National Institute for Health and Clinical Excellence

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

Responses to comments on the draft scope issued September 2008

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Celgene Ltd	We believe that it would be inappriopriate for this topic to be appraised by NICE using the Single Technology Appraisal (STA) process. The remit for this proposed appraisal is for multiple products (bortezomib and thalidomide), while the STA process is designed by definition for the appraisal of a single technology. Specifically, the NICE Guide to the STA process states that "The STA process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor." Since the remit of this appraisal is for multiple products (bortezomib and thalidomide) the appropriate process for this appraisal is the Multuple Technology Appraisal (MTA) process. The Glossary of NICE's Guide to the Topic Selection Process Interim process manual states that NICE's multiple technology appraisal (MTA) process focuses on evaluating evidence to determine whether groups of drugs, devices or health technologies used to treat a disease are clinically and cost effective. It is typically used for a group of products, some of which may already be in use within the NHS.	Comment noted. NICE has received referral of this topic as a multiple technology appraisal.

Section	Consultees	Comments	Action
	Myeloma UK	Thalidomide Pharmion and bortezomib are both licensed for the first-line treatment of myeloma. Therefore it is appropriate for NICE to consider their appraisal. We hope that appraising bortezomib and thalidomide can also incorporate an evaluation of important data from phase III RCT that are in progress. Emerging data from the MRC-supported Myeloma IX trial is expected to lead to the validation of combinations that offer significant clinical benefit to patients. It is important that all available combinations for this stage of the disease are examined in their entirety so as to make decisions that represent clinical excellence, and that are aligned with clinical reality.	Comment noted. The final remit is 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. All relevant evidence of the best available quality will need to be collated systematically and synthesised in a transparent and reproducible manner. NICE will be supporting the Assessment Group in liaising with those responsible for the Myeloma IX study in identifying the evidence that can be reasonably be expected to be included within the timelines of the appraisal. For further details, please see the Guide to Methods of Technology Appraisal http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459
	RCPath, BSH, UKMF	It is now appropriate and timely that NICE appraise both these combinations because of the recent licensing of these agents and in particular the large clinical experience with CTDa in the UK as part of Myeloma IX.	Comment noted.
	NCRI/RCP/RCR/ACP/JCCO	It is now appropriate and timely that NICE appraise both these combinations because of the recent licensing of these agents and in particular the large clinical experience with CTDa in the UK as part of Myeloma IX.	Comment noted.
	Janssen-Cilag Ltd	No comment	No action required.

Section	Consultees	Comments	Action
Wording	Celgene Ltd	The wording of the remit is appropriate and reflects issues of clinical and cost-effectiveness regarding Thalidomide Pharmion. It is important to note that Thalidomide Pharmion has been studied in phase III clinical trials in combination with a number of alkylating agents (e.g. cyclophosphamide or melphalan) and corticosteroids (e.g. dexamethasone or prednisolone). However, to our knowledge bortezomib has only been studied in combination with a single alkylating agent (melphalan) and corticosteroid (prednisolone). Therefore, the wording of the remit may not be appropriate for bortezomib.	Comment noted. NICE has received referral of this topic as a multiple technology appraisal. The remit is 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.
	RCPath, BSH, UKMF	We approve of the wording that refers to the combination of thalidomide with any alkylating agent and any steroid. This is how these agents are used in practice. We expect that there will be data from the Myeloma IX trial shortly available that will confirm the efficacy of a thalidomide containing regimen for induction.	Comment noted.
	NCRI/RCP/RCR/ACP/JCCO	We approve of the wording that refers to the combination of thalidomide with any alkylating agent and any steroid. This is how these agents are used in practice. We expect that there will be data from the Myeloma IX trial shortly available that will confirm the efficacy of a thalidomide containing regimen for induction.	Comment noted.
	Myeloma UK	The wording of the remit reflects the licensed indication of both Thalidomide Pharmion and bortezomib. Referring to the alkylating agent and a corticosteriod reflects the likely clinical use of both treatments.	Comment noted.
	Janssen-Cilag Ltd	No comment	No action required.

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Timing Issues	Celgene Ltd	No suggested timing for submission of evidence was proposed in the cover letter. However, consideration should be given to the availability of results of the ongoing UK NCRI Myeloma IX study. Myeloma IX is the largest cancer trial ever conducted in the UK and the larget multiple myeloma trial ever conducted globally.	Comment noted. NICE will be supporting the Assessment Group in liaising with those responsible for the Myeloma IX study in identifying the evidence that can be reasonably be expected to be included within the timelines of the appraisal. For further details, please see the Guide to Methods of Technology Appraisal http://www.nice.org.uk/aboutnice/howwework/devnicetech /technologyappraisalprocessguides/ guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459
	Myeloma UK	It is important that new and effective treatments and indications are made available in a timely manner to patients who need them. We urge NICE to be mindful of emerging data from relevant and high quality UK-based clinical trials. The widespread participation in the MRC-supported trial Myeloma IX has allowed clinicians to gain experience and confidence in using thalidomide-containing regimens. Myeloma UK considers it appropriate for NICE to incorporate the Myeloma IX data (as it is reported) in the proposed appraisal as its inclucison will better reflect the current clinical reality in the management of myeloma.	Comment noted. NICE will be supporting the Assessment Group in liaising with those responsible for the Myeloma IX study in identifying the evidence that can be reasonably be expected to be included within the timelines of the appraisal. For further details, please see the Guide to Methods of Technology Appraisal http://www.nice.org.uk/aboutnice/howwework/devnicetech /technologyappraisalprocessguides/ guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459

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	Janssen-Cilag Ltd	Bortezomib was originally referred for a single technology appraisal as part of the 18th wave until a proposal was made immediately prior to the first scoping meeting to include thalidomide. During consultations on the original scope, we indicated that we were content with this proposal as long as the timelines for bortezomib's appraisal were not unduly affected. Despite this, it is disappointing that the appraisal of our technology has already been significantly delayed by events that are not linked to bortezomib. We are also unclear as to what this delay has actually achieved. Although the scope has clearly been widened to allow inclusion of the CTDa regimen, we cannot see what the benefit of this is given that the Myeloma IX data, (upon which assessment of CTDa hinges) is immature. To our knowledge only initial response data will be available and it will be sometime before mature survival data become available. If there is a strong desire to appraise CTDa, it may be most appropriate to delay assessment of that regimen until the data matures. In this case, we would propose that a Single Technology Appraisal for bortezomib would be the most appropriate way forward. We are in a position to proceed towards a submission now and would like to work with NICE to avoid any further delays.	Comment noted. Further to the written consultation and scoping workshops held in May and June 2008 respectively for this proposed appraisal, the Department of Health requested that the Institute complete another consultation on a revised draft remit and scope and hold a subsequent scoping workshop. The final referral for this appraisal was received in March 2009.

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	RCPath, BSH, UKMF	As with all cancer drugs, there is urgency to ensure access to appropriate and effective treatment. We believe these technologies to be major advances in the treatment of this patient group conferring benefits in terms of prolongation of survival and improved quality of life. There are data from phase III trials that these agents produce significantly higher response rates and longer remission periods that will translate into improved quality of life.	Comment noted.
	NCRI/RCP/RCR/ACP/JCCO	As with all cancer drugs, there is urgency to ensure access to appropriate and effective treatment. We believe these technologies to be major advances in the treatment of this patient group conferring benefits in terms of prolongation of survival and improved quality of life. There are data from phase III trials that these agents produce significantly higher response rates and longer remission periods that will translate into improved quality of life	Comment noted.
Additional comments on the draft remit	RCPath, BSH, UKMF	We wish to emphasise again that myeloma is a heterogeneous disease and we are anxious to ensure that the process in which an alkylator, a steroid and thalidomide, is compared to an alkylator, a steroid and bortezomib should not result in clinicians being unable to select the most suitable agent for an individual patient according to the type of myeloma and other clinical circmustances specific to that patient.	Comment noted. The remit is 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.
	NCRI/RCP/RCR/ACP/JCCO	Patients with multiple myeloma and renal failure present a very specific therapeutic challenge and the needs of this group of patients needs to be considered carefully and specifically.	The 'Other considerations' section of the scope has been amended to include reference to people with renal impairment.

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	Myeloma UK	Myeloma is a complex, heterogeneous disease. It is individual to each patient, and all aspects of its management are underpinned by difficult treatment decisions and unpredictable treatment outcomes and side-effects. It is imperative that the recommendation of one combination does not exclude the use of other effective regimens needed for particular subsets of patients. Clinicians should be able to select the most suitable agent for an individual patient according to the type of myeloma and other clinical circumstances specific to that patient.	Comment noted. The remit is 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.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Celgene Ltd	The background information is adequate. We note that Thalidomide is explicitly referred to as current treatment option for the first line treatment of patients who are not eligible for HDT and stem-cell transplantation. We acknowledge that Thalidomide containing regimens are commonly used for the first line treatment of multiple myeloma in the NHS. This appears to have influenced the "standard comparators", which includes halidomide in combination with attenuated dexamethasone (without an alkylating agent). Given that Thalidomide is one of the two technologies to be appraised it would be inappropriate for any Thalidomide containing regimen to be used as a comparator in this appraisal.	Comment noted. The interventions will be compared with each other. The scope has been amended to remove the comparator of thalidomide and dexamethasone without an alkylating agent.
	NCRI/RCP/RCR /ACP/JCCO	Adequate.	Comment noted.
	RCPath, BSH, UKMF	This section adequately describes the background.	Comment noted.
	Myeloma UK	Satisfactory.	Comment noted.
	Janssen-Cilag Ltd	No comment	No action required.
The technology/ intervention	Janssen-Cilag Ltd	We believe that the wording in this section is pragmatic. However, we would like to make the point that there are no well-designed randomised controlled trials demonstrating that CTDa and MPT are equivalent and are therefore interchangeable. Until such time, the evidence base for these two regimens must be considered separately. Therefore we would recommend to be more specific in the description of the technologies to be appraised (Thalidomide and Bortezomib) to avoid any ambiguity. The wording recommended would be Bortezomib or Thalidomide in combination with melphalan and prednisolone.	Comment noted. The wording in the intervention section of the scope reflects the remit.

Section	Consultees	Comments	Action
	NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
	RCPath, BSH, UKMF	Yes	Comment noted.
	Myeloma UK	Yes	Comment noted.
Population	RCPath, BSH, UKMF	Yes, the population is defined appropriately. In addition, we wish to point out that patients who present in renal failure are at risk of becoming dialysis dependent and therefore present a therapeutic challenge. Renal failure affects up to 30 % of myeloma patients at presentation. Reversing renal impariment improves survival. Dialysis costs approximately £30,000 per person per annum so avoiding or reversing dialysis not only affects outcome but has cost effectiveness implications . To have a single treatment pathway for all could disadvantage this group of patients who we believe should be given special consideration. It is also the case that evidence is accumulating that subgroups of patients with certain cytogenetic abnormalities may do better with one drug rather than another.	Comment noted. The 'other considerations' section of the scope states that if evidence allows subgroups by comorbidities such as renal impairment will be considered.
	NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
	Janssen-Cilag Ltd	The population defined in the draft scope is appropriate for Bortezomib but is wider than the license for Thalidomide as it is not restricted to those aged >=65 years (or ineligible for high dose chemotherapy). The license of Thalidomide states that Thalidomide Pharmion is indicated 'in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged 65 years or ineligible for high dose chemotherapy'	Comment noted.

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	Myeloma UK	The population is defined appropriately but due to the hetergenous nature of myeloma, presenting patients could well be disadvantaged by an imposed single treatment pathway (for example those patients who present in renal failure)	Comment noted.
	Janssen-Cilag Ltd	The population is appropriately defined.	
Comparators	Celgene Ltd	The standard care treatment of an alkylating agent (e.g. cyclophosphamide or melphalan) and a corticosteroid (e.g. dexamethasone or prednisolone) is the appropriate comparator for this appraisal. However, thalidomide in combination with attenuated dexamethasone (without an alkylating agent) is not an appropriate comparator. Given that thalidomide is one of the two technologies to be appraised it would be inappropriate for any thalidomide containing regimen to be used as a comparator.	Comment noted The scope has been amended to remove this comparator.

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	Janssen-Cilag Ltd	Melphalan and prednisone is a standard of care; the use of this combination remains widespread in the UK In UK clinical practice there is a preference for using thalidomide, in combination with cyclophosphamide and attenuated dexamethasone. This combination is being studied in the on-going MRC Myeloma IX study; so far only response rate data are available. In the absence of mature survival data from well designed randomized controlled trials on CTDa a comparison between this regimen and melphalan-prednisolone-thalidomide or melphalan-prednisolone-bortezomib will be difficult. Thalidomide in combination with dexamethasone is not routine practice in the UK and we would therefore recommend it is removed as a comparator.	Comment noted. The comparator section of the scope has been amended. NICE will be supporting the Assessment Group in liaising with those responsible for the Myeloma IX study in identifying the evidence that can be reasonably be expected to be included within the timelines of the appraisal.
	RCPath, BSH, UKMF	We do not believe that thalidomide and dexamethasone should be a comparator because of its similarity to MPT and CTDa. Additionally, much of the data regarding thalidomide /dexamethasone is in the relapse setting. It should be remembered that this combination was initially listed as a comparator when an STA of VMP against M and P was being considered. Under the current remit we now feel that this would be inappropriate.	Comment noted. The scope has been amended to remove this comparator.

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	NCRI/RCP/RCR /ACP/JCCO	We do not believe that thalidomide and dexamethasone should be a comparator because of its similarity to MPT and CTDa. Additionally, much of the data regarding thal/dex is in the relapse setting This combination was initially suggested as a comparator when it was thought that an STA of VMP against M and P would be undertaken. Under the current remit, we now feel that this would be inappropriate.	Comment noted. The scope has been amended to remove this comparator.
	Myeloma UK	Thalidomide and dexamethasone should not be a comparator because thalidomide is an active agent in the appraisial. Under the current MTA remit, this would not be an appropriate comparator combination.	Comment noted. The scope has been amended to remove this comparator.
Outcomes	RCPath, BSH, UKMF	Yes	No action required.
	NCRI/RCP/RCR /ACP/JCCO	Yes	No action required.
	Myeloma UK	Yes	No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene	The outcome measures are appropriate.	No action required.

Section	Consultees	Comments	Action
Economic analysis	RCPath, BSH, UKMF	We understand that the QALY has been developed as a tool to standardise measurement of benefit between interventions in different diseases, however it may not accurately reflect patient-centred benefits in cancer, because these patients are coming from a very different level of functioning and expectation. Thus, in patients with a severe disease whose prospects of health are poor, more value and significance should be attached to smaller QALY gains. We encourage NICE to consier the use of quality modifying tools in the final evaluation	Comment noted. The Institute has as strong preference for expressing health gains in terms of QALYs and this is the measure used in the NICE reference case. Data collected using condition-specific preference-based measures may be presented in separate analyses. The Appraisal Committee considers many factors when appraising cost effectiveness – please see sections 6.2.13 to 6.2.26 of the Guide to the Methods of Technology Appraisal.
	NCRI/RCP/RCR /ACP/JCCO	We understand that the QALY has been developed as a tool to standardise measurement of benefit between interventions in different diseases, however it may not accurately reflect patient-centred benefits in cancer, because these patients are coming from a very different level of functioning and expectation. Thus, in patients with a severe disease whose prospects of health are poor, more value and significance should be attached to smaller QALY gains. We encourage NICE to consier the use of quality modifying tools in the final evaluation	Comment noted. Please see response above.
	Myeloma UK	We recognise that incremental cost per quality-adjusted life year is the best tool currently available to measure the value of treatments across different disease types. However we wish to cite our concern that it may not appropriately reflect issues of severity and unmet clinical need. In patients with a severe disease such as myeloma whose prospects of significant health gain can be low, more value should be attributed to QALY gains	Comment noted. Please see response above.
	Janssen-Cilag Ltd	No comment	No action required.

Section	Consultees	Comments	Action
	Celgene	No comment	No action required.
Equality and Diversity	RCPath, BSH, UKMF	Myeloma is a cancer in which bone disease is a prominent feature at presentation, affecting up to 80% of patients, and causing bone pain, vertebral fractures, deformity, immobility and impaired physical functioning. Because of this considerable bone morbidity that myeloma patients suffer, any effective disease-directed therapy, will, by halting bone destruction, have a disproportionatly large incremental health gain and improvement in quality of life. In addition, effective therapy at diagnosis may result in maximal benefit from other NICE approved technologies such as vertebroplasty/kyphoplasty. Myeloma is more common in Afro-Caribbean populations and any negative appraisal would disadvantage them disproportionately.	Comments noted. The Guide to the Methods of Technology Appraisal states that the Committee will take into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality.
	NCRI/RCP/RCR /ACP/JCCO	Myeloma is a unique cancer where bone disease is a prominent feature affecting up to 80% of patients, and causes bone pain, vertebral fractures, deformity, immobility and impaired physical functioning. Because of the considerable bone morbidity that these patients suffer, any effective disease-directed therapy, by halting bone destruction, will have a disproportionatly large incremental health gain and improvement in quality of life Myeloma is twice as common in the Afro-Caribbean population and so the outcome of these considerations will significantly affect this population of patients in addition, effective therapy at diagnosis may result in maximal benefit from other NICE approved technologies such as vertebroplasty/kyphoplasty	Comments noted. The Guide to the Methods of Technology Appraisal states that the Committee will take into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality.
	Myeloma UK	No comment	No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene	No comment	No action required.

Section	Consultees	Comments	Action
Other considerations	Myeloma UK	As mentioned, we consider that emerging data from Myeloma IX should be incorporated in the proposed appraisal to ensure that the decisions made are informed by the best available evidence, relevant to the UK setting.	NICE will be supporting the Assessment Group in liaising with those responsible for the Myeloma IX study in identifying the evidence that can be reasonably be expected to be included within the timelines of the appraisal.
	Janssen-Cilag Ltd	Subgroup: current consideration are appropriate We would suggest that the total therapeutic burden associated with the administration of Thalidomide (e.g. prophylactic antithrombotics) be taken into consideration in the economic evaluation of Thalidomide.Also given the teratogenic effect of Thalidomide, as recommended in the SmPC, the conditions of the Thalidomide Pharmion Pregnancy Prevention Programme must be fulfilled for all male and female patients	Comment noted. The Guide to the Methods of Technology states that in the reference case analysis, costs should relate to resources that are under the control of the NHS and PSS when differential effects on costs between the technologies under comparison are possible.
	Celgene	No comment	No action required.
Questions for consultation	RCPath, BSH, UKMF	Both combinations are clinically and cost-effective Particular subsets of patients with specific genetic abnormalitites who have in the past respoded poorly to conventional therapies may stand to gain from early exposure to bortezomib	The 'other considerations' section of the scope states that if evidence allows subgroups determined by cytogenetic features may be considered.
	NCRI/RCP/RCR /ACP/JCCO	Both combinations are clinically and cost-effective Particular subsets of patients with specific genetic abnormalitites who have in the past respoded poorly to conventional therapies stand to gain from early exposure to bortezomib	The 'other considerations' section of the scope states that if evidence allows subgroups determined by cytogenetic features may be considered.

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	Janssen-Cilag Ltd	A comparison with Cyclophosphamide-Thalidomide-Dexamethasone attenuated (CTDa) as part of this MTA will be difficult given that only response rate data are currently available for this combination. Waiting for mature survival data, evidence required for the appraisal, would delay the appraisal process.	NICE will be supporting the Assessment Group in liaising with those responsible for the Myeloma IX study in identifying the evidence that can be reasonably be expected to be included within the timelines of the appraisal.
	Myeloma UK	Myeloma UK consider that the MTA process is the most appropriate process to appraise these two treatments. If there are a number of effective combinations being licensed in the same time frame then it seems practical to consider them together, and the management of myeloma can only benefit from having access to as many novel combinations as possible.	NICE has received referral of this topic as a multiple technology appraisal.
	Celgene	No comment	No action required.
Additional comments on the draft scope.	RCPath, BSH, UKMF	We would like to make clear that the above comments are those of clinicians representing the organisations listed who are working together to produce this joint document which sets out our unanimous views.	Comment noted.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit	Celgene	Yes, Thalidomide Pharmion is licensed for use in combination with melphalan (an alkylating agent) and prednisone (a corticosteroid) as first line treatment of patients with untreated multiple myeloma, aged ≥65 years or ineligible for high dose chemotherapy. Thalidomide Pharmion is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.	Comment noted.
	Janssen-Cilag Ltd	No comment	No action required.

Section	Consultees	Comments	Action
Current or proposed marketing authorisation	Celgene	Thalidomide has been granted a licence by the European Medicines Agency (EMEA): "Thalidomide Pharmion in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥65 years or ineligible for high dose chemotherapy". Thalidomide Pharmion is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme. Thalidomide Pharmion is already licensed.	Comment noted.
	Janssen-Cilag Ltd	VELCADE in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant. VELCADE is indicated as mono-therapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. Confidential information has been removed.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

The Royal Pharmaceutical Society
RICE – The Research Institute for the Care of Older People
Welsh Assembly Government
Schering-Plough
Royal College of Nursing
Marie Curie Cancer Care
Actavis UK