NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

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

Final recommendation post consultation
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.

1. Background

This guidance was issued in July 2011.

At the GE meeting of 6 January 2015 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

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.

3. Rationale for selecting this proposal

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.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Merck Sharp & Dohme **Response to proposal:** Request change to matrix of stakeholders Merck Sharp & Dohme has been invited to comment on the above mentioned GE proposal, in our capacity as manufacturer of dexamethasone. However, earlier in 2014, Aspen Pharmacare UK was granted the transfer of Marketing Authorization for Dexamethasone 4mg/ml Injection from MSD - Aspen Pharmacare are now responsible for the distribution of this product in the UK. Therefore MSD will no longer need to be included in the provisional list of stakeholders for the above appraisal.	**Comment from Technology Appraisals** Comment noted.

Respondent: GlaxoSmithKline **Response to proposal:** No comment GlaxoSmithKline has no specific comments on this approach.	**Comment from Technology Appraisals** Comment noted.

Respondent: Napp Pharmaceuticals **Response to proposal:** Agree Napp Pharmaceuticals Limited agree with the proposal made by NICE to move TA228 to the technology appraisal static list and for the recommendations to be incorporated into the forthcoming clinical guideline list.	**Comment from Technology Appraisals** Comment noted.

Respondent: Elimination of Leukaemia Fund **Response to proposal:** No comment.	**Comment from Technology Appraisals** Comment noted.

Respondent: UK Myeloma Forum **Response to proposal:** Disagree We are writing on behalf of the executive committee of the UK Myeloma Forum which represents Haematologists with a Specialist interest in Myeloma. Thank you for the opportunity to comment on the Review of NICE TAG228. We note that it is intended to place TAG228 on the static list rather than review the previous recommendations. We note that the evidence stated to support this decision is that 1. A NICE myeloma Guideline is in development and 2. That the appraisal group consider updated published results to reinforce the clinical effectiveness data that led to the decisions taken in TAG228. We disagree with the NICE committee and request that there is reassessment of "Bortezomib and Thalidomide for the firstline treatment of myeloma". We note that TA228 was published in July 2011 and it is now time to reappraise NICE guidance on First-line therapy for Myeloma patients who are Transplant Ineligible. Firstly, it is our understanding that the Myeloma Guidelines Development Group are unable to comment on the first-line treatment of myeloma as according to NICE regulations previous NICE Technology Appraisals in existence are incorporated into subsequent guidelines without further review. Hence, the development of NICE Myeloma guidelines will have no impact on treatment decisions in the patient population described in TA228.	**Comment from Technology Appraisals** Comments noted. The review proposal recommended that TA228 should be incorporated into the on-going clinical guideline for the diagnosis and management of myeloma. This means that the clinical guideline will include the verbatim recommendations from TA228, and will not review evidence or update the recommendations.
Secondly, we believe that the subsequently published clinical evidence for the three regimens under consideration has a significant impact on the conclusions in TA228. We note that these are referenced in the Guidance Executive document that	Section 4.1.13 of the guidance refers to several interim analyses of the VISTA trial, with median follow-up of 2 to 3 years. These analyses showed a

accompanied the recent announcement, however we are confused regarding the statement that these publications “reinforce the clinical effectiveness data”, and “would not lead to a change in the existing recommendations”. Since the NICE recommendation TA228, long term follow-up data from the VISTA Phase 3 study of VMP v MP has been published (San Miguel et al. 2013). With a median follow-up of 60 months there is a clear significant overall survival advantage for the patients who received VMP (in comparison to MP) as per VISTA protocol (56.4 v 43.1 months, HR 0.695, p<0.001). This is a 31% risk of death for patients treated with VMP compared with MP. The survival advantage was maintained in all pre-defined subgroups examined and was not associated with inferior subsequent survival at the time of relapse.	statistically significant survival benefit for bortezomib, melphalan and prednisolone/prednisone (VMP) compared with melphalan and prednisolone/prednisone alone (MP). After median follow-up of 26 months, the hazard ratio was 0.64. The Appraisal Committee acknowledged that VISTA showed a survival benefit for bortezomib (see section 4.3.5 of the guidance). This survival benefit was incorporated into the Assessment Group’s model. The 5-year results of the VISTA trial (San Miguel et al. 2013) reinforce the interim results already considered by the Appraisal Committee. The updated results are unlikely to affect the recommendations.
We note that at the time of TA228 the Myeloma IX trial comparing CTDa versus MP had not been published in a peer reviewed publication although data from this study informed the NICE appraisal. Subsequent publication of the Myeloma IX Trial outcomes (Morgan et al. Blood 2011) have demonstrated that whilst CTDa leads to better overall responses than MP, on an intention to treat basis it offers no advantage in terms of overall survival (median follow-up 44 months, OS 33.2 v 30.6m HR 0.89, p 0.24). Similarly there have been no publications since TA228 that have consistently demonstrated overall survival advantage for MPT (versus MP).	Unpublished data on overall survival in the Multiple Myeloma IX (MMIX) trial, with a median follow-up of 44 months, were available at the time of the appraisal (see section 4.1.9 of the guidance). These data were excluded from the Assessment Group’s systematic review because some participants received maintenance therapy with thalidomide, which was outside the scope of the appraisal. During the appraisal, the MMIX trial management group provided data on overall survival for participants who did not receive maintenance thalidomide. These data were considered carefully by the Appraisal Committee when formulating its recommendations (see section 4.1.10 of the guidance). The results published by Morgan et al. (2011) were discussed by the Committee at the time of the appraisal, and there

	are no new data from MMIX to inform an update of the guidance.
We note that a recent retrospective case matched analysis of VMP versus MPT in newly diagnosed elderly myeloma patients observed a significant superior progression free and overall survival for patients who received VMP (Morabito et al. Am J Hematol 2014;89:355-62). Thus the clinical effectiveness data on which TA228 was based have NOT been reinforced for thalidomide, as the results of Myeloma IX suggest no survival benefit for thalidomide. On the other hand, the survival benefit for VMP versus MP has been confirmed by long term follow up data.	Thank you for notifying NICE of the case-matched study by Morabito et al. (2014). The Appraisal Committee has a strong preference for randomised trials, because randomisation aims to prevent systematic differences between treatment groups in terms of both known and unknown confounders (see section 3.3.1–6 of the NICE Guide to the methods of technology appraisal). There are several randomised trials of bortezomib and thalidomide (each in combination with an alkylating agent and a corticosteroid) compared with melphalan and prednisolone/prednisone (MP). If NICE updated TA228, the search for evidence would focus on randomised trials rather than non-randomised studies. For this reason, the findings of Morabito et al. (2014) are unlikely to affect the Committee's recommendations. Accordingly, this new evidence is not sufficient to prompt an update of TA228.
It is also important to recognise that since the enrolment period and publication of the original VISTA trial (December 2004 to September 2006) there have been significant advances in the management of bortezomib associated toxicity which markedly improve its overall tolerability whilst maintaining efficacy. Subcutaneous administration of bortezomib is now universal with a significant reduction in associated peripheral neuropathy and other toxicity with equivalent efficacy to intravenous bortezomib administration (Moreau et al. Lancet Oncol 2011;12:431-40).	NICE acknowledges that the availability of subcutaneous bortezomib and a potential reduction in adverse events are important to patients. However, adverse events were not a key driver in the economic evaluation conducted for TA228 (see the summary table on page 41 of the guidance PDF). For this reason, a reduction in the frequency of adverse events is unlikely to affect the Committee's recommendations. The subcutaneous

	formulation of bortezomib has the same acquisition cost as the intravenous formulation. Accordingly, this new evidence is not sufficient to prompt an update of TA228.
In addition the use of weekly bortezomib treatment approaches has also been examined in the Phase 3 trial setting (e.g. Mateos et al. Blood 2014;124:1887-1893) with evidence of significantly superior toxicity profile leading to marked reduction in early treatment discontinuation due to drug related adverse events. This approach is associated with at least equivalent and arguably much improved progression free and overall survival (given the difficulty in comparing across Phase 3 studies).	The summary of product characteristics for bortezomib states that it should be given twice per week for the first 4 cycles of treatment and then weekly for the next 5 cycles. Mateos et al. (2014) used an alternative regimen, with bortezomib twice per week for the first cycle and weekly for the next 5 cycles. TA228 does not make recommendations outside the terms of the marketing authorisation for bortezomib, as published in the summary of product characteristics (see section 6.1.12 of the NICE Guide to the methods of technology appraisal). Accordingly, evidence on alternative dosing regimens for bortezomib is unlikely to affect the Committee's recommendations. Therefore, this new evidence is not sufficient to prompt an update of TA228.
On the basis of the clear overall survival and progression free survival advantage reported for VMP we would suggest there is an urgent need to reassess the TAG228 recommendations to ensure that all newly diagnosed myeloma patients have access to the best possible treatments. This is particularly vital for this group of older patients as their ability to undergo further therapies at relapse is far less than is the case for younger fitter patients.	NICE is grateful for this detailed response to consultation and it acknowledges the importance to patients and clinicians of having a choice of treatments. For the reasons detailed above, the new evidence (that is, evidence that was unavailable during the appraisal) is unlikely to affect the Appraisal Committee's recommendations. Therefore, the new evidence is not sufficient to prompt an update of TA228 at the present time. The review proposal recommended that TA228

	should be incorporated into the on-going clinical guideline for the diagnosis and management of myeloma. This means that the clinical guideline will include the verbatim recommendations from TA228.

Respondent: Pfizer **Response to proposal:** Agree Pfizer are not aware of any new evidence, and therefore agree that it would be appropriate to move TA228 to the technology appraisal static list.	**Comment from Technology Appraisals** Comment noted.

Respondent: Myeloma UK **Response to proposal:** Disagree Whilst we appreciate that due to time constraints and limited resources NICE cannot consider all its workload high-priority, we do believe that a review of TA228 should be factored into the NICE work programme to ensure that the guidance is up-to-date, reflects current NHS England practice and allows treatment flexibility in patients. More specifically, we think a review of the guidance is necessary for the following reasons: • The remit of NICE is to make the best use of NHS resources to the benefit of patients but in the case of NICE TA228 we do not think that NICE achieved this. As Myeloma UK argued in our response to the original appraisal consultation document (ACD) and final appraisal determination (FAD), it defies logic that where myeloma doctors think that Velcade would be the best treatment for their myeloma patient, they first have to demonstrate that thalidomide does not work before being allowed to prescribe their medicine of choice. This does not allow	**Comment from Technology Appraisals** Comments noted. During the appraisal, the Committee considered carefully the responses to the appraisal consultation document and the final appraisal determination. A formal response to those comments was issued and is available here: http://www.nice.org.uk/guidance/ta228/documents

treatment flexibility or decision-making choice and is potentially a waste of NHS resources	
• Velcade has been approved for use in the setting covered by the appraisal through NHS England baseline commissioning since 2013. This means that regardless of the NICE guidance, newly diagnosed myeloma patients ineligible for high -dose therapy and stem cell transplantation (HDTSCT), have been able to access both Velcade and thalidomide routinely on the NHS. This means that the NICE guidance has been at odds with clinical practice in England • The approval of Velcade through baseline commissioning has put myeloma patients living in Wales at a significant disadvantage in terms of access to treatments in this setting. The AWMSG approved Velcade in combination with melphalan and prednisolone in 2010 which was then superseded by NICE TA228 which significantly restricted access to Velcade. NICE should review TA228 to determine what can be done to bring Welsh access up to the level that patients in England have benefited from. This would also be beneficial to myeloma patients in Northern Ireland, who typically follow NICE guidance • Whilst NHS baseline commissioning is a good avenue to make Velcade available to patients, long term access would be secured through reviewing and updating NICE guidance. NHS England commissioning is currently volatile and unpredictable, so myeloma patients would benefit from the stability that NICE guidance brings – particularly as it seems in the draft NHS England Myeloma Algorithm, Velcade in the newly diagnosed setting is likely to be restricted	NICE technology appraisal guidance applies to England and also selectively in Northern Ireland, Scotland and Wales (positive TA guidance carries a statutory obligation on the Welsh NHS to implement). Variation in clinical practice between England, Wales and Northern Ireland would not necessarily be reduced by updating TA228. The available new evidence is unlikely to change the Appraisal Committee's recommendations. Therefore, the new evidence is not sufficient to prompt an update of TA228 at the present time.
• Velcade is a routinely used treatment in myeloma and doctors have a wealth of experience administering it in patients in the setting covered by TA228 (including through NICE baseline commissioning), as an induction treatment and at different stages of relapse. Patients receiving Velcade in the setting covered by NICE TA228 report a good experience with Velcade and lower rates of peripheral neuropathy since the availability of subcutaneous Velcade • The availability of subcutaneous Velcade and the reduced side-effect profile attributed to this method of administration is cost-saving to the NHS and should	NICE acknowledges that the availability of subcutaneous bortezomib and a potential reduction in adverse events are important to patients. However, adverse events were not a key driver in the economic evaluation conducted for TA228 (see the summary table on page 41 of the guidance PDF). For this reason, a reduction in the frequency of adverse events is unlikely to affect the

also be factored into the review	Committee's recommendations. The subcutaneous formulation of bortezomib has the same acquisition cost as the intravenous formulation. Accordingly, the availability of subcutaneous bortezomib is not sufficient to prompt an update of TA228.
• The publication of the updated results from both the VISTA trial and the Myeloma IX trial demonstrate that both thalidomide and Velcade in this setting are very effective and well-tolerated treatments compared to melphalan and prednisolone (MP). Whilst Velcade is more expensive than thalidomide, in the VISTA trial it led to a significant overall survival advantage and we believe that it should be made available on an equal basis to thalidomide to allow doctor choice and flexibility in treating their patients. Whilst there is no large Phase III trial comparing Velcade and thalidomide in this setting a recent article was published by Morabito et al demonstrated a survival advantage in patients receiving Velcade (Morabito et al 2014) For the reasons we have outlined above, we do not agree with the decision of NICE to move TA228 onto the static list of approved treatments and amalgamated into a clinical guideline. We hope that NICE take these points into account and factor a review of TA228 into their ongoing work programme.	Updated results from the VISTA trial reinforce the clinical effectiveness data available at the time of the appraisal and are not expected to affect the recommendations in TA228. The results of the Myeloma IX (MMIX) trial were discussed by the Committee at the time of the appraisal, and there are no new data from MMIX to inform an update of the guidance. Thank you for notifying NICE of the study by Morabito et al. (2014). The Appraisal Committee has a strong preference for randomised trials, because randomisation aims to prevent systematic differences between treatment groups in terms of both known and unknown confounders (see section 3.3.1–6 of the NICE Guide to the methods of technology appraisal). There are several randomised trials of bortezomib and thalidomide (each in combination with an alkylating agent and a corticosteroid) compared with melphalan and prednisolone/prednisone (MP). If NICE updated TA228, the search for evidence would focus on randomised trials rather than non-randomised studies. For this reason, the findings of Morabito et al. (2014) are unlikely to affect the Committee's recommendations.

	NICE is grateful for this detailed response to consultation and it acknowledges the importance to patients and clinicians of having a choice of treatments. For the reasons detailed above, the new evidence (that is, evidence that was unavailable during the appraisal) is unlikely to affect the Appraisal Committee's recommendations. Therefore, the new evidence is not sufficient to prompt an update of TA228 at the present time. The review proposal recommended that TA228 should be incorporated into the on-going clinical guideline for the diagnosis and management of myeloma. This means that the clinical guideline will include the verbatim recommendations from TA228.

Respondent: Celgene **Response to proposal:** Agree Celgene agree with the Institute's appraisal of the available evidence and are not aware of any further evidence which would alter this recommendation. Celgene agree with the recommendation to move TA228 to the static list and incorporate the guidance into the clinical guideline for the diagnosis and management of myeloma which is currently in development.	**Comment from Technology Appraisals** Comment noted.

Respondent: National Collaborating Centre for Cancer / Royal College of Pathologists **Response to proposal:** Disagree	**Comment from Technology Appraisals** Comments noted. Section 4.1.13 of the guidance refers to several

It should be noted that the Myeloma GDG does not propose to make any recommendations on the use of chemotherapeutic agents in myeloma. The existing TAGs are therefore of very considerable importance and regular review remains crucial. With respect to the Review Group's opinion that updated published results reinforce the clinical effectiveness data that led to TAG228 we would make the following points: • The long term follow up data from the VISTA trial continues to show a very significant overall survival benefit for the patients receiving VMP (compared to MP) of over 13 months (56.4 v 43.1 months, HR 0.695, p<0.001) maintained in all subgroups. Furthermore, and unlike some other studies this benefit was not negated by an inferior survival following relapse.	interim analyses of the VISTA trial, with median follow-up of 2 to 3 years. These analyses showed a statistically significant survival benefit for bortezomib, melphalan and prednisolone/prednisone (VMP) compared with melphalan and prednisolone/prednisone alone (MP). After median follow-up of 26 months, the hazard ratio was 0.64. The Appraisal Committee acknowledged that VISTA showed a survival benefit for bortezomib (see section 4.3.5 of the guidance). This survival benefit was incorporated into the Assessment Group's model. The 5-year results of the VISTA trial (San Miguel et al. 2013) reinforce the interim results already considered by the Appraisal Committee. The updated results are unlikely to affect the recommendations. The review proposal recommended that TA228 should be incorporated into the on-going clinical guideline for the diagnosis and management of myeloma. This means that the clinical guideline will include the verbatim recommendations on the use of bortezomib and thalidomide from TA228.
• Since the recruitment period of the VISTA trial there have been two improvements in our practical usage of bortezomib, reducing its toxicity without any apparent loss of efficacy. Subcutaneous administration of bortezomib has been show to be safe and effective while at the same time reduc-ing the toxicities of the drug (both neuropathy and others) (Moreau et al. Lancet Oncol 2011;12:431-40). A further Phase 3 clinical trial has also shown that bortezomib may be given weekly again with no impact on efficacy but with a significant improvement in toxicity profile (Mateos et al. Blood 2014;124:1887-1893). These approaches are mutually compatible and now widely used in the UK with benefits	NICE acknowledges that the availability of subcutaneous bortezomib and a potential reduction in adverse events are important to patients. However, adverse events were not a key driver in the economic evaluation conducted for TA228 (see the summary table on page 41 of the guidance PDF). For this reason, a reduction in the frequency of adverse events is unlikely to affect the Committee's recommendations. The subcutaneous

for both patients and the use of hospital resources (once weekly hospital visits instead of twice weekly, less time needed in day clinic, no IV drip for each administration, and patients like it)	formulation of bortezomib has the same acquisition cost as the intravenous formulation. The summary of product characteristics for bortezomib states that it should be given twice per week for the first 4 cycles of treatment and then weekly for the next 5 cycles. Mateos et al. (2014) used an alternative regimen, with bortezomib given twice per week for the first cycle and weekly for the next 5 cycles. TA228 does not make recommendations outside the terms of the marketing authorisation for bortezomib, as published in the summary of product characteristics (see section 6.1.12 of the NICE Guide to the methods of technology appraisal). Accordingly, evidence on alternative dosing regimens for bortezomib is unlikely to affect the Committee's recommendations. Therefore, this new evidence is not sufficient to prompt an update of TA228.
• While direct comparisons of bortezomib with thalidomide in a randomised clinical trial are still not available the Myeloma IX trial comparing CTDa with MP are now published and have demonstrated that while CTDa leads to better overall responses than MP, on an intention to treat basis CDTa offers no advantage in terms of overall survival (median follow-up 44 months, OS 33.2 v 30.6months, HR 0.89, p 0.24). • Since the publication of TAG228 there have not been any publications showing an overall survival advantage for MPT over MP, presumably mostly due the use of thalidomide or other effective salvage protocols following relapse.	The results of the Myeloma IX (MMIX) were discussed by the Committee at the time of the appraisal, and there are no new data from MMIX to inform an update of the guidance. The consideration of maintenance therapy or 'salvage' therapy is outside the scope of TA228 and its review.

• A retrospective case matched analysis of VMP v. MPT in newly diagnosed elderly myeloma patients demonstrated a significant superior progression free and overall survival for patients who received VMP (Morabito et al. Am J Hematol 2014;89:355-62).	Thank you for notifying NICE of the study by Morabito et al. (2014). The Appraisal Committee has a strong preference for randomised trials, because randomisation aims to prevent systematic differences between treatment groups in terms of both known and unknown confounders (see section 3.3.1–6 of the NICE Guide to the methods of technology appraisal). There are several randomised trials of bortezomib and thalidomide (each in combination with an alkylating agent and a corticosteroid) compared with melphalan and prednisolone/prednisone (MP). If NICE updated TA228, the search for evidence would focus on randomised trials rather than non-randomised studies. Accordingly, the findings of Morabito et al. (2014) are unlikely to affect the Appraisal Committee's recommendations.
This leads us to conclude the clinical effectiveness data on which TAG228 was based have not been reinforced for thalidomide in any of the studies mentioned above, whereas the survival benefit for VMP has been further reinforced by the long term follow up data and that placing TAG228 on the static list may be erroneous. Indeed as older patients have a reduced ability to receive further therapies at relapse there is a need to reassess TAG228 and its recommendations to ensure all myeloma patients are able to access the best possible treatments.	NICE is grateful for this detailed response to consultation and it acknowledges the importance to patients and clinicians of having a choice of treatments. For the reasons detailed above, the new evidence (that is, evidence that was unavailable during the appraisal) is unlikely to affect the Appraisal Committee's recommendations. Therefore, the new evidence is not sufficient to prompt an update of TA228 at the present time. The review proposal recommended that TA228 should be incorporated into the on-going clinical guideline for the diagnosis and management of myeloma. This means that the clinical guideline will include the verbatim recommendations on the use

	of bortezomib and thalidomide from TA228.

Respondent: Royal College of Nursing **Response to proposal:** Agree The Royal College of Nursing invited members who expressed interest in this area of health to comment on the review proposal of the above consultation. The feedback received suggests that the course of action (incorporating this into a forthcoming clinical guideline) proposed by NICE seems to be “sensible and reasonable”.	**Comment from Technology Appraisals** Comment noted.

Respondent: Janssen **Response to proposal:** Agree Janssen is content with this proposal.	**Comment from Technology Appraisals** Comment noted.

Respondent: Royal College of Physicians / National Cancer Research Institute / Association of Cancer Physicians / Royal College of Radiologists **Response to proposal:** Disagree The NCRI/RCP/RCR/ACP wishes to endorse the response submitted by the UK Myeloma Forum to the above consultation.	**Comment from Technology Appraisals** Please see the detailed comments above.

Paper signed off by: Frances Sutcliffe, 12 March 2015

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