Daratumumab SC Monotherapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>As monotherapy for the treatment of adult patients with relapsed and</td>
<td>C90</td>
<td>00604a</td>
<td>ODMS 01/07/2020</td>
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<tr>
<td>refractory multiple myeloma, whose prior therapy included a proteasome</td>
<td></td>
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<tr>
<td>inhibitor and an immunomodulatory agent and who have demonstrated</td>
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<tr>
<td>disease progression on the last therapy</td>
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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 patient's individual clinical circumstances.

Treatment with daratumumab is administered as a subcutaneous injection according to the dosing schedule in Table 1 and treatment Table 2 below until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Table 1: Dosing schedule of daratumumab

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Weeks</th>
</tr>
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<tbody>
<tr>
<td>Weekly (total of 8 doses)</td>
<td>Weeks 1 to 8</td>
</tr>
<tr>
<td>Every two weeks (total of 8</td>
<td>Weeks 9 to 24&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>doses)</td>
<td></td>
</tr>
<tr>
<td>Every four weeks</td>
<td>Week 25 onwards until disease progression&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup> First dose of the every-2-week dosing schedule is given at Week 9
<sup>b</sup> First dose of the every-4-week dosing schedule is given at Week 25

Table 2: Treatment table for daratumumab

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Daratumumab</td>
<td>1800mg</td>
<td>S.C</td>
<td>Over 3 to 5 minutes</td>
<td>As per table 1 dosing schedule</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.

ELIGIBILITY:

- Indications as above
- ECOG 0-2
EXCLUSIONS:

- Hypersensitivity to daratumumab or any of the excipients
- Pregnancy
- Breastfeeding
- 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
- Inform patient and transfusion laboratory that patient is due to commence daratumumab. Send a ‘Group and Save’ sample to the transfusion laboratory for red cell phenotyping as all cross matching will be positive following treatment with Daratumumab 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. See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation.

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: Dose modification of daratumumab in renal and hepatic impairment**

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
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<tbody>
<tr>
<td>No formal studies of daratumumab in patients with renal impairment have been conducted.</td>
<td>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.</td>
</tr>
<tr>
<td>Based on a population pharmacokinetic (PK) analysis no dosage adjustment is necessary for patients with renal impairment.</td>
<td></td>
</tr>
</tbody>
</table>

**SUPPORTIVE CARE:**

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

**PREMEDICATIONS:**

Pre-dose medications (oral or intravenous) should be administered to reduce the risk of Infusion related reactions (IRRs) to all patients 1 hour prior to every dose of daratumumab as follows:

- Corticosteroid (long-acting or intermediate –acting) e.g. dexamethasone 20mg PO or equivalent. Following the second infusion, the dose of corticosteroid may be reduced dexamethasone 12mg PO.
- oral antipyretics (e.g. paracetamol 1,000 mg)
- oral or intravenous antihistamine (e.g. Chlorphenamine 4mg PO/ 10mg IV or equivalent)
- Consider use of montelukast 10mg PO 60 minutes pre-daratumumab before the first dose only to reduce the incidence of infusion-related reactions

See other supportive care for recommended post-injection 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-injection medications
For the prevention of delayed IRRs, oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local policy) should be administered on each of the two days following all injections (beginning the day after the injection).

- If the patient experiences no major IRRs after the first three injections, post-injection corticosteroids (excluding any background regimen corticosteroids) may be discontinued.
- Additionally, for patients with a history of obstructive pulmonary disorder, the use of post-injection medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered.
- Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection 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.

• 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 administration. 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.
  o 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.

• 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

**REFERENCES**


4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at:

5. 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

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>23/07/2020</td>
<td></td>
<td>NCCP Plasma Cell Disorder Clinical Advisory Group</td>
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</table>

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