National Institute for Health and Clinical Excellence

Lenalidomide for multiple myeloma in people who have received at least one prior therapy

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	Members of our organisations see a clear need to improve the survival prospects and quality of life of patients with multiple myeloma. We welcome the development and introduction into clinical practice of new agents designed to achieve this and support in principal their early evaluation by the NICE appraisal process.	Comments noted
	Pharmion Ltd	Yes	No action required
	Rarer Cancers Forum	Yes, definitely. It is important that this group of patients who relapse have options for treatment at present they have few if no choices left so it fills an unmet need. The treatment has been shown to improve survival of patients to improve quality of life without any major toxicity	Comments noted

Section	Consultees	Comments	Action
	Celgene Limited	Myeloma is an incurable rare cancer which significantly impacts the length and quality of life of those it affects and for which there are few treatment options available. In that context Celgene believes that it is entirely appropriate that consideration be given to making Revlimid (lenalidomide) accessible to patients in the UK.	Comments noted
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	The review is appropriate and important. The issue of acquisition cost is important, especially in the context of the "cost per qualy", for rare diseases such as myeloma. Calculating a qualy, based on what is effectively a cross over study, in this instance, will be an issue. It is also important to distinguish relapse/refractory, a group that has specific meaning in the USA from a patient at first and subsequent relapse.	Comments noted. The remit has since been revised to be as stated in the scope.

Section	Consultees	Comments	Action
	Myeloma UK	Myeloma is currently an incurable cancer which significantly impacts on the length and quality of life of those it affects. There are relatively limited treatment options for the treatment of myeloma, and lenalidomide is a clinically important treatment development. For this reason it is appropriate that it be appraised by NICE as part of the process to making it available on the NHS to those who need it.	Comments noted
Wording	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	Lenalidomide is now licensed in Europe and we support its appraisal according to this licensed indication, namely in combination with Dexamethasone after at least one prior treatment.	Comments noted. The scope has been revised accordingly.
	Pharmion Ltd	Yes	No action required
	Rarer Cancers Forum	Yes	No action required

Section	Consultees	Comments	Action
	Celgene Ltd	The wording of the remit we believe to require alteration as it does not reflect the licensed indication of lenalidomide in two respects, both of which may impact decisions regarding cost effectiveness. Firstly the licence for lenalidomide is for its use in combination with dexamethasone. The two compounds have a synergistic effect when used in combination.	Comments noted. The technology will be appraised according to its marketing authorisation and the supporting evidence base.

Section	Consultees	Comments	Action
	Celgene Ltd	Some agents are approved for use only as single agents and care must be taken to ensure that at all stages in any appraisal this distinction is recognised. Secondly the licensed indication for the combination of lenalidomide and dexamethasone is for use in 'patients who have received at least one prior therapy.' This is not the same as 'relapsed and/or refractory' as this latter definition excludes patients who, although responding to a particular treatment, are intolerant of it.	

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	Celgene Ltd	Tolerance of therapy is a major factor in determining a clinician's choice of therapy for myeloma and it is expected that some patients will be treated with lenalidomide and dexamethasone for reasons of safety and tolerance rather than purely efficacy. The Summary of Product Characteristics (SPC) gives the indication as follows: 'Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.'	

Section	Consultees	Comments	Action
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	While Thalidomide is used widely at presentation and relapse, it is still unlicensed and consequently, including it in the analysis may be difficult. If Thalidomide is considered, then given the side effects, it is important to consider both the therapeutic effect and side effect profile of Lenalidomide in comparison	Comments noted. It is not necessary for comparators to have a marketing authorisation if they are used in current standard practice.

Section	Consultees	Comments	Action
	Myeloma UK	The wording of the remit should be altered to better reflect the licensed indication of lenalidomide. It is licensed for use in combination with dexamethasone in patients who have had at least one prior therapy. To limit to 'relapsed and/or refractory' excludes those who are intolerant to an alternative treatment and may need lenalidomide for this reason. We suggest the remit is changed to read: "To appraise the clinical and cost effectiveness of lenalidomide in combination with dexamethasone in the treatment of multiple myeloma patients who have had at least one prior therapy."	Comments noted. The technology will be appraised according to its marketing authorisation and the supporting evidence base.

Section	Consultees	Comments	Action
Timing Issues	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	Whilst it is important for the benefit of patients to evaluate new agents such as Lenalidomide as quickly as possible, experience has shown that such evaluations can be complex and challenging. There is a risk that in evaluating new agents before studies have matured and a full range of data has been collected that the appraisal process can become unduly protracted, thus inadvertently delaying benefit to patients. We therefore feel it is important to ensure that before the appraisal process begins that all necessary data to ensure adequate evaluation is available.	Comments noted. When appraisals are scheduled, factors such as this are taken into consideration, along with the need to develop timely guidance on referred topics.
	Pharmion Ltd	Yes	No action required
	Rarer Cancers Forum	For patients with the symptoms of Multiple Myeloma a treatment that improve their quality of life and extend their survival time is needed now	Comments noted

Section	Consultees	Comments	Action
	Celgene Ltd	Whilst it is important to ensure that products with a proven survival benefit are considered quickly it is essential that data upon which to base a decision are available. Celgene has instigated a specific study to provide a health economic data-set on multiple myeloma which, with further UK clinical data, we believe will enhance the rigour of the review. These data will be available mid 2008 allowing the Company to provide all this information to an STA initiated at that time.	When appraisals are scheduled, factors such as this are taken into consideration, along with the need to develop timely guidance on referred topics.
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	The timing of the review is appropriate. Lenalidomide is an important new agent for the treatment of myeloma and its impact needs to be fully assessed. However, given the requirements of NICE for data on qualy's, it is important that data is available to calculate a qualy at the time of the review.	When appraisals are scheduled, factors such as this are taken into consideration, along with the need to developed timely guidance on referred topics.

Section	Consultees	Comments	Action
	Myeloma UK	It is important that new and effective treatments are made available in a timely manner to patients who need them. However, we urge NICE that before embarking on this appraisal they are absolutely satisfied that the essential data is in place to ensure that the appraisal goes as smoothly as possible and the best possible outcome can be reached.	When appraisals are scheduled, factors such as this are taken into consideration, along with the need to develop timely guidance on referred topics.

Section	Consultees	Comments	Action
Additional comments on the draft remit	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	We strongly endorse the proposed evaluation of Lenalidomide in combination with high dose Dexamethasone, not only because this is within the licensed indication but also because this is how physicians will use it in clinical practice, based on their knowledge of its increased efficiency when used in this way. We are anxious that the appraisal committee take into consideration the full range of available evidence, not just phase III randomised studies, but phase I and II studies and also the relevant clinical experience of physicians using Lenalidomide in the UK.	Comments noted. All evidence submitted in accordance with the appropriate process and methods will be appraised. See section 3.2 of the Guide to Methods of Technology Appraisal http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf , and section 5 of the Specification for Manufacturer/Sponsor submission of evidence http://www.nice.org.uk/niceMedia/pdf/STASpecManufacturerSubofEvidence.pdf
	Pharmion Ltd	None	No action required
	Rarer Cancers Forum	None	No action required
	Celgene Ltd	None	No action required

Section	Consultees	Comments	Action
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	The population for consideration is appropriate. The evidence base for the use of Revlimid at presentation is currently lacking. It is important to note that this evidence will become available in the next 2-3 year period. In addition in this time period the use of Revlimid in combination with alkylating agents will become more important. In particular MPR will be important for the elderly group. Its use in induction and maintenance of younger patients in the context of transplantation will also be important. At this point in time it is the combination Lenalidomide and Dexamethasone which should be considered.	Comments noted
	Myeloma UK	None	No action required

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	We agree that this is in general a fair and accurate description of the context. However, it might be better to describe the aim of therapy as being to reduce or control disease as effectively as possible rather than to 'slow disease progression', the latter suggesting a less active approach to myeloma treatment than is now the case.	Comments noted. The scope has been revised accordingly.
	Pharmion Ltd	No comment	No action required
	Rarer Cancers Forum	None	No action required
	Celgene Ltd	Celgene has the following comments on the background information: • Whilst the raw numbers of cases of myeloma can make the disease appear common it is in fact, relative to many other cancers, an uncommon condition. It fulfils the European Medicines Evaluation Agency (EMEA) criteria for an orphan disease and this point should be added. These criteria were established partly in order that people with serious less common disease are not penalised by the lack of investment in the development of therapies for them. The EMEA defines orphan medicines as those being developed for the treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the European Union.	Comments noted. NICE has a Citizen's Council which develops Social Value Judgements: Principles for the development of NICE guidance. A draft second edition of this document has recently been issued - see http://www.nice.org.uk/media/998/50/SVJ2ForPublicConsultation.pdf - which states that NICE considers that it should assess drugs to treat rare conditions or diseases in the same way as any other treatment.
		Data are available regarding survival rates in patients with relapsed and/or refractory myeloma. Data from the MRC reflecting survival prior to the introduction of new agents such as bortezomib indicates that median survival is in the order of 1.2 years following first relapse. Celgene would be happy to provide the reference	Comments noted. The scope is intended to provide a brief summary of relevant background information.
		• Age should be added as an important prognostic factor.	Comments noted. The scope has been revised accordingly

Section	Consultees	Comments	Action
	Celgene Ltd	• Within aims of therapy it should be added that one aim is to minimise negative effects of treatment. All treatments for myeloma have significant but differing side-effect profiles. It is an individual's response in terms of side-effects almost as much as efficacy which determines future treatment for that individual. This should be recognised within the scope. Related to this 'tolerability' should be added to the list of factors which determine treatment. Because of the seriousness of the disease and the lack of effective licensed treatments, unlicensed therapies are currently used. Thalidomide, for which there were previously no alternatives within the same class, falls into this category and this should be explicit in the background information.	Comments noted. The scope states that one of the aims of treatment is to maximise quality of life. One aspect of doing so is to minimise adverse effects. Comments noted. It is not necessary for comparators to be licensed as long as it is current standard practice in the UK
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	There are some inaccuracies in this, but the broad meaning is correct.	Comment noted. There have been some revisions to the scope.
	Myeloma UK	We consider it appropriate to add to this section that myeloma fulfils the European Medicines Evaluation Agency (EMEA) criteria for an orphan disease. Another important aim of therapy is to minimise negative effects of the differing side-effect profiles of myeloma treatments. An individual's response in terms of side-effects and tolerability can dictate the future treatment choice as much as the efficacy of the treatment.	Comments noted. NICE has a Citizen's Council which develops Social Value Judgements: Principles for the development of NICE guidance. A draft second edition of this document has recently been issued - see http://www.nice.org.uk/media/998/50/SVJ2ForPublicConsultation.pdf - which states that NICE considers that it should assess drugs to treat rare conditions or diseases in the same way as any other treatment.

Section	Consultees	Comments	Action
The technology/ intervention	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	We strongly endorse the proposed evaluation of Lenalidomide in combination with high dose Dexamethasone, not only because this is within the licensed indication but also because this is how physicians will use it in clinical practice, based on their knowledge of its increased efficacy when used in this way.	Comments noted
	Pharmion Ltd	Lenalidomide has been reported to have an apparent lack of some, or a decreased amount of, adverse effects associated with thalidomide, possibly including teratogenicity but has a different side effect profile including significant neutropenia and thrombocytopenia.	Comments noted
	Rarer Cancers Forum	Yes	No action required
	Celgene Ltd	Celgene has the following comments on the description of the technology within the draft scope. • The product received EMEA approval on 14th June 2007 and therefore references to it being in development or not yet licensed should be amended. • Re-iterating our comment above, it should at all points in this scope be made clear that the appraisal is of lenalidomide in combination with dexamethasone. • Re-iterating our comment above, it should at all points in the scope be made clear that the appraisal of lenalidomide should be in line with the licensed indication in 'patients who have received at least one prior therapy.' This is not the same as 'relapsed and/or refractory'	Comments noted. The scope has been revised accordingly.

Section	Consultees	Comments	Action
	Celgene Ltd	• The remark that lenalidomide has a 'decreased' amount of side-effects compared to thalidomide is inaccurate. The safety profile is different and some important side-effects may be less common. In particular we cannot support any implication at this stage that the risk of human teratogenicity is reduced. Whilst pre-clinical evidence of teratogenic effects similar to thalidomide has not been found this cannot be taken to imply any reduction of risk to a human foetus. The Company has invested heavily in the Revlimid Pregnancy Prevention Programme, agreed with the MHRA, to minimise the risk of foetal exposure. • It should be acknowledged that while lenalidomide is structurally similar to thalidomide, it is pharmacodynamically, physiologically (sharing no metabolites) and clinically distinct from thalidomide. Specifically, it is a more potent inhibitor of both inflammatory cytokines and cellular adhesion molecules, a more potent stimulator of the direct myeloma cell arrest mechanism and a more potent enhancer of T-cell and NK immunity. Whilst the starting dose of lenalidomide is quoted accurately it must be remembered that significant numbers of patients reduce their dose according to criteria outlined in the SPC in order for side-effects to be managed. At the time of unblinding of the phase III clinical trials approximately 40% of patients had experienced at least one dose reduction.	Comments noted. The scope has been revised accordingly. Comments noted. The scope has been revised accordingly. The technology section of the scope provides a brief summary of key details, but is not intended to give a detailed and comprehensive description of mode of action.

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	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	Yes, combination with alkylating agents has been carried out but the randomised evidence for these is lacking currently. Therefore, the Revlimid/Dexamethasone combination is the appropriate therapeutic modality for consideration.	Comments noted. The scope has been revised accordingly.
	Myeloma UK	Lenalidomide received its European license in June 2007 so this should be clarified in the document. It should be made explicit that the intervention to be appraised is that of lenalidomide in combination with dexamethasone in patients who have received at least one prior therapy, in line with its licensed indication.	Comments noted. The scope has been revised accordingly.
Population	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	The population in which Lenalidomide should be evaluated are not only those patients who have relapsed or progressed after one line of therapy, as per license, but also those whose treatment has to be changed because of unacceptable side effects or toxicities.	Comments noted. The technology will be appraised according to its marketing authorisation and the supporting evidence base.
	Pharmion Ltd	The SmPC definition is very broad and could potentially encompass patients that have received any form of initial therapy such as stem cell transplant.	Comments noted. See the 'other considerations' section of the scope.
	Rarer Cancers Forum	All patients with MM who have relapsed should be considered for this treatment	Comments noted.
	Celgene Ltd	The description of the population is inaccurate and, as stated above, should reflect the population for whom the drug is licensed i.e. …for patients who have received at least one prior therapy. As explained above this is not the same as saying the drug is indicated for relapsed or refractory myeloma.	Comments noted. The wording of the population section of the scope has been revised accordingly.
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	Yes, it would be appropriate to consider patients at first and subsequent relapse independently. The value in different prognostic groups, defined by the ISS/B_2M groups, as well as in different cytogenetic groups, may be appropriate depending upon access to data.	Comments noted. Subgroups of patients will be considered where evidence allows – see the 'other considerations' section.

Section	Consultees	Comments	Action
	Myeloma UK	The description of the population is inaccurate as it does not fully reflect the population for whom the drug is licensed: for patients who have received at least one prior therapy.	Comments noted. The scope has been revised accordingly.
Comparators	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	We believe this list should include repeat high dose therapy which is, as acknowledged in the background information in Appendix B, used in a significant number of patients at relapse. We note that this list includes thalidomide which whilst it is used in this setting is unlicensed for this indication which is a cause of some concern.	Comments noted. It is not necessary for comparators to have a marketing authorisation if they are used in current standard practice.
	Pharmion Ltd	Thalidomide Pharmion 200mg daily should be regarded as the comparator in this instance as reflected in the BCSH guidelines, the NICE assessment of Bortezomib and the submission dossier to the EMEA for Thalidomide Pharmion.	Comments noted.
	Rarer Cancers Forum	The comparators all have some serious side effects and frequently the associated toxicities (sedation, neuropathy and constipation) may prevent the maximum does being administered. Lenalidomide appears to lack these side effects and has the advantage of being an oral therapy	Comments noted. Adverse effects of treatment are one of the outcomes to be assessed.
	Celgene Ltd	In serious disease when there are limited treatment options and no alternative licensed therapy within the same class it is understandable that clinicians look to unlicensed therapies such as thalidomide. However, now that a therapy within the same class as thalidomide has received full regulatory scrutiny and approval within the European Union, Celgene does not feel it appropriate for NICE to include thalidomide as a comparator. In further support of this principle the Company would like to make the following points: • Using thalidomide as a comparator may ultimately lead to advice which indirectly sanctions the use of (unlicensed) thalidomide in certain indications and ahead of a licensed alternative in the same class. This we believe undermines the European regulatory process.	Comments noted. It is not necessary for comparators to have a marketing authorisation if they are used in current standard practice.

Section	Consultees	Comments	Action
		• Related to the above, Celgene has been able to gain a licence for lenalidomide only after developing and implementing with European regulatory agencies, a stringent risk management programme to reduce the risk of foetal exposure. Thalidomide has been through no such process and whilst some supply to the UK market is subject to safety controls, other supply is not. The Company does not feel it equitable to make comparisons of cost with agents in the same class which have not had to implement risk minimisation procedures. The value of the safety measures in place is unlikely to be reflected in any cost-effectiveness comparison.	Comments noted. NICE reference case requires considerations of the health and cost consequences of adverse events associated with technologies. Notably, thalidomide received an EMEA CHMP positive opinion in January 2008, which specifies that Thalidomide Pharmion be dispensed and prescribed in accordance with the Thalidomide Pharmion Pregnancy Prevention Programme. http://www.emea.europa.eu/pdfs/human/opinion/Thalidomide_2877308en.pdf
		• Whilst thalidomide seems effective for patients who have had prior myeloma treatments the level of evidence is much lower than that for lenalidomide and is not sufficient for it to be subject to regulatory scrutiny. Thalidomide is currently under review with the EMEA for treatment of myeloma but this is for a first line indication.	Comments noted. It was established at the scoping workshop that thalidomide is used in relapsed disease as well as at first-line.
		• Again, because it does not have licence, thalidomide itself has been exempt from health technology appraisal. Apart from this being inequitable this also means that the health economic data, in addition to the clinical data, will be limited.	It is not necessary for comparators to have a marketing authorisation if they are used in current standard practice.

Section	Consultees	Comments	Action
		• Celgene believe that NICE have set a precedent regarding the use of thalidomide as a comparator in their single technology appraisal (STA) of bortezomib for multiple myeloma. Specifically, the appeal panel decision document published on the NICE website on 29 March 2007 (http://guidance.nice.org.uk/page.aspx?o=419544) states that thalidomide does not have marketing authorization in the United Kingdom and that the appraisal committee had not used it as a comparator when assessing the value of bortezomib.	Comments noted. Note that section 4.4 of the guidance (TA129) for bortezomib monotherapy for relapsed monotherapy (issued October 2007) states that thalidomide is considered an important treatment for multiple myeloma and is currently being used both at first line and for relapse. See also sections 4.5 and 6.1. http://www.nice.org.uk/guidance/index.jsp?action=download&o=38001
		In addition to removing thalidomide as a comparator the Company would like to suggest that second stem cell transplant is included as a comparator. It is a treatment option in younger patients who have shown a good first response to this treatment.	Comments noted. Second stem cell transplant was discussed at the scoping workshop; it was not considered to be an appropriate comparator to include in the scope in terms of potentially being displaced by lenalidomide in the pathway of care.

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	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	The combination groups laid out are broadly correct and should involve VAD like regimens, single agent alkylators, Velcade/Dex, HDD and stem cell transplantation. The comparison in the pivotal trial was with the Dexamethasone, which is appropriate. The comparison to Thalidomide is more difficult. It is in wide use at both presentation and relapse. In these settings, we now use it in combination with Dexamethasone and alkylating agents. Lenalidomide can also be combined in a similar fashion, a comparison of Rev/Dex with CTD or MPT would be inappropriate, as they would be unfair comparisons. It is also important to note that the molecular structure and mode of action of Revlimid is different to Thalidomide and consequently it should be considered as such i.e. as a different drug.	Comments noted. Following the scoping workshop, the list of comparators has been revised. Single agent alkylators and stem cell transplant were discussed: they were not considered to be appropriate comparators to include in the scope in terms of potentially being displaced by lenalidomide in the pathway of care.
	Myeloma UK	We suggest the inclusion of second stem cell transplant as a comparator. It is a treatment option in younger patients who achieved a good response to their first transplant. Whilst recognising that due to limited treatment options it is understandable that doctors may have to look to unlicensed alternatives, Myeloma UK wishes to cite its concern about the current unlicensed status of thalidomide.	Comments noted. Second stem cell transplant was discussed at the scoping workshop; it was not considered to be an appropriate comparator to include in the scope in terms of potentially being displaced by lenalidomide in the pathway of care. It is not necessary for comparators to have a marketing authorisation if they are used in current standard practice.

Section	Consultees	Comments	Action
Outcomes	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	We support the inclusion of the outcome measures listed, but would also wish to see included time to progression, (TTP) which may demonstrate a more defined end point than overall survival in circumstances where patients go on to have further treatment after relapse.	Comments noted. The scope.
	Pharmion Ltd	Yes	No action required
	Rarer Cancers Forum	The drug Lenalidomide has the enormous advantage of being oral. This means fewer visits to hospitals and or home visits. There will be a reduction in the risks associated with IV therapy or continuous pump therapy (infection, extravasation, pump failure) and an improvement of quality of life and reduction of anxiety.	Comments noted. The economic evaluation should take into account all relevant differences in costs and health outcomes. See section 5.6 of the Guide to Methods of Technology Appraisal http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf
	Celgene Ltd	The primary efficacy endpoint in the lenalidomide phase III studies was time to progression (TTP). We suggest this is added to the outcome measures listed	Comments noted. The scope has been revised accordingly.
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	Need to capture responses as per EBMT criteria, PFS, and OS. There is also a need to consider side effects, especially neurological and VTE events. Many side effects will be due to the Dexamethasone.	Comments noted. The scope has been revised accordingly – see the sections on Outcomes and Other considerations.
	Myeloma UK	It would be appropriate to add time to progression (TTP) to the outcome measures, as it was a primary endpoint of efficacy in the lenalidomide phase III studies.	Comments noted. The scope has been revised accordingly.

Section	Consultees	Comments	Action
Economic analysis	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	We acknowledge that cost per QALY is an acceptable tool for evaluating cost effectiveness. We would welcome clarification of the statement 'the time horizon for the economic evaluation should reflect the period over which costs and benefits can reasonably be expected given the prognosis of multiple myeloma'	Comments noted. 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. See section 5.3.4 of the Guide to the Methods of Technology Appraisal: http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf
	Pharmion Ltd	No comment	No action required
	Rarer Cancers Forum	Less use of staff time less use of equipment and less use of hospital equipment	The economic evaluation should take into account all relevant differences in costs and health outcomes. See section 5.6 of the Guide to Methods of Technology Appraisal http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf
	Celgene Ltd	We appreciate that the NICE reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Re-iterating our comment above regarding timing issues, Celgene has instigated a specific multi-site study to provide a health economic data-set on multiple myeloma which, with further UK clinical data, we believe will enhance the rigour of the review and enable us to provide cost-effectiveness in terms of incremental cost per quality-adjusted life year. These data will be available mid 2008 allowing the Company to provide data in line with the NICE reference case to an STA initiated at that time.	Comments noted When appraisals are scheduled, factors such as this are taken into consideration, along with the need to developed timely guidance on referred topics.

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	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	This is complicated by the cross over nature of the protocol and so will rely on modelling analysis. The methodology for calculating a qualy for myeloma needs to be fully addressed in a scientific setting, as currently the approach seems subjective in this setting.	Comments noted.
	Myeloma UK	We recognise that incremental cost per quality-adjusted life year is the best tool currently available to express cost effectiveness. However, we wish to cite our concern that the QALY is a blunt instrument that may not be the most appropriate measurement to use in every assessment. To ensure that the health economic analysis can be as compelling as possible, and that the appraisal can go as smoothly as is feasible, we appeal to NICE to ensure they are confident that the manufacturer has presented them an economic model that it is the best it can be before embarking on the process.	Comments noted. When appraisals are scheduled, factors such as this are taken into consideration, along with the need to developed timely guidance on referred topics.
Other considerations	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	We wish to emphasise our view that Lenalidomide should be appraised in accordance with its marketing authorisation combination with Dexamethasone. We also agree that whilst subgroup analysis of available trials is important and likely to be of value we are also anxious to ensure that such analysis does not serve to limit the potential benefits of Lenalidomide to as wide a population as possible.	Comments noted.
	Pharmion Ltd	None	No action required
	Rarer Cancers Forum	None	No action required

Section	Consultees	Comments	Action
	Celgene Ltd	The Company agrees with the principle that this treatment should only be considered within licensed indications. Therefore, it would be contradictory to compare with an unlicensed treatment (thalidomide) and we refer to our comments above regarding the removal of thalidomide as a comparator in the absence of a licensed indication. The Company would like the scope to include consideration of the orphan nature of the disease, its seriousness and the lack of licensed treatment options. The Company would like the scope to acknowledge the innovative nature of the technology in this area of high unmet medical need.	Comments noted. It is not necessary for comparators to have a marketing authorisation if they are used in current standard practice. NICE has a Citizen's Council which develops Social Value Judgements: Principles for the development of NICE guidance. A draft second edition of this document has recently been issued - see http://www.nice.org.uk/media/998/50/SVJ2ForPublicConsultation.pdf - which states that NICE considers that it should assess drugs to treat rare conditions or diseases in the same way as any other treatment.
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	If included the quality of life and tolerability of Revlimid compared to Thalidomide needs to be addressed.	Comments noted.

Section	Consultees	Comments	Action
	Myeloma UK	Myeloma UK would like the proposed appraisal to be mindful of the orphan nature of myeloma, the relatively limited treatment options currently available, and the innovative nature of the technology. Myeloma UK would encourage the Appraisal Committee considering this technology to consider other types of data (in addition to randomised control trial data). For example, data gathered from clinical experience can also bring important evidence to the table and should not be dismissed.	Comments noted. NICE has a Citizen's Council which develops Social Value Judgements: Principles for the development of NICE guidance. A draft second edition of this document has recently been issued - see http://www.nice.org.uk/media/998/50/SVJ2ForPublicConsultation.pdf - which states that NICE considers that it should assess drugs to treat rare conditions or diseases in the same way as any other treatment.
Questions for consultation	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	None	No action required
	Pharmion Ltd	Question 1: Treatment pathways need to be defined and the number of relapses now treatable with the novel therapies may also need to be taken into account. Question 2: It may be appropriate to assess the IMID class of agents as a whole.	Comments noted – see the 'other considerations' section of the scope. Comments noted. This appraisal will be limited to the remit referred to NICE.
	Rarer Cancers Forum	This is suitable for a single technology appraisal	Comments noted

Section	Consultees	Comments	Action
	Celgene Ltd	In line with our comments on the licensed indication we would advise that the question be expressed as: 'What is the appropriate place of lenalidomide in combination with dexamethasone in treatment pathways for patients with multiple myeloma who have had at least one prior therapy?' We believe lenalidomide and dexamethasone combination is suitable for STA however we refer to our earlier comments and would request that such an appraisal begins in mid 2008 when more data is available enabling us to submit robust evidence in line with the NICE reference case of incremental cost per quality-adjusted life year.	Comments noted. See responses above.
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	The effectiveness of Lenalidomide in patients previously treated with Thalidomide needs to be addressed i.e. is it effective in individuals who have been exposed to Thalidomide previously. In addition we need to address the question, "Do we use the drug with the poor safety profile first, and then the drug with the better safety profile second, or is the reverse the correct way to use the drug?" A view of drug safety and risk management may also be appropriate.	Comments noted. See the 'Other Considerations', and 'Outcomes' sections of the scope.
	Myeloma UK	In line with our previous comments, we suggest that the first question for consultation reads: "What is the appropriate place for lenalidomide in combination with dexamethasone in treatment pathways for patients with multiple myeloma who have had at least one prior therapy?" As NICE have acknowledged in previous appraisals, due to the heterogeneous nature and the clinical course of myeloma, the treatment appropriate for each patient at any one time may differ. Choice of therapy for an individual is influenced by initial treatment and the response to it, the inherent characteristics of the diseases and the patient's performance status and preferences. This is the reality in myeloma, and for this reason the appropriate place for lenalidomide is as an option for all suitable patients who have had one prior therapy. We consider this technology to be appropriate for the STA process, but due to the reliance of an STA on evidence from the manufacturer, we again urge NICE to ensure this appraisal begins when the most robust evidence is in place.	Comments noted. See responses above.

Section	Consultees	Comments	Action
Additional comments on the draft scope.	British Society of Haematologists, Royal College of Pathologists, Royal College of Physicians and UK Myeloma Forum	None	No action required
	Pharmion Ltd	No	No action required
	Rarer Cancers Forum	None	No action required
	Celgene Ltd	None	No action required
	The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust	Revlimid is clearly an important new drug, which will bring benefits to patients. While this statement is undoubtedly correct, there remain issues around its cost effectiveness, which need to be addressed in the context of orphan drug indications.	Comment noted
	Myeloma UK	None	No action required

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit	Celgene Ltd	No. The reasons are given above. Our suggested wording is: To appraise the clinical and cost effectiveness of lenalidomide and dexamethasone in the treatment of multiple myeloma patients who have received at least one prior therapy.	Comments noted. The scope has been revised accordingly.
Current or proposed marketing authorisation	Celgene Ltd	Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy	Comments noted. The scope has been revised accordingly.
		Commercial-in-confidence information removed	Comments noted
		Commercial-in-confidence information removed	Comments noted
		Commercial-in-confidence information removed	No action required

Section	Consultees	Comments	Action
		Commercial-in-confidence information removed	No action required
		Commercial-in-confidence information removed	No action required
		Commercial-in-confidence information removed	No action required

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

- Royal College of Pathologists
- Royal College of Nursing
- Royal Pharmaceutical Society
- Department of Health
- MacMillan Cancer Support
- Royal College of Anaesthetists
- NHSQIS