Daratumumab Monotherapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
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<tbody>
<tr>
<td>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</td>
<td>C90</td>
<td>00426a</td>
<td>ODMS (01/04/2018)</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process*

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.

Facilities to treat anaphylaxis MUST be present when daratumumab is administered

**Table 1: Dosing schedule of daratumumab**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td>Weeks 1 to 8</td>
</tr>
<tr>
<td>Every two weeks</td>
<td>Weeks 9 to 24</td>
</tr>
<tr>
<td>Every four weeks</td>
<td>Week 25 onwards until disease progression</td>
</tr>
</tbody>
</table>

**Table 2: Treatment table for daratumumab**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent and Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Daratumumab</td>
<td>16mg/kg</td>
<td>IV infusion</td>
<td>0.9% NaCl (Ref Table 3 for volume and infusion rates)</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>First infusion</th>
<th>Second infusionb</th>
<th>Subsequent infusionsc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilution volume</td>
<td>Initial infusion rate (first hour)</td>
<td>Increments of infusion rate</td>
</tr>
<tr>
<td>1000ml</td>
<td>50ml/hour</td>
<td>50ml/hour every hour</td>
</tr>
<tr>
<td>500ml</td>
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</tr>
<tr>
<td>500ml</td>
<td>100ml/hour</td>
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</tr>
</tbody>
</table>

Maximum infusion rate:

- 200ml/hour

Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

* A dilution volume of 500ml should only be used if there were no IRRs during the first 3 hours. Otherwise continue to use a dilution volume of 1000ml and instructions for first infusion.

* A modified initial rate for subsequent infusions (i.e., third infusion onwards) should only be used if the first 2 infusions of daratumumab were well-tolerated as defined by an absence of ≥ Grade 1 Infusion Related Reactions during a final infusion rate of ≥ 100 mL/hr. Otherwise use instructions for the second infusion.
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
- **Hepatitis B Reactivation**: Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with Lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards (Refer to local policy). Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.

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

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

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Management of infusion related reactions (IRRs):

Table 5: Dose modification schedule based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Related Reactions (IRRs)</td>
<td></td>
</tr>
</tbody>
</table>
| Grade 1-2 | • 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 | • 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).  
The procedure above should be repeated in the event of recurrence of Grade 3 symptoms. |
| Second occurrence | |
| 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

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 premedicated 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 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-κ band and low measurable M protein (≤2 g/L) to assess the presence of (stringent)CR.

**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

**REFERENCES:**

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<th>Version number: 2</th>
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<td>Tumour Group: Lymphoma and Myeloma</td>
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<td>NCCP Regimen Code: 00426</td>
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<tr>
<td>IHS Contributors: Prof Michael O'Dwyer</td>
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The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is the responsibly of the prescribing clinician, and is subject to HSE’s terms of use available at http://www.hse.ie/eng/Disclaimer. This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

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<th>Amendment</th>
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<tr>
<td>1</td>
<td>16/03/2018</td>
<td></td>
<td>Prof Michael O’Dwyer</td>
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<tr>
<td>2</td>
<td>03/12/2018</td>
<td>Updated to include details of infusion administration set and clarification of dilution volumes and infusion rate</td>
<td>Prof Michael O’Dwyer</td>
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/proinfo/medonc/cdmp/