National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least 1 prior therapy

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Novartis Pharmaceuticals UK	Yes	Comment noted.
	Myeloma UK	Myeloma UK considers this to be an appropriate topic to refer to the NICE Appraisal Committee.	Comment noted.
	National Collaborating Centre for Cancer	Given the timelines of NICE it is appropriate that this topic is referred to NICE for appraisal, as the Phase III data will imminently be available. Myeloma is an incurable disease and any agent with a novel mechanism of action that is different from currently available technologies, and that demonstrates benefit above that achieved with existing technologies should be considered.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Janssen-Cilag	We believe it is appropriate that this topic is referred to NICE for appraisal.	Comment noted.
Wording	Novartis Pharmaceuticals	The current wording of the remit does not reflect the anticipated licence population and therefore we propose the following wording:	Comment noted. Following the scoping

Section	Consultee/ Commentator	Comments	Action
	UK	"To appraise the clinical and cost effectiveness of panobinostat, in combination with bortezomib (BTZ) and dexamethasone (DEX), within its anticipated indication for the treatment of patients with relapsed or relapsed-and-refractory multiple myeloma who have received at least one prior therapy."	workshop the draft remit has been amended to 'To appraise the clinical and cost effectiveness of panobinostat within its marketing authorisation for treating multiple myeloma in people who have received at least 1 prior therapy'.
	Myeloma UK	We consider there to be a number of issues with the wording of the draft remit and with the population covered by the appraisal that we hope will be discussed and agreed at the NICE scoping workshop. In particular, the remit states that NICE will assess panobinostat within its licensed indiction for treating relapsed and refractory patients previously treated with bortezomib. This doesn't make it clear which relapse the treatment will be slotted into. During the scoping meeting we need to consider: - Whether the remit/population will cover first relapse for patients who had received Velcade® in the initial setting. In this case, if patients are refractory to Velcade it is unlikely they would have relapsed at the same time. This would be called primary refractory disease - Whether it will cover patients at third relapse where they have had Velcade at first relapse and have subsequently received and become refractory to Revlimid® - Whether it will be for patients beyond third relapse who then require Velcade	Comment noted. Following the scoping workshop the draft remit has been amended to 'To appraise the clinical and cost effectiveness of panobinostat within its marketing authorisation for treating multiple myeloma in people who have received at least 1 prior therapy'. Comment noted. If the evidence allows, subgroup analyses

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		retreatment (with the addition of panobinostat) - Whether patients need to be refractory only to Velcade (or if patients could be refractory to other lines of therapy such as Revlimid) and if so, whether Velcade has to have been their last treatment or whether they could have been refractory to it earlier on in the treatment pathway - whether it will be for patients who have received pomalidomide (on the Cancer Drugs Fund, but it will be assessed by the NICE Appraisal Committee in the coming months) - whether the scope of the appraisal should be relapse and refractory or relapsed and/or refractory myeloma We need to ensure that panobinostat is given to patients at the stage of the disease where it offers the most benefit to patients and makes the most sense clinically when considered against other treatments in the current pathway.	based on number of lines of previous therapy will be considered. This has been noted in the other considerations section in the scope. Comment noted. Guidance will be issued in accordance with the marketing authorisation for panobinostat.
	National Collaborating Centre for Cancer	The description of the technology is accurate	Comment noted.
	Janssen-Cilag	No comment	Comment noted.
Timing Issues	Novartis Pharmaceuticals UK	N/a	Comment noted.
	Myeloma UK	We have no comments on timing issues relating to this appraisal.	Comment noted.

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	National Collaborating Centre for Cancer	The available clinical data on panobinostat is limited to relapsed patients.The data on a phase III trial in combination with bortezomib and dexamethasone should be available imminently. The drug is not yet licensed but it is believed that this will be applied for in 2014	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Janssen-Cilag	No comment	Comment noted.
Additional comments on the draft remit	Novartis Pharmaceuticals UK	The suggested broader wording to the remit is supported by the following information from the pivotal Panorama-1 trial: • In Panorama-1 RCT a significant proportion of the patients ([redacted] patients out of 769 enrolled) did not receive prior bortezomib treatment. Therefore restricting the remit to patients who were previously treated with bortezomib is not in line with the trial population and the anticipated licence. • In Panorama-1 RCT a significant proportion of the patients ([redacted] in the active arm and [redacted] in the control arm) were relapsed, but not relapsed *and* refractory patients. Therefore restricting the remit to patients with relapsed and refractory multiple myeloma is not in line with the trial population and the anticipated licence. [redacted]	Comment noted. Following the scoping workshop the draft remit has been amended to 'To appraise the clinical and cost effectiveness of panobinostat within its marketing authorisation for treating multiple myeloma in people who have received at least 1 prior therapy'.

Section	Consultee/ Commentator	Comments	Action
		[redacted]	
	Janssen-Cilag	None	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Novartis Pharmaceuticals UK	Please add the following additional information after the first sentence in the last paragraph: With each relapse, the following remission is usually shorter than the previous one and more difficult to treat in part due to the development of bone, renal and/or haematological complications .	Comment noted. The background section of the scope is only intended to provide a brief description of the condition and current treatment options. A detailed description of these aspects should be included in the company's evidence submission and will be considered during the appraisal.
	Myeloma UK	In the background section, it would be useful to update it with information about induction treatment for transplant-eligible myeloma patients as patients	Comment noted. The background section of

Section	Consultee/ Commentator	Comments	Action
		will usually receive cyclophosphamide, thalidomide and dexamethasone (CTD) and NICE have recently approved Velcade induction treatment, in combination with thalidomide and/or dexamethasone. It should be noted in the background information that NICE TA129 is almost always given in combination with dexamethasone and/or a chemotherapy agent. As NHS England are starting to develop algorithms of treatment for clinicians to prescribe (whilst not yet agreed) it would be useful for NICE to discuss this in the background section as it will impact on the treatment pathway myeloma patients have. Whilst in theory "subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference" it should also be noted that it is mostly determined by what NICE and NHS England make available to patients in England and Wales - it is not as flexible as the background information outlines. It would also be useful to reflect upcoming NICE guidance (whether positive or negative) in this section - for instance Revlimid as a second line treatment (in patients who have received one prior treatment with Velcade and who are intolerant to thalidomide) and pomalidomide in relapsed and refractory myeloma (in patients who have received prior treatment with Velcade and Revlimid) as this will guide/affect how panobinostat will be slotted into the myeloma treatment pathway in England - particularly as they are currently approved through the Cancer Drugs Fund in England.	the scope is only intended to provide a brief description of the condition and current treatment options, and focus on the patient population for the appraisal. A complete list of related NICE guidance and NICE pathways is included in the Related NICE recommendations and NICE pathways section in the scope. Comment noted.

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		Finally the section that says "may include repeating high-dose therapy and stem cell transplantation or chemotherapy with alkalating agents and anthracyclines, thalidomide and corticosteroids" needs to be made clearer as we are not sure what this relates to.	
	National Collaborating Centre for Cancer	The background information is correct and currently data on panobinostat is limited to early phase trials with data on phase III trials hopefully emerging in the near future. The drug does not currently have a license for use in myeloma but there is a presumption this will be applied for in 2014	Comment noted.
	Janssen-Cilag	No comment	Comment noted.
The technology/ intervention	Novartis Pharmaceuticals UK	Please note that panobinostat is expected to be given as an add on therapy with bortezomib and dexamethasone in UK clinical practice.	Comment noted.
	Myeloma UK	Yes	Comment noted.
	National Collaborating Centre for Cancer	The description of the technology is accurate	Comment noted.
	Janssen-Cilag	No comment	Comment noted.
Population	Novartis Pharmaceuticals UK	Alternative wording suggested: In order to reflect the anticipated licensed population patients with relapsed or relapsed and refractory multiple myeloma previously treated with at least 1 prior treatment should be included in the scope.	Comment noted. Following the scoping workshop the population in the scope is defined as 'People

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		There are no sub-groups that should be considered separately. The results from the pivotal Panorama-1 trial indicate that Progression Free Survival (PFS) benefit was maintained across all of the subgroups analysed.	with multiple myeloma who have received at least 1 prior therapy'. If the evidence allows, a subgroup analyses based on number of lines of previous therapy will be considered. This subgroup has been noted in the other considerations section in the scope.
	Myeloma UK	See comments on wording in above section. Myeloma UK hopes that the scoping workshop will include a detailed discussion of and agreement on where the treatment fits in the UK myeloma pathway most effectively.	Comment noted. Following the scoping workshop the population in the scope is defined as 'People with multiple myeloma who have received at least 1 prior therapy'.
	National Collaborating Centre for Cancer	Although currently available phase 2 clinical data on panobinostat (in combination with bortezomib) relates to bortezomib-exposed patients, the phase III study was in relapsed patients independent of previous treatment. The definiton should therefore include all patients who have failed at least one prior therapy. The current wording of the scope limits this to patients who have previously had bortezomib. Caution is needed in defining the myeloma population further at the current time until more data is available.	Comment noted. Following the scoping workshop the population in the scope is defined as 'People with multiple myeloma who have received at

Section	Consultee/ Commentator	Comments	Action
			least 1 prior therapy'.
	Janssen-Cilag	We believe the population is defined appropriately.	Comment noted. Following the scoping workshop the population in the scope is defined as 'People with multiple myeloma who have received at least 1 prior therapy'.
Comparators	Novartis Pharmaceuticals UK	Alternative wording suggested: Analysing the treatments used in accordance with the UK Myeloma Forum (UKMF) UK clinical guideline, NICE guidance and those approved via the Cancer Drugs Fund (nCDF), bortezomib ± dexamthasone after 1st or 2nd relapse (2nd or 3rd line) should be considered as a comparator.	Comment noted. Following the scoping workshop bortezomib plus dexamethasone, and lenalidomide plus dexamethasone have been listed in the comparators section in the scope.
	Myeloma UK	The comparator expressed in the scoping document "established clinical management without panobinostat" is vague and cannot be used expressly as a comparator. However, the exact comparators for use in this appraisal are not yet clear as it is uncertain which relapse the appraisal is going to focus on. Depending on where panobinostat is going to be entered in the myeloma	Comment noted. Following the scoping workshop bortezomib plus dexamethasone, and lenalidomide plus dexamethasone have been listed in the comparators section in the scope.

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		clinical pathway, potential comparators could include: - Velcade and dexamethsone (at first relapse) - Revlimid and dexamethasone (if at second relapse) Beyond second relapse there is no routine standard of care in England and Wales, however - Pomalidomide is currently being assessed by NICE and a final decision will be made by NICE before the end of the panobinostat appraisal. It is also approved by the Cancer Drugs Fund so may form a comparator for multiply relapsed and/or refractory patients - Bendamustine is approved by the Cancer Drugs Fund and is used by clincians across the UK as a treatment in multiply relapsed and/or refractory patients - Other comparators would be retreatment with previously used novel agents and other chemotherapy/steroid combinations	It was considered at the scoping workshop that bendamustine and pomalidomide do not constitute appropriate comparators for panobinostat.
	National Collaborating Centre for Cancer	It is difficult to define a standard in this group of patients. The scope is for patients previously treated with bortezomib and most data on panobinostat is in combination with bortezomib/dexamethasone. For patients who have previously responded to bortezomib regimens retreatment may be possible in patients who have had a good response and the comparator then would be bortezomib/dexamethasone. It is important at this stage to not exclude comparison to other regimens used in myeloma including lenaldiomide, other bortezomib based regimens and thalidomide as data comparing these regimens to panobinostat may become available.	Comment noted. Following the scoping workshop bortezomib plus dexamethasone, and lenalidomide plus dexamethasone have been listed in the comparators section in the scope.
	Janssen-Cilag	No comment	Comment noted.
Outcomes	Novartis Pharmaceuticals	No change suggested.	Comment noted. Following the scoping

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	UK		workshop the outcomes in the scope have been updated to include time to next treatment.
	Myeloma UK	Myeloma UK considers these to be the most important outcome measures for NICE to consider in the appraisal.	Comment noted. Following the scoping workshop the outcomes in the scope have been updated to include time to next treatment.
	National Collaborating Centre for Cancer	The outcome measures described are the most important outcome measures (namely overall survival, progression-free survival and/or time to progression, response rates, adverse effects of treatment and health-related quality of life.	Comment noted. Following the scoping workshop the outcomes in the scope have been updated to include time to next treatment.
	Janssen-Cilag	No comment	Comment noted. Following the scoping workshop the outcomes in the scope have been updated to include time to next treatment.
Economic analysis	Novartis Pharmaceuticals UK	No change suggested.	Comment noted.

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	Myeloma UK	No comments	Comment noted.
	National Collaborating Centre for Cancer	Do not have access to any health economic data 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 consider the use of quality modifying tools in the final evaluation.	Comment noted. For the cost-effectiveness analyses health effects should be expressed in QALYs. When formulating its recommendations to the Institute, the Appraisal Committee has discretion to consider those factors it believes are most appropriate to each appraisal. The Committee can consider other benefits that are considered socially valuable but are not directly related to health and are not easily captured in a cost per QALY analysis (please see sections 5.3.1 and 6 of the Guide to the Methods of Technology Appraisals

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			2013).
	Janssen-Cilag	No comment	Comment noted.
Equality and Diversity	Novartis Pharmaceuticals UK	N/a	Comment noted.
	Myeloma UK	No comments	Comment noted.
	National Collaborating Centre for Cancer	Unaware of any issues relating to equality.	Comment noted.
	Janssen-Cilag	No comment	Comment noted.
Innovation	Novartis Pharmaceuticals UK	Histone deacetylases (HDACs) are important class of enzymes that deacetylate the ε amino group of the lysine residues in the histone tails to form a closed chromatin configuration resulting in the downregulation of gene expression. Inhibition of these HDACs enzymes have been identified as one of the promising approaches for cancer treatment including multiple myeloma. Panobinostat has low nanomolar activity against all class I, II and IV histone deacetylase (HDAC) enzymes. Through the inhibition of HDAC enzymes, panobinostat prevents increased deacetylation of histone proteins and subsequent transcription of gene products involved in multiple oncogenetic pathways.	Comment noted. The potential for panobinostat to be considered an innovative technology will be considered by the Appraisal Committee at the appraisal stage.
	Myeloma UK	The evidence published to date on panobinostat suggests that it is an	Comment noted. The

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		innovative technology in terms of its method of action. It is also well documented that histone deacetylase inhibitors (HDACs) play a critical role in bortezomib induced cytotoxicity. The results published so far on PANORAMA-1 at the annual meeting of ASH, have shown that panobinostat extends progression free survival in myeloma patients with relapsed or relapsed and refractory myeloma when compared to patients on bortezomib and dexamethasone alone. Data published to date on PANORAMA-2 study has also highlighted that patients who have become refractory to Velcade, are able to respond again when given in combination with panobinostat. If panobinostat is approved for use on the NHS, it would become the first-in-class HDAC inhibitor to become available to myeloma patients on the NHS.	potential for panobinostat to be considered an innovative technology will be considered by the Appraisal Committee at the appraisal stage.
	National Collaborating Centre for Cancer	This technology is innovative in terms of its mode of action and potential for synergy with existing anti-myeloma agents such as bortezomib.	Comment noted. The potential for panobinostat to be considered an innovative technology will be considered by the Appraisal Committee at the appraisal stage.
	Janssen-Cilag	No comment	Comment noted.

Section	Consultee/ Commentator	Comments	Action
Other considerations	National Collaborating Centre for Cancer	Until phase III data is available it is difficult to be clear as to the use of panobinostat in myeloma and it is not possible to define which subgroup if any would be more likely to benefit currently	Comment noted. If the evidence allows, subgroup analyses based on number of lines of previous therapy will be considered. This subgroup has been noted in the other considerations section in the scope.
	Janssen-Cilag	No comment	Comment noted.
NICE Pathways	National Collaborating Centre for Cancer	In the relapsed setting with Bortezomib and dexamethasone, pending data from phase III study	Comment noted.
Questions for consultation	Novartis Pharmaceuticals UK	Already covered in the above sections	Comment noted.
	National Collaborating Centre for Cancer	Will panobinostat be given as an add on therapy with bortezomib and dexamethasone or is it likely to be given as a monotherapy in UK clinical practice? ANSWER It has limited activity as a single agent and undoubtedly is best used in synergy with other anti-myeloma agents. Given the phase III study, it is likely that it will be given in combination with bortezomib and dexamethasone. Have all relevant comparators for panobinostat been included in the scope?	Comment noted. Following the workshop bortezomib plus dexamethasone, and lenalidomide plus dexamethasone have

Section	Consultee/ Commentator	Comments	Action
		Which treatments are considered to be established clinical practice in the NHS for relapsed and refractory multiple myeloma previously treated with bortezomib? ANSWER It is important at this stage to not exclude comparison to other regimens used in myeloma including other bortezomib based regimens, thalidomide and lenalidomide based regimens as data comparing these regimens to panobinostat may become available.	been listed in the comparators section in the scope.
	Janssen-Cilag	No comment	Comment noted.
Additional comments on the draft scope	Novartis Pharmaceuticals UK	Any additional comments on the draft scope 1. The proposed population should not be limited to people with "relapsed and refractory" multiple myeloma as it is anticipated that the licence will include patients who are relapsed as well as those that are relapsed and refractory. This reflects the population of patients evaluated in the pivotal clinical trial, Panorama-1. • [redacted] Prior bortezomib treatment will not be a criterion for assessing the eligible	Comment noted. Following the workshop the population in the scope is defined as 'People with multiple myeloma who have received at least 1 prior therapy'.

Section	Consultee/ Commentator	Comments	Action
		patient population as it was neither an inclusion criteria in the Panorama-1 study, nor will it be part of the proposed EMA label. In the pivotal Panorama-1 trial [redacted] and [redacted] of the patients in the PAN+BTZ+DEX and the PBO+BTZ+DEX treatment arms respectively received prior bortezomib treatment. Having prior bortezomib treatment as a requirement to access the combination treatment would either push the combination treatment into a later line or would exclude those patients who are eligible for thalidomide as a first line therapy. Neither consequence can be justified in light of the Panorama-1 study design and preliminary results. 2. [redacted]	
	National Collaborating Centre for Cancer	It is very difficult to comment when the phase III data has yet to be published	Comment noted.
	Janssen-Cilag	None	Comment noted.

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

Department of Health
Healthcare Improvement Scotland
Merck Sharp & Dohme
Royal College of Nursing

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Lymphoma Association	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Lymphoma Association has been added to the matrix of consultees and commentators under 'patient/carer groups'

2.	British Society for Haematology	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. British Society for Haematology has been added to the matrix of consultees and commentators under 'professional groups'
3.	Leuka	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Leuka has been added to the matrix of consultees and commentators under 'Relevant research groups'

4.	Leukaemia Busters	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Leukaemia Busters has been added to the matrix of consultees and commentators under 'Relevant research groups'