Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Plitidepsin in combination with dexamethasone for treating relapsed or refractory multiple myeloma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of plitidepsin in combination 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 supress 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, infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

In 2014, 4,652 people were diagnosed with multiple myeloma in England[1], with 45% of those people being aged 75 years and over.[2] Multiple myeloma is more common in men than in women and the incidence is also reported to be higher in people of African and Caribbean family origin.[3] The 5-year survival rate for adults with multiple myeloma in England is estimated to be 47%.[4]

Multiple myeloma is an incurable disease. Therapy aims to prolong survival and maintain a good quality of life. There are a number of possible sequences of treatments for relapsed or refractory multiple myeloma:

- The first treatment is either thalidomide (an immunomodulatory agent) or bortezomib (a proteasome inhibitor), plus an alkylating agent (for example, melphalan or chlorambucil) and a corticosteroid, as recommended in NICE technology appraisal guidance 228.

- If treatment is not successful, people may have bortezomib monotherapy as described in NICE technology appraisal guidance 129.

- If these 2 lines of treatment are not successful, NICE technology appraisal guidance 171 recommends lenalidomide for the treatment of multiple myeloma in people who have received at least 1 prior therapy.

- As fourth-line treatment, panobinostat plus bortezomib and dexamethasone may be offered, or pomalidomide plus dexamethasone, as recommended in NICE technology appraisal guidance 380 and 427 respectively.

- At fifth line, few people reach this stage, and there is no standard of care at this point.

Carfilzomib [ID934], daratumumab [ID933] and ixazomib citrate [ID807] are each subject to ongoing NICE appraisals for relapsed and refractory multiple myeloma.

The technology

Plitidepsin (Aplidin, PharmaMar) is a cyclic depsipeptide thought to activate apoptosis (cell death) in tumour cells, and to inhibit vascular endothelial growth factor (VEGF), thereby blocking cell proliferation. It also inhibits elongation factor 1-a, interfering with protein synthesis, and induces G1 arrest and G2 blockade. Plitidepsin is administered intravenously.

Plitidepsin does not currently have a marketing authorisation in the UK for treating multiple myeloma. It has been studied in clinical trials in combination with dexamethasone, compared with dexamethasone alone, in adults with relapsed or refractory multiple myeloma previously treated with 3 or more therapeutic regimens.

Intervention(s)	Plitidepsin in combination with dexamethasone
Population(s)	People with relapsed or refractory multiple myeloma previously treated with 3 or more lines of therapy.
Comparators	• Pomalidomide in combination with low-dose dexamethasone • Panobinostat in combination with bortezomib and dexamethasone • Daratumumab monotherapy (subject to NICE guidance [ID933]) • Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates

	• adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	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.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib' (2017). NICE Technology Appraisal 427. Review date January 2020. 'Panobinostat for treating multiple myeloma after at least 2 previous treatments' (2016). NICE Technology Appraisal 380. Review date January 2019. 'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy' (2009). NICE Technology Appraisal 171. Static list. 'Bortezomib monotherapy for relapsed multiple myeloma' (2007). NICE Technology Appraisal 129. Static list. Appraisals in development (including suspended appraisals): 'Multiple myeloma (treated) – carfilzomib' NICE technology appraisals guidance [ID934]. Publication expected May 2017. 'Daratumumab for multiple myeloma' NICE technology appraisals guidance [ID933]. Publication expected July

	2017. 'Multiple myeloma (relapsed, refractory) – ixazomib citrate' NICE technology appraisals guidance [ID807]. Publication expected August 2017. 'Multiple myeloma (previously treated) – elotuzumab' Proposed NICE technology appraisal [ID855]. Publication date to be confirmed. 'Pembrolizumab for previously treated multiple myeloma' NICE technology appraisals guidance [ID1139]. Publication date to be confirmed. 'Bortezomib for treating multiple myeloma after second or subsequent relapse' NICE technology appraisals guidance [ID1120]. Publication date to be confirmed. Related Guidelines: 'Myeloma: diagnosis and management' (2016). NICE guideline 35. Review date February 2019. Related NICE Pathways: Myeloma NICE pathway http://pathways.nice.org.uk/pathways/myeloma
Related National Policy	National service framework: 'Improving outcomes: a strategy for cancer', December 2014 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/388160/fourth_annual_report.pdf NHS England Manual for prescribed specialised services 2013/2014. Blood and marrow transplantation services (all ages) Chapter 29 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1,2,4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for plitidepsin in combination with dexamethasone been included in the scope? Is carfilzomib a relevant comparator at the stage in therapy at which plitidepsin is likely to be used (subject to NICE guidance [ID934])?

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Which treatments are considered to be established clinical practice in the NHS for multiple myeloma after 3 previous therapies?

Are the outcomes listed appropriate?

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

Where do you consider plitidepsin in combination with dexamethasone will fit into the existing NICE pathway for 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 plitidepsin in combination with dexamethasone 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 plitidepsin in combination with dexamethasone 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 plitidepsin in combination with dexamethasone 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.

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

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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. We welcome comments on the appropriateness and suitability of the cost comparison methodology to 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] Cancer Research UK 'Myeloma incidence statistics'. Accessed March 2017.
[2] Cancer Research UK 'Myeloma incidence statistics'. Accessed March 2017.
[3] Cancer Research UK 'Myeloma incidence statistics'. Accessed March 2017.
[4] Cancer Research UK 'Myeloma survival statistics'. Accessed March 2017.