRs) were reported in approximately half of all patients treated with daratumumab. Patients should be monitored throughout the infusion and the post-infusion period. The majority (95%) of IRRs occurred at the first infusion. Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with daratumumab. Daratumumab infusion should be interrupted for IRRs of any severity. Medical management/supportive treatment for IRRs should be instituted as needed. The infusion rate should be reduced when re-starting the infusion For the prevention of delayed IRRs see details outlined under supportive care above.
- **Interference with Indirect Antiglobulin Test (Indirect Coombs Test):** Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

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

In the event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests. 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

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immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

- Consider use of daratumumab-specific IFE reflex assay (DIRA) to distinguish the therapeutic from the patient's M protein. The DIRA assay can be used to determine whether additional testing, including determination of the sFLC ratio and BM evaluation, is warranted in patients with IgG-k band and low measurable M protein (≤ 2 g/L) to assess the presence of (stringent)CR.
- **Hepatitis B Reactivation:** Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with daratumumab. HBV screening should be performed in all patients before initiation of treatment with daratumumab. 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 daratumumab 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 daratumumab, suspend treatment with daratumumab and institute appropriate treatment. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV

DRUG INTERACTIONS:

- No interaction studies have been performed.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Daratumumab - L01XC24

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

[http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results/item?pano=EU/1/16/1101/001-002&t=DARZALEX%20\(PREVIOUSLY%20KNOWN%20AS%20DARATUMUMAB%20JANSSEN-CILAG\)#edumat](http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results/item?pano=EU/1/16/1101/001-002&t=DARZALEX%20(PREVIOUSLY%20KNOWN%20AS%20DARATUMUMAB%20JANSSEN-CILAG)#edumat)

REFERENCES:

1. Lonial S, Weiss LS, Usmani BM et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet*. 2016;387 (10027):1551-1560.
2. Daratumumab (DARZALEX®) Summary of Product Characteristics. Last updated: 23/01/2020. Accessed April 2020 Available at https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf
3. Van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. *Blood*. 2018 Jan 4;131(1):13-29. doi:10.1182/blood-2017-06-740944. Epub 2017 Nov 8. Review. PubMed PMID: 29118010
4. HPRA Direct Healthcare professional communication 26/06/2019. Daratumumab (DARZALEX®) and risk of reactivation of hepatitis B virus: Hepatitis B virus status to be established in patients receiving DARZALEX® Available at: [https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---darzalex-\(daratumumab\).pdf?sfvrsn=0](https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---darzalex-(daratumumab).pdf?sfvrsn=0)

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5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf>

Version	Date	Amendment	Approved By
1	16/03/2018		Prof Michael O'Dwyer
2	03/12/2018	Updated to include details of infusion administration set and clarification of dilution volumes and infusion rate	Prof Michael O'Dwyer
3	27/03/2019	Updated to include option for split dosing over two consecutive days for the first cycle as per SmPC	Prof Michael O'Dwyer
4	01/07/2020	Reviewed. Updated Adverse Effects with respect to Hepatitis B reactivation	Prof Michael O'Dwyer

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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