

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Melphalan flufenamide with dexamethasone for treating relapsed or refractory multiple myeloma

Draft scope

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of melphalan flufenamide with dexamethasone within its marketing authorisation for treating relapsed or refractory multiple myeloma.

**Background**

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells suppress the development of normal blood cells that are responsible for fighting infection (white blood cells), carrying oxygen around the body (red blood cells) and blood clotting (platelets). The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (as a result of anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

There were 5,034 newly diagnosed cases of multiple myeloma in England in 2017.<sup>1</sup> Of these 43% were in people aged 75 years and over.<sup>1</sup> Multiple myeloma is more common in men than in women and the incidence is also reported to be higher in people of African family origin. The 5-year survival rate for adults with multiple myeloma in England and Wales is about 52%.<sup>3</sup>

Multiple myeloma is an incurable disease. Therapy aims to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms. If the disease progresses after initial treatment, the choice of subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference.

For people whose disease is relapsed or refractory after at least 2 prior therapies:

- NICE technology appraisal guidance 171 recommends lenalidomide plus dexamethasone as a treatment option for people who have had at least 2 previous therapies.
- NICE technology appraisal guidance 380 recommends panobinostat plus bortezomib and dexamethasone as a treatment option for adults who have had at least 2 previous therapies including bortezomib and an immunomodulatory agent.
- NICE technology appraisal guidance 505 recommends ixazomib citrate plus lenalidomide and dexamethasone for use within the Cancer Drugs Fund as a treatment option for adults who have had 2 or 3 previous therapies.

For people who have had at least 3 prior therapies:

- NICE technology appraisal guidance 427 recommends pomalidomide plus low-dose dexamethasone as a treatment option for adults who have had at least 3 previous treatments including both lenalidomide and bortezomib.
- NICE technology appraisal guidance 510 recommends daratumumab monotherapy for use within the Cancer Drugs Fund as a treatment option for adults who have had 3 previous therapies including a proteasome inhibitor and an immunomodulator.

**The technology**

Melphalan flufenamide (Melflufen, Oncopeptides AB) is a peptide-drug conjugate that delivers an alkylating agent into myeloma cells. This induces irreversible DNA damage leading to apoptosis of myeloma cells. Melphalan flufenamide is administered as an intravenous infusion.

Melphalan flufenamide does not have a marketing authorisation in the UK for relapsed or refractory multiple myeloma. It is being studied in combination with dexamethasone in a single arm trial or compared with pomalidomide in combination with dexamethasone in people with relapsed or refractory multiple myeloma .

<b>Intervention(s)</b>	Melphalan flufenamide with dexamethasone
<b>Population(s)</b>	People with relapsed or refractory multiple myeloma who have had 2-4 previous therapies
<b>Comparators</b>	<p>For people who have had 2 previous therapies:</p> <ul style="list-style-type: none"> <li>• lenalidomide plus dexamethasone</li> <li>• panobinostat plus bortezomib and dexamethasone</li> </ul> <p>For people who have had 3 or more previous therapies:</p> <ul style="list-style-type: none"> <li>• carfilzomib plus dexamethasone and lenalidomide (subject to ongoing NICE appraisal)</li> <li>• isatuximab plus pomalidomide and dexamethasone</li> <li>• lenalidomide plus dexamethasone</li> <li>• panobinostat plus bortezomib and dexamethasone</li> <li>• pomalidomide plus dexamethasone</li> </ul> <p>For people who have received any number of previous therapies:</p> <ul style="list-style-type: none"> <li>• conventional chemotherapy regimens (for example, melphalan and cyclophosphamide)</li> <li>• best supportive care</li> </ul>

<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• response rates</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>
<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technologies appraisal guidance for the same indication a cost comparison may be carried out.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.</p>
<b>Other considerations</b>	<p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p><b>Related Technology Appraisals:</b></p> <p><a href="#">Carfilzomib for previously treated multiple myeloma</a>. (2020) NICE technology appraisal guidance 657. Review date expected 2023.</p> <p><a href="#">Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma</a> (2020) NICE technology appraisal guidance 658. Review date to be confirmed.</p> <p><a href="#">Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib</a>. (2019) NICE technology appraisal guidance 586. Review date expected 2022.</p> <p><a href="#">Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma</a>. (2019) NICE technology appraisal guidance 573. Review date expected 2021.</p>

	<p><a href="#">Daratumumab monotherapy for treating relapsed and refractory multiple myeloma</a>. (2018) NICE technology appraisal guidance 510. Review date expected November 2020.</p> <p><a href="#">Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma</a>. (2018) NICE technology appraisal guidance 505. Review date expected December 2019.</p> <p><a href="#">Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib</a> (2017) NICE technology appraisal guidance 427. Review date expected 2020.</p> <p><a href="#">Panobinostat for treating multiple myeloma after at least 2 previous treatments</a>. (2016) NICE technology appraisal guidance 380. Reviewed January 2019</p> <p><a href="#">Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies</a>. (2009). NICE technology appraisal guidance 171. Guidance on static list 2014.</p> <p><a href="#">Bortezomib monotherapy for relapsed multiple myeloma</a>. (2007) NICE technology appraisal guidance 129. Guidance on static list 2012.</p> <p><b>Terminated appraisals</b></p> <p><a href="#">Pomalidomide with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma</a> (terminated appraisal) (2019) NICE technology appraisal guidance 602.</p> <p><a href="#">Bortezomib for treating multiple myeloma after second or subsequent relapse</a> (terminated appraisal) (2017) NICE technology appraisal guidance 453.</p> <p><a href="#">Daratumumab with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma</a> (terminated appraisal) (2017) NICE technology appraisal guidance 454.</p> <p><a href="#">Elotuzumab for previously treated multiple myeloma</a> (terminated appraisal) (2017) NICE technology appraisal guidance 434.</p> <p><b>Appraisals in development (including suspended appraisals)</b></p> <p><a href="#">Selinexor with low-dose dexamethasone for treating refractory multiple myeloma</a> [ID1535]. Publication expected January 2021.</p> <p><a href="#">Idecabtagene vicleucel for treating relapsed and refractory multiple myeloma in people who have received at least 3 prior therapies publication expected</a> [1442]. Publication expected August 2021.</p> <p><a href="#">Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy</a> [ID1493]. Expected March 2021.</p> <p><a href="#">Carfilzomib with daratumumab and dexamethasone for</a></p>
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	<p><a href="#">treating relapsed or refractory multiple myeloma</a> [ID2709]. Publication date to be confirmed.</p> <p><a href="#">Selinexor with bortezomib and low-dose dexamethasone for treating relapsed refractory multiple myeloma</a> [ID3797]. Publication date to be confirmed.</p> <p><a href="#">Elotuzumab for multiple myeloma</a> [ID966]. NICE technology appraisals guidance. Publication date to be confirmed.</p> <p><a href="#">Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 3 therapies</a> [ID2701]. Publication date to be confirmed</p> <p><a href="#">Isatuximab with carfilzomib and dexamethasone for treating relapsed or refractory multiple myeloma</a> [ID1620]. (suspended).</p> <p><a href="#">Elotuzumab with pomalidomide and dexamethasone for treating multiple myeloma after 2 therapies</a> [ID1467]. [Suspended].</p> <p><a href="#">Multiple myeloma (one prior therapy) - vorinostat (with bortezomib)</a> [ID501]. [Suspended].</p> <p><a href="#">Pembrolizumab for previously treated multiple myeloma</a> [ID1139]. [Suspended].</p> <p><a href="#">Plitidepsin in combination with dexamethasone for treating relapsed or refractory multiple myeloma</a> [ID1081]. [Suspended].</p> <p><a href="#">Daratumumab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma</a> [ID3775]. [Suspended]</p> <p><a href="#">Pelareorep for treating relapsed or refractory multiple myeloma</a> [ID1028] [suspended]</p> <p><a href="#">Multiple myeloma - carfilzomib (with lenalidomide and dexamethasone, after prior therapy)</a> [ID677] NICE technology appraisal guidance. (terminated appraisal).</p> <p><b>Related Guidelines:</b></p> <p><a href="#">COVID-19 rapid guideline: delivery of systemic anticancer treatments</a> (2020) NICE guideline NG161</p> <p><a href="#">Myeloma: diagnosis and management</a> (2016). NICE guideline 35. Review date February 2019.</p> <p><a href="#">Haematological cancers – improving outcomes</a> (2016) NICE guideline 47 Review date to be confirmed.</p> <p><b>Related Quality Standards:</b></p> <p><a href="#">Haematological cancers</a> (2017) NICE quality standard 150</p> <p><b>Related NICE Pathways:</b></p> <p><a href="#">Myeloma</a> (2017) NICE pathway</p>
<b>Related National Policy</b>	<p>The NHS Long Term Plan, 2019. <a href="#">NHS Long Term Plan</a> NHS England (2018/2019) <a href="#">NHS manual for prescribed</a></p>

	<p><a href="#">specialist services (2018/2019)</a> Blood and marrow transplantation services (adults and children) [section 29, pages 98-100]</p> <p>Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2, 4 and 5.  <a href="https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017">https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017</a></p> <p>Independent Cancer Taskforce (2015) <a href="#">Achieving world-class cancer outcomes: a strategy for England 2015-2020</a></p>
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### Questions for consultation

Have all relevant comparators for melphalan flufenamide been included in the scope? Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory multiple myeloma after 2 therapies?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom melphalan flufenamide is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider melphalan flufenamide will fit into the existing NICE pathway, [Myeloma](#)?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which melphalan flufenamide will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider melphalan flufenamide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of melphalan flufenamide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>).

NICE has published an addendum to its guide to the methods of technology appraisal (available at <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf>), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

### References

1. Office of national statistics '[Cancer registration statistics, England](#)'. (2017) Accessed December 2020.
2. Cancer Research UK '[Myeloma](#)'. Accessed December 2020.