NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma

This guidance was issued in July 2011.

The review date for this guidance is July 2014.

1. Recommendation

The technology appraisal 228 guidance should be placed on the static list and be incorporated into an on-going clinical guideline for the diagnosis and management of myeloma. That we consult on this proposal.

2. Original remit(s)

“To appraise the clinical and cost effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma”.

3. Current guidance

1.1. Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.

1.2. Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:

- high-dose chemotherapy with stem cell transplantation is considered inappropriate and
- the person is unable to tolerate or has contraindications to thalidomide.

4. Rationale

Technology appraisal 228 was informed by data from the VISTA and MMIX trials. Updated results from both trials have been published. However, the updated results reinforce the clinical effectiveness data in TA228 and are not expected to affect the recommendations in TA228.

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1 A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper
5. Implications for other guidance producing programmes
The clinical guideline for the diagnosis and management of myeloma is due to be published in January 2016. It is anticipated that the recommendations from TA228 will be incorporated into the guideline.

6. New evidence
The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase in June 2014. References from December 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the ‘Summary of evidence and implications for review’ section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review
Since the guidance was issued, a new indication has been added to the marketing authorisation for bortezomib. The new indication is outside the scope of technology appraisal 228 and has been considered in a separate technology appraisal (TA311, see Appendix 2). At the time of technology appraisal 228, the summary of product characteristics for bortezomib stated that it should be administered intravenously. This has been updated to state that bortezomib can also be administered via subcutaneous injection. The cost of bortezomib is the same regardless of the mode of administration; the cost has not changed since the time of the appraisal. The marketing authorisation and cost of thalidomide have not changed since the time of the appraisal.

An alternative intervention for multiple myeloma is lenalidomide (Revlimid, Celgene). Lenalidomide does not currently have a UK marketing authorisation for the first-line treatment of multiple myeloma. A clinical trial has compared lenalidomide and low-dose dexamethasone with melphalan, prednisone and thalidomide (Facon et al. 2013). The patients in the trial had newly diagnosed multiple myeloma and were not eligible for stem cell transplantation. NICE anticipates that a technology appraisal of lenalidomide for treating newly diagnosed multiple myeloma (ID474) will begin during June 2015; the expected publication date is April 2016.

Technology appraisal 228 was informed by data from the VISTA and MMIX trials. Updated results from both trials have been published (VISTA: San Miguel et al. 2013; MMIX: Child et al. 2010, Davies et al. 2011, Morgan et al. 2011, Morgan et al. 2012). The updated results are consistent with those that were available at the time of the appraisal. Briefly, the results indicate that a regimen of bortezomib, melphalan and prednisolone/prednisone (VMP) or a regimen of cyclophosphamide, thalidomide, and attenuated dexamethasone (CTDa) is more effective than a regimen of melphalan and prednisolone/prednisone (MP). The updated results are not expected to affect the recommendations in technology appraisal 228.

Three published randomised controlled trials have compared thalidomide in combination with melphalan and prednisolone/prednisone (MPT) with MP alone in the population relevant to technology appraisal 228. These 3 trials were unavailable, or available only as an abstract, at the time of the Assessment Group’s original
systematic review. The trials were conducted in Turkey (n=122; Beksac et al. 2011), the Nordic countries (n=363; Waage et al. 2010), and the Netherlands and Belgium (n=344; Wijermans et al. 2010). All 3 trials found that response rates were significantly higher with MPT than with MP. One study reported a significant benefit of MPT for progression-free survival (Wijermans et al. 2010) whereas the other 2 studies did not report this benefit (Beksac et al. 2011, Waage et al. 2010). The Nordic and Dutch-Belgian trials included maintenance therapy with thalidomide, which is outside the scope of technology appraisal 228. In line with the approach taken by the Assessment Group, the present review proposal did not take into account the overall survival results from trials that included maintenance therapy with thalidomide. The Turkish trial did not include maintenance therapy with thalidomide but it did permit treatment switching 3 months after randomisation. The Turkish trial did not find a significant difference between treatment arms for the secondary outcome measure of overall survival.

The potential impact of the 3 new trials on the recommendations of technology appraisal 228 can be assessed by considering a meta-analysis that compared MPT with MP (Fayers et al. 2011). The analysis included 3 trials that were included in the appraisal and the 3 new trials described above. The results showed that response rates were significantly higher with MPT than with MP (partial response or better was 59% on MPT and 37% on MP). Progression-free survival was significantly longer with MPT than with MP (hazard ratio 0.68, 95% confidence interval 0.61 to 0.76). Thus, the results of the meta-analysis support the recommendations of technology appraisal 228. The present review proposal did not take into account the overall survival results because several of the trials included maintenance therapy with thalidomide. Overall, the results of the new trials and the meta-analysis of Fayers et al. (2011) are not expected to affect the recommendations in technology appraisal 228.

A recent economic evaluation used a cost-utility Markov model to compare VMP, MPT and a regimen containing lenalidomide (Garrison et al. 2013). The study adopted the perspective of a payer for healthcare in the USA. The results indicated that VMP dominated MPT, meaning VMP incurred lower costs and accrued more quality-adjusted life years than MPT. In contrast, the Assessment Group’s economic model for technology appraisal 228 showed that VMP was dominated by MPT or, under different assumptions, that VMP had a very high incremental cost-effectiveness ratio compared with MPT. One reason for the difference in results is that thalidomide is more expensive in the USA than in the UK. A pack of 28 thalidomide capsules costs $3556 in the USA and £298 in the UK (about $472). Therefore, the results of Garrison and colleagues do not generalise to the UK. It should also be noted that the estimates of efficacy in the Garrison model were not based on a systematic review and network meta-analysis, and the study was funded by Janssen. On balance, the results of this economic evaluation are not expected to affect the recommendations in technology appraisal 228.

During the appraisal, clinical experts advised that people with impaired renal function would be offered bortezomib rather than thalidomide. However, the Committee was not presented with evidence of clinical or cost effectiveness that was specific to the subgroup with impaired renal function. The Committee noted that comorbidities such as renal impairment are highlighted in the summary of product characteristics for
thalidomide, which states that patients with renal impairment should be monitored for adverse events. The Committee understood that thalidomide could be prescribed to people with renal impairment and it agreed that the summary of product characteristics for thalidomide covered the safety risks adequately. Accordingly, technology appraisal 228 did not make specific recommendations for the subgroup of people with renal impairment.

Two studies that are relevant to the subgroup of people with renal impairment have since been published. Dimopoulos and colleagues (2009) analysed a subgroup (n=227) of patients with renal impairment in the VISTA trial. Over the course of treatment, renal function improved to a glomerular filtration rate above 60 ml/min for 44% of patients treated with VMP and 34% of patients treated with MP (p=0.07). The second study was a meta-analysis that compared MP, MPT, VMP, and bortezomib in combination with thalidomide (Bringhen et al. 2013). Overall, patients with renal failure had higher mortality than patients without renal failure. However, in people treated with VMP, levels of mortality were similar in patients with renal failure and patients without renal failure (hazard ratio 0.91, 95% confidence interval 0.22 to 2.58). The authors concluded that ‘bortezomib-based combinations may overcome the negative impact of renal failure’. The results should be considered with caution because only 89 patients (6%) had renal failure. Overall, these 2 studies do not provide strong evidence that VMP is more effective or safer than MPT for patients with renal failure. It is unclear whether any potential benefit of VMP compared with MPT in this subgroup would be large enough to result in acceptable cost-effectiveness, given the high incremental cost of bortezomib. Given the uncertainty in the evidence, and bearing in mind that the appraisal did not make specific recommendations for the subgroup with renal impairment, this new evidence is not expected to affect the recommendations in technology appraisal 228.

Since the appraisal, several trials have examined the effectiveness of bortezomib in combination with either thalidomide or lenalidomide as a first-line treatment for multiple myeloma. The relevant data were included in 2 meta-analyses (Wang et al. 2012, Atkins et al. 2013). These drug combinations are also the subject of 3 ongoing or unpublished clinical trials (NCT01063179, NCT00507416, NCT00644228). However, the combination of bortezomib and thalidomide, or bortezomib and lenalidomide, is outside the terms of the marketing authorisations and outside the scope of technology appraisal 228. Therefore, this new evidence is unlikely to affect the recommendations in technology appraisal 228.

In summary, there are no changes to the costs of bortezomib and thalidomide and no new comparators have been appraised by NICE. Approximately 90 references were identified in the literature search, most of which were related to populations or interventions that are outside the scope of technology appraisal 228. The relevant new evidence broadly supports the recommendations in technology appraisal 228. One published economic evaluation does not support the recommendations in technology appraisal 228, but the evaluation was specific to the USA. Overall, the new evidence is not expected to affect the recommendations in the guidance. Based on the available evidence, it is proposed that technology appraisal 228 be placed on the static list and incorporated into the ongoing clinical guideline on the diagnosis and management of myeloma.
8. Implementation

A submission from Implementation is included in Appendix 3. The number of prescriptions for thalidomide has been roughly stable since the publication of technology appraisal 228, whilst the number of prescriptions for bortezomib has risen. The information about prescriptions for bortezomib is difficult to interpret because bortezomib has a marketing authorisation for use at multiple stages of the treatment pathway and in 2 populations (those eligible and those not eligible for stem-cell transplantation). It is not possible to determine how many prescriptions of bortezomib were for the population and line of therapy considered in technology appraisal 228.

9. Equality issues

No equalities issues were raised during technology appraisal 228.

GE paper sign off: Frances Sutcliffe, Associate Director, 16 December 2014

Contributors to this paper:

Information Specialist: Tom Hudson
Technical Lead: Rosie Lovett
Project Manager: Andrew Kenyon
CPP/CPHE input: Katie Perryman Ford
## Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

<table>
<thead>
<tr>
<th>Options</th>
<th>Consequence</th>
<th>Selected – ‘Yes/No’</th>
</tr>
</thead>
<tbody>
<tr>
<td>A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the (single or multiple) technology appraisal process.</td>
<td>A review of the appraisal will be planned into the NICE’s work programme.</td>
<td>No</td>
</tr>
<tr>
<td>The decision to review the guidance should be deferred (to a specific date).</td>
<td>NICE will reconsider whether a review is necessary at the specified date.</td>
<td>No</td>
</tr>
<tr>
<td>A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.</td>
<td>A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.</td>
<td>No</td>
</tr>
<tr>
<td>A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.</td>
<td>A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.</td>
<td>No</td>
</tr>
<tr>
<td>The guidance should be incorporated into an on-going clinical guideline.</td>
<td>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</td>
<td>Yes</td>
</tr>
<tr>
<td>Options</td>
<td>Consequence</td>
<td>Selected – ‘Yes/No’</td>
</tr>
<tr>
<td>--------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>The guidance should be updated in an on-going clinical guideline.</td>
<td>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</td>
<td>No</td>
</tr>
<tr>
<td>The guidance should be transferred to the ‘static guidance list’.</td>
<td>The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

   - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
   - There is evidence of unjustified variation across the country in access to a treatment
   - There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.
Appendix 2 – supporting information

Relevant Institute work

Published

In progress


Suspended/terminated
Bortezomib for consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma. NICE Technology Appraisal ID529. Suspended in 2014 after the company informed NICE that it will no longer be pursuing a licensing application for bortezomib in this indication.

Details of changes to the indications of the technology

<table>
<thead>
<tr>
<th>Indication considered in original appraisal</th>
<th>Proposed indication (for this appraisal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib</strong></td>
<td>No change. An additional indication for induction therapy has been considered separately in NICE TA311.</td>
</tr>
<tr>
<td>Treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.</td>
<td></td>
</tr>
<tr>
<td><strong>Thalidomide</strong></td>
<td>No change.</td>
</tr>
<tr>
<td>(In combination with melphalan and prednisone) - first-line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.</td>
<td></td>
</tr>
</tbody>
</table>
## Details of new products

<table>
<thead>
<tr>
<th>Drug (manufacturer)</th>
<th>Details (phase of development, expected launch date, )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afuresertib (GSK)</td>
<td>Phase III trial in combination with bortezomib and dexamethasone scheduled to begin this year.</td>
</tr>
</tbody>
</table>
| Carfilzomib (Onyx)  | Phase III trials underway:  
Trial of bortezomib, lenalidomide & dexamethasone vs. carfilzomib, lenalidomide, dexamethasone & maintenance for newly diagnosed multiple myeloma due to complete in May 2016.  
Trial of carfilzomib, melphalan & prednisone vs. bortezomib, melphalan & prednisone in transplant-ineligible patients with newly diagnosed multiple myeloma due to complete April 16. |
| Elotuzumab (Bristol-Myers Squibb) | Phase III in combination with lenalidomide/ dexamethasone for previously untreated multiple myeloma. Study due to complete: August 2016. |
| Zoledronic acid (Novartis) | Positive phase III results (as an add-on to chemotherapy) announced in 2010. Launched in the US. UK licensing plans unknown |

## Registered and unpublished trials

<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
</table>
| Velcade, Melphalan, Prednisone And Thalidomide Versus Velcade, Melphalan, Prednisone in Multiple Myeloma Patients  
NCT01063179; GIMEMA-MM-03-05, 2005-004745-33. | n = 511  
Estimated completion date: January 2015.  
Bortezomib, melphalan, prednisone & thalidomide followed by thalidomide & bortezomib maintenance vs. bortezomib, melphalan, prednisone with no maintenance follow-up.  
Includes participants aged > 65 who aren’t candidates for stem cell transplant, or younger participants who refuse or are not eligible for high-dose therapy. |
<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velcade, Thalidomide, and Dexamethasone Versus Velcade and Dexamethasone Versus Velcade, Melphalan, and Prednisone NCT00507416; C05009.</td>
<td>Completed ~March 2013 n = 502</td>
</tr>
<tr>
<td>Lenalidomide and Dexamethasone With or Without Bortezomib in Treating Patients With Previously Untreated Multiple Myeloma NCT00644228; NCI-2009-00798, NCI-2009-00798, SWOG-S0777, CDR0000590321, S0777, S0777, U10CA032102.</td>
<td>Stated as ‘ongoing’ Estimated completion date: August 2013 n = 440</td>
</tr>
</tbody>
</table>

**Relevant services covered by NHS England specialised commissioning**

Specialist cancer services for adults are [nationally commissioned](#).

**References**


Child A, Davies F, Gregory W et al. (2010) Thalidomide maintenance significantly improves progression free (PFS) but not overall survival (OS) of myeloma patients, with PFS benefits in favourable fish subgroups only: MRC myeloma IX results [Abstract No. 1095]. *Haematologica* 92 (Suppl 2): 450-451

Dimopoulos MA, Richardson PG, Schlag R et al. (2009) VMP (Bortezomib, Melphalan, and Prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. *Journal of Clinical Oncology* 27 (36): 6086-6093.

Facon T, Dimopoulos MA, Dispenzieri A et al. (2013) Initial phase 3 results of the first (frontline investigation of lenalidomide+dexamethasone versus standard thalidomide) trial (mm-020/IFM 07 01) in newly diagnosed multiple myeloma (NDMM) patients (PTS) ineligible for stem cell transplantation (SCT). *Blood* 122 (21).


Appendix 3 – Implementation submission

1. Routine healthcare activity data

1.1. ePACT data
This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of bortezomib and thalidomide prescribed in hospitals and dispensed in the community in England between March 2009 and March 2014.

Figure 1 Cost and volume of bortezomib prescribed in hospital and dispensed in the community in England between March 2009 and March 2014.

*Please note data in quarter 4 (2009/10 and 2013/14) is incomplete.

Please note the NIC and volume trend lines are almost exact, therefore it is difficult to see the NIC data points.
Figure 2 Cost and volume of thalidomide prescribed in hospital and dispensed in the community in England between March 2009 and March 2014.

*Please note data in quarter 4 (2009/10 and 2013/14) is incomplete.
1.2. Hospital Pharmacy Audit Index data
This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of bortezomib and thalidomide prescribed and dispensed in hospitals in England between January 2011 and December 2012.

Figure 3 Cost and volume of bortezomib prescribed in hospitals in England

![Figure 3 Cost and volume of bortezomib prescribed in hospitals in England](image)

Source: IMS Health Pharmacy Audit Index

Figure 4 Cost and volume of thalidomide prescribed in hospitals in England

![Figure 4 Cost and volume of thalidomide prescribed in hospitals in England](image)

Source: IMS Health Pharmacy Audit Index
2. Implementation studies from published literature
Nothing to report from the uptake database website.

3. Qualitative input from the field team
The implementation field team have not recorded any feedback in relation to this guidance.

4. Implementation studies from shared learning
A search of the shared learning website highlighted no examples of TA228 being implemented.
Healthcare activity data definitions

**ePACT**

*Prescribing analysis and cost tool system*

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in hospitals, mental health units and private prescriptions, are not included in PACT data.

**Measures of prescribing**

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

**Data limitations (national prescriptions)**

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

**IMS HEALTH Hospital Pharmacy Audit Index**

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

**Measures of prescribing**

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

**Data limitations**

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.