NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Panobinostat for treating multiple myeloma after at least 2 previous treatments

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using panobinostat in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using panobinostat in the NHS in England.

For further details, see the Guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 6th October 2015

Second Appraisal Committee meeting: 20th October 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

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1 Appraisal Committee's preliminary recommendations

1.1 Panobinostat in combination with bortezomib and dexamethasone is not recommended within its marketing authorisation for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent'.

1.2 People whose treatment with panobinostat was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Panobinostat (Farydak, Novartis Pharmaceuticals UK) is an oral potent histone deacetylase inhibitor that disrupts a key mechanism in the transformation of normal cells to cancerous cells and selectively targets tumour cells for cell death. Panobinostat has received a marketing authorisation, 'in combination with bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 previous regimens including bortezomib and an immunomodulatory agent'.

2.2 In the PANORAMA-1 trial (comparing panobinostat plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone), diarrhoea, thrombocytopenia, anaemia, fatigue and nausea occurred more often with panobinostat plus bortezomib

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and dexamethasone than with placebo plus bortezomib and dexamethasone.

2.3 Panobinostat costs £776 per 20 mg tablet. The recommended starting dose of panobinostat is 20 mg, taken orally once a day, on days 1, 3, 5, 8, 10 and 12 of a 21-day cycle. Patients should have panobinostat for 8 cycles, after which it is recommended that patients showing clinical benefit continue the treatment for 4 additional cycles of 6 weeks each. The company has agreed a patient access scheme with the Department of Health. The level of the discount is commercial in confidence. If panobinostat had been recommended, this scheme would provide a simple discount to the list price of panobinostat with the discount applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 9) considered evidence submitted by Novartis and a review of this submission by the Evidence Review Group (ERG; section 10).

Clinical effectiveness

3.1 The company included 1 randomised controlled trial, PANORAMA-1, which compared panobinostat, bortezomib and dexamethasone with bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma, and who have had 1–3 previous treatments. The trial spanned 34 countries and 215 centres (30 of which were in the UK). Patients (n=768) were randomly assigned 1:1 to either panobinostat (n=387) or placebo (n=381) (both in combination with bortezomib and dexamethasone) and were stratified by number of previous treatments and previous

bortezomib treatment. Approximately one third (35% in the intervention group and 37% in the comparator group) of patients in the trial had relapsed and refractory multiple myeloma and approximately half had received more than 2 lines of treatment (48.8% for the intervention group and 48% for the comparator group).

3.2   Treatment allocation in the trial was blinded and no crossover occurred. The trial was divided into phase 1 (24 weeks; 8 cycles of 21 days' each) and phase 2 (24 weeks; 4 cycles of 42 days' each). During phase 1, in week 1 and 2 of each cycle patients had either panobinostat (20 mg) or placebo 3 times a week, bortezomib (1.3 mg/m^2) twice a week and dexamethasone (20 mg) 4 times a week. There was no treatment in the third week of the cycle. Patients moved onto phase 2 if they experienced clinical benefit, defined as at least no disease progression on day 1 of cycle 8 (as assessed by the modified European Group for Blood and Marrow Transplantation criteria).

3.3   The primary outcome was progression-free survival with response assessed at 3-week intervals during the treatment phases and at 6-week intervals thereafter. Progression-free survival (as assessed by the investigators on the basis of the modified European Group for Blood and Bone Marrow Transplant criteria) was defined as the time from randomisation until documented disease progression, relapse from complete response or death, whichever came first. The final analysis for progression-free survival was done at median follow-up of 31 months. Progression-free survival observations were censored at the date of the last response assessment for people who had either not progressed or had a different treatment.

3.4   The key secondary outcome was overall survival, which was defined as the time from randomisation to death from any cause.

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An interim overall survival analysis was conducted at the time of the final progression-free survival analysis; a second analysis was done when 86.5% of the 415 events needed for the final overall survival analysis were observed (the final analysis will be done when all 415 overall survival events have been observed). Other secondary outcomes included overall response rate (complete response, near complete response and partial response), time to progression, time to response and duration of response, safety and health-related quality of life.

3.5   The trial had a number of subgroups including number of previous lines of therapy (1, 2 or 3) and type of previous treatments. A subgroup containing patients who had at least 2 previous lines of treatment, including 1 immunomodulatory drug (for example thalidomide) plus bortezomib (n=147, 19% of the trial population), was a post hoc subgroup whereas other subgroups were pre-specified in the trial. This is the subgroup who received the marketing authorisation.

3.6   The PANORAMA-1 trial contained the full population and a subgroup of people who had at least 2 previous lines of treatment, including 1 immunomodulatory drug plus bortezomib. In the PANORAMA-1 trial, patients in the subgroup having panobinostat plus bortezomib and dexamethasone had a median progression-free survival extension of 7.8 months compared with placebo, representing a 53% reduction in the risk of progression. Overall survival data were confidential and cannot be reported here.

3.7   The company did an indirect comparison for both the full population and the subgroup of people who had at least 2 previous lines of treatment, including 1 immunomodulatory drug plus bortezomib, to compare panobinostat plus bortezomib and dexamethasone with bortezomib, thalidomide, lenalidomide, dexamethasone and

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pegylated liposomal doxorubicin. The indirect comparison included PANORAMA-1, MM-009 and MM-010 for lenalidomide plus dexamethasone, DOXIL-MMY-3001for bortezomib plus dexamethasone, and APEX for bortezomib.

3.8   Four different methods were used for the indirect treatment comparison. For the full population, the common comparators method, naïve comparison, unadjusted Cox regression and matching adjusted indirect treatment comparison were used. For the subgroup who had at least 2 previous therapies, only naïve comparison, unadjusted Cox regression and matching adjusted indirect treatment comparison methods were used. The company considered lenalidomide plus dexamethasone to be the only relevant comparator for the subgroup.

3.9   Results of the naïve comparison indicated that progression-free survival and overall survival for panobinostat plus bortezomib and dexamethasone was similar to that of lenalidomide plus dexamethasone, assuming exponential survival models for the 2 outcomes. Uncertainty around the 2 outcomes was not reported and therefore uncertainty around the hazard ratios could not be reported.

3.10   The unadjusted Cox method was also used to estimate hazard ratios for progression-free survival and overall survival when comparing panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone. Patient-level data from the PANORAMA-1 trial were used for the panobinostat group whereas patient-level data were simulated for the lenalidomide group. For the subgroup who had at least 2 previous treatments, the hazard ratios for progression-free survival and overall survival were 1.061 and 1.075 respectively.

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3.11   For the matching adjusted indirect treatment comparison, patient-level data from the PANORAMA-1 trial were used for the panobinostat group whereas data from the pooled analysis of the MM-009 and MM-010 studies and a subgroup from Stadtmauer et al. (2009) were used for the lenalidomide plus dexamethasone group. Individual patient-level data from the PANORAMA-1 trial were reweighted such that the median baseline characteristics matched those reported from the MM-009 and MM-010 trials. These variables included age, sex, time since diagnosis, ECOG score, number and type of previous treatments (immunomodulatory drugs and bortezomib) and serum beta-2 microglobulin level. For the subgroup of patients who had at least 2 previous treatments, the hazard ratios for progression-free survival and overall survival were 1.108 and 1.413 respectively.

3.12   Adverse events were reported for the PANORAMA-1 trial. The numbers of patients in the panobinostat plus bortezomib and dexamethasone group who needed at least 1 dose change were 194 (51%) for panobinostat, 231 (61%) for bortezomib and 93 (24%) for dexamethasone. In the placebo plus bortezomib and dexamethasone group, the equivalent numbers were 86 (23%) for placebo, 158 (42%) for bortezomib and 65 (17%) for dexamethasone. The most frequent ($\geq 2\%$) adverse events leading to treatment discontinuation were diarrhoea, fatigue, asthenia and peripheral neuropathy in the panobinostat plus bortezomib and dexamethasone group, and fatigue and pneumonia in the placebo plus bortezomib and dexamethasone group. The incidence of adverse events was much lower during phase 2, when bortezomib and dexamethasone were administered less frequently.

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Cost effectiveness

3.13   The company developed 2 models – 1 for the full population in PANORAMA-1 and 1 for the subgroup who had at least 2 previous treatments including an immunomodulatory drug and bortezomib. This section relates only to the subgroup.

3.14   The company developed a decision analytic semi-Markov model consisting of 3 health states: pre-progression, post-progression and death. The time horizon of the model was 25 years and the cycle length was 3 weeks with a half-cycle correction applied. Discounting of 3.5% was incorporated for both effects and costs and the analysis was done from an NHS and personal social services perspective.

3.15   Transition probabilities for panobinostat plus bortezomib and dexamethasone were derived from post hoc patient-level data from PANORAMA-1, and included progression-free survival, treatment exposure and overall survival.

3.16   The probabilities for risk of progression or pre-progression death (based on progression-free survival data), risk of treatment discontinuation (based on exposure to treatment data) and risk of death (based on overall survival data) were generated by fitting parametric curves to the Kaplan–Meier data, allowing for transition probabilities for panobinostat plus bortezomib and dexamethasone to be estimated. The time between randomisation and progression, death or censoring was considered to be the length of treatment exposure.

3.17   To determine the proportion of patients who were on or off treatment, patient-level discontinuation data from the PANORAMA-1 trial were used to estimate the risk of treatment discontinuation in a 3-week cycle. In this analysis, the length of treatment exposure

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for a patient was considered the time to treatment discontinuation. All patients discontinued treatment before or at the time of a progression-free survival event, so no patient was censored. Transition probabilities for the risk of death in a given cycle were estimated using patient-level data from the PANORAMA-1 trial after parametric curves had been fitted.

3.18   For the overall survival analysis, time between randomisation and death or censoring was considered as treatment exposure. Patients were censored at the last contact date if they were lost to follow-up for survival status measurements.

3.19   Patients in the PANORAMA-1 trial completed an EORTC QLQ-C30 questionnaire, which was mapped to obtain the corresponding EQ-5D utility value. Cycle-specific as well as overall average and median utility values were estimated for the treatment arms.

3.20   No utility data were available for lenalidomide plus dexamethasone in people who had at least 2 previous treatments including an immunomodulatory drug and bortezomib, so 2 scenarios were explored. In the first, the utility value for lenalidomide plus dexamethasone treatment was assumed to be the same as that for bortezomib plus dexamethasone. In the second scenario, it was assumed to be the same as the utility value associated with the progression-free no treatment health state. The first scenario was considered for the base-case analysis.

3.21   The cost of lenalidomide applied in the model was calculated as a weighted average of daily doses across all patient days in the MM-010 study. The resulting weighted average 28-day cycle cost for lenalidomide was £3773, which translated into a 3-weekly (21-day) cycle cost of £2830. Because the manufacturer of lenalidomide has agreed a patient access scheme (in which the manufacturer agrees

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to meet the cost of lenalidomide for patients who remain on treatment for more than 26 cycles of 28 days), lenalidomide costs in the model were only applied for 35 3-weekly cycles (approximately 26x28/21). The cost for dexamethasone was £2.59 per 28-day cycle (£1.94 per 3-weekly cycle). The panobinostat costs included in the model are confidential because a patient access scheme has been agreed between the company and the Department of Health.

3.22   The company considered that the unadjusted Cox method in the subgroup who had at least 2 previous treatments was the most appropriate approach to derive the relative efficacy of panobinostat plus bortezomib and dexamethasone compared with lenalidomide plus dexamethasone. Having incorporated the patient access scheme (PAS), the company's base-case incremental cost-effectiveness ratio (ICER) for panobinostat plus bortezomib and dexamethasone, incorporating subcutaneous bortezomib (see section 4.1), dominated lenalidomide plus dexamethasone (that is, it costs less and is more effective). When the company incorporated intravenously administered bortezomib, the ICER was £64,819 per quality adjusted life year (QALY) gained.

3.23   The company provided a number of scenarios which were: changes to the discount rate, how overall and progression-free survival were calculated, time to discontinuation, distribution of post-progression treatments, utility values associated with lenalidomide plus dexamethasone, how hazard ratios were generated and threshold analyses. For a number of these scenarios, panobinostat plus bortezomib and dexamethasone continued to dominate lenalidomide plus dexamethasone. However, when the hazard ratios were altered or generated using an alternative method to unadjusted Cox regression, the ICER ranged from £5096 to £362,561 per QALY gained. Furthermore,

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when the company changed how overall survival was calculated, the ICER ranged from £935 to £19,198 per QALY gained.

ERG's critique and exploratory analyses

3.24   The ERG considered that the population in the PANORAMA-1 trial generally reflected relapsed and refractory multiple myeloma patients in the UK, although it noted that with a median age of 63 years, the trial population was younger than most UK patients. It also considered that people in the trial had bortezomib up to cycle 16, but in UK clinical practice patients do not have bortezomib beyond cycle 8, with a stopping rule at 4 cycles if no response is seen. The ERG noted that patients in the trial were administered bortezomib intravenously but that in UK clinical practice it is becoming more common to administer bortezomib subcutaneously.

3.25   The ERG noted that the subgroup of interest – people who have had at least 2 previous treatments – was not analysed in the indirect comparison using the common comparisons analysis, but that the company did not explain why this was the case. The ERG also noted that the populations included in the trials were broader than the subgroup of interest.

3.26   The ERG considered the use of parametric curves fitted to the Kaplan–Meier data to be appropriate to extrapolate beyond the trial time horizon, and noted that the use of logistic regression was particularly appropriate because of the binary nature of the responses (progressed or not progressed). However, the ERG noted that the lenalidomide plus dexamethasone overall survival curve had not been compared with the underlying trial data.

3.27   The ERG also observed that the hazard ratios for progression-free survival and overall survival were calculated using 2 methods of indirect comparison: unadjusted Cox regression and matching

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adjusted indirect treatment comparison (MAIC). For the unadjusted Cox regression, the proportional hazards assumption was not consistent with the shape of the Kaplan–Meier curves for progression-free survival or overall survival for patients having either treatment. The ERG noted that the curves crossed, suggesting that hazard ratios were likely an invalid method of estimating relative effectiveness. The ERG therefore considered that the MAIC approach was a more potentially valid method of obtaining point estimates of relative effectiveness. However, after making the adjustments to the PANORAMA-1 trial data needed for the MAIC method, the effective sample size in the full trial sample analysis was reduced from 314 to 137. This suggests that the MAIC estimates are also likely to be unreliable and biased by unobserved confounding.

3.28   The ERG considered that the costs and resources used in the model were generally acceptable. The company included a cost for lymphopenia, but the clinical experts advising the ERG had suggested that the cost of lymphopenia should be 0. The ERG's clinical experts commented that tests would normally be administered no more than every 6 months, and not in every cycle as in the company's model. They also advised that patients would see a specialist every other cycle, rather than every cycle of treatment. The clinical experts also confirmed that most patients have bortezomib subcutaneously because of better tolerance.

3.29   The ERG considered the MAIC method to be the most appropriate for calculating hazard ratios, but it acknowledged that they may be unreliable because of low statistical power.

3.30   The ERG did a number of exploratory analyses using the company's base-case assumptions, including subcutaneous bortezomib. Using the naïve comparison method, panobinostat plus

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bortezomib and dexamethasone had a with-PAS ICER of £341,896 per QALY gained. Using the MAIC method, the ICER was £95,683 per QALY gained.

3.31   When the ERG used its preferred assumptions of lymphopenia cost set at 0, specialist visit frequency every second cycle instead of every cycle and subcutaneous bortezomib instead of intravenous, the deterministic ICER was £92,306 per QALY gained and the probabilistic ICER (the ERG's preferred ICER) was £99,880 per QALY gained.

3.32   Full details of all the evidence are in the [Committee papers](#).

4   Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of panobinostat, having considered evidence on the nature of multiple myeloma and the value placed on the benefits of panobinostat by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical need and practice

4.1   The Committee considered the current pathway for people with multiple myeloma. It heard from the clinical experts that the pathway of treatment is heterogeneous and people could have either thalidomide or bortezomib, plus an alkylating agent (for example melphalan or chlorambucil) and a corticosteroid (for example dexamethasone), as first-line treatment as recommended in NICE technology appraisal guidance on [bortezomib and thalidomide for the first‑line treatment of multiple myeloma.](#) This may be followed by bortezomib and then lenalidomide (see NICE technology appraisal guidance on [bortezomib for relapsed multiple](#)

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myeloma and lenalidomide as a subsequent treatment for people who have received at least 2 previous treatments). The Committee heard from the clinical experts that almost all patients have bortezomib by subcutaneous rather than intravenous administration, even though recommendations in the current 'British Committee for Standards in Haematology' guideline for the diagnosis and management of multiple myeloma (2014) suggest either can be used. The Committee concluded that treatment with an immunomodulatory agent and bortezomib was established practice in the NHS and that bortezomib was most often administered to patients subcutaneously.

4.2   The Committee heard from patient experts about the nature of multiple myeloma and their experiences of treatment. It heard that multiple myeloma is a life-long condition that has a serious effect on quality of life. It can develop at a young age, and affects all aspects of life including education, work, self-care, and social and family life. The Committee heard from the patient experts that desired treatment outcomes are about both survival and quality of life. It also heard that people can be anxious about relapsing because few treatment options are available if they do, and that people consider a range of treatments to be important because they have different experiences with different treatments. The Committee heard from the clinical and patient experts that the multiple myeloma population is heterogeneous and has life-long disease, so there may be a place in the treatment pathway for another therapy with a different mechanism of action. The Committee also heard from the clinical and patient experts that there is a clinical need for alternative treatments for multiple myeloma in people who have had at least 2 previous treatments including an immunomodulatory agent and bortezomib. The Committee recognised the importance of having effective and

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tolerable treatment options for people with multiple myeloma who have had at least 2 previous treatments.

Clinical effectiveness

4.3 The Committee considered the evidence presented by the company on the clinical effectiveness of panobinostat. It noted that the main source of evidence was the PANORAMA-1 trial that compared panobinostat plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone in patients who had relapsed or relapsed and refractory multiple myeloma and had received 1–3 previous treatments (see sections 3.1 and 3.2). The Committee noted that the trial was well conducted and showed that progression-free survival was statistically significantly greater for the panobinostat plus bortezomib and dexamethasone group than for the placebo plus bortezomib and dexamethasone group. The Committee considered the generalisability of the PANORAMA-1 trial to UK clinical practice. It noted that, compared with clinical practice, the population in the trial was generally younger, a greater number of patients in the trial had a previous stem cell transplant, and bortezomib was prescribed for longer (up to 12 cycles in the trial rather than 8 used in established practice in the NHS). The Committee also noted that only a subset of the trial population matched the population for which panobinostat had received a marketing authorisation (that is, people with relapsed and refractory multiple myeloma who have had at least 2 treatments including an immunomodulatory treatment and bortezomib). It noted that this subgroup analysis was not pre-specified in the trial. It further noted the marketing authorisation for panobinostat was for the subgroup and not for the full population in the PANORAMA-1 trial but the Committee was not aware of the reasons for this. Nevertheless, the Committee accepted that the results from the PANORAMA-1 trial used in the post hoc subgroup analysis were relevant and

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generalisable to patients who have had at least 2 previous treatments in established practice in the NHS and considered that panobinostat plus bortezomib and dexamethasone was clinically effective.

4.4   The Committee considered the comparators in the indirect comparison and the indirect methods used by the company. The Committee heard from the clinical experts that comparing the lenalidomide trials MM-009 and MM-010 with the PANORAMA-1 trial was difficult because the baseline characteristics of the patients were very different. The clinical experts commented that the lenalidomide trials took place when fewer and less effective treatment options were available, making a comparison based on previous lines of treatment unreliable. The Committee heard from the company that it had not compared panobinostat plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone for this subgroup, because bortezomib had been removed from the Cancer Drugs Fund for this indication and patients do not have bortezomib after 2 previous treatments in established practice in the NHS. The Committee considered the company's indirect comparison of panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone, one of the comparators in the NICE scope and included in the company's submission (see section 3.8). It heard from the ERG that the methods used to identify both published and unpublished studies for the network meta-analysis were appropriate, and the studies were mostly well reported. However, the clinical experts indicated that for some patients re-treatment with bortezomib is useful. The Committee noted that the results of the indirect compairson showed panobinostat plus bortezomib and dexamethasone to be similar or better (depending on the indirect method) than lenalidomide plus dexamethasone. The Committee concluded that although

lenalidomide plus dexamethasone was the main comparator, it would have liked the company to also provide a comparison with bortezomib and dexamethasone for the subgroup of interest given its use in established practice in the NHS.

4.5   The Committee considered the adverse event profile associated with panobinostat in the PANORAMA-1 trial. It noted that diarrhoea was the most common adverse event in the trial, and was more frequent in the panobinostat plus bortezomib and dexamethasone group than in the placebo plus bortezomib and dexamethasone group in treatment phases 1 and 2. It also noted that frequently observed adverse events with panobinostat included thrombocytopenia, anaemia, fatigue and nausea. The Committee noted consultee statements from a patient and carer group which highlighted patients' concerns that some of the adverse events may lead to increased hospitalisation, but it was also aware that clinical experts considered it possible to adequately manage the adverse events. The Committee was also aware that the rates of discontinuation because of adverse events and on-treatment deaths with panobinostat plus bortezomib and dexamethasone were within the ranges reported for lenalidomide plus bortezomib, but were higher than in the bortezomib plus dexamethasone group in the trial (36% compared with 20%). The Committee concluded that although there were some adverse events associated with panobinostat plus bortezomib and dexamethasone treatment, they were manageable in clinical practice.

Cost effectiveness

4.6   The Committee considered the company's economic analysis and the ERG's critique of the analysis. The Committee noted that the company had submitted 2 models, but focused its discussion on

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the one for the subgroup for which panobinostat had received its marketing authorisation.

4.7   The Committee noted that the company had calculated hazard ratios for progression-free survival and overall survival for lenalidomide plus dexamethasone compared with panobinostat plus bortezomib and dexamethasone using 3 indirect comparison methods (naïve comparison, unadjusted Cox regression and matching adjusted indirect treatment comparison). The Committee noted that the company favoured the unadjusted Cox method. It heard from the ERG that unadjusted Cox regression was not suitable to calculate a hazard ratio for progression-free survival, because when plotting the lenalidomide plus dexamethasone Kaplan–Meier curve alongside the panobinostat plus bortezomib and dexamethasone Kaplan–Meier curve the curves cross at approximately 14 months. The Committee understood that this means that the proportional hazards assumption (that 'the hazard ratio between groups is constant irrespective of time') should not be applied. The Committee would have preferred independently fitted parametric curves to be fitted to the panobinostat and lenalidomide data, to determine how sensitive the ICER was to the assumptions, and to have provided a plot of log (cumulative hazard) against log (time). The Committee concluded that for these data it was inappropriate for the company to use the proportional hazards assumption.

4.8   The Committee considered the ERG's preferred analyses using the matching adjusted independent treatment comparison. It noted that the method used individual patient-level data and adjusted for baseline patient characteristics, but that after applying this method only 23 patients from the PANORAMA-1 trial remained in the analysis. The Committee discussed the ERG's use of the patient weightings to develop hazard ratios but considered that this would

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again violate the proportional hazards assumption, and that such an assumption is not a requirement of the matched adjusted indirect treatment comparison method. The Committee would have preferred survival curves fitted independently to the lenalidomide and panobinostat data and concluded that an alternative approach, such as this, should have been applied to the matched adjusted indirect treatment comparison-adjusted data.

4.9   The Committee discussed how health-related quality of life was incorporated into the economic model, noting that the company had measured health-related quality of life in the PANORAMA-1 trial using the EORTC QLQ-C30 questionnaire, MM-specific module and EORTC-MY20 and mapped it onto the EQ–5D to provide utility values for the pre-progression with panobinostat treatment health state. The Committee noted that EQ-5D data were not available for lenalidomide plus dexamethasone and that the company used 2 scenarios for the utility value for pre-progression patients having lenalidomide (see section 3.20), but that both of these estimates were conservative and favoured lenalidomide. The Committee noted that the utility value for pre-progression no treatment was taken from Acaster et al. and was higher than pre-progression with treatment, but considered this to be an acceptable assumption because patients in this health state would not experience adverse events (because they are assumed to have no treatment). The Committee also noted that disutilities had not been incorporated in the model. However, because health-related quality of life data were collected in the PANORAMA-1 trial, these values would have included chronic adverse events. The Committee concluded that the utility values used by the company were appropriate.

4.10   The Committee considered the comparators in the cost-effectiveness analyses. The Committee recalled that the clinical experts had stated that people with multiple myeloma have different

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treatment sequences (see section 4.1). It also heard that most patients would have bortezomib as the first treatment and at relapse, but that some patients may have bortezomib for relapsed and refractory multiple myeloma (see section 4.4). Therefore, although bortezomib is not the main comparator for people who have had at least 2 previous treatment, the Committee concluded that it would have liked to see panobinostat plus bortezomib and dexamethasone compared with placebo plus bortezomib and dexamethasone.

4.11   The Committee discussed the costs included in the model, particularly the administration costs of bortezomib. It noted that the company had provided 2 base cases, one incorporating intravenous bortezomib and the other subcutaneous. The Committee heard from the clinical experts that almost all patients have bortezomib by subcutaneous administration (see section 4.1) and so it concluded this to be the most appropriate bortezomib cost to be included in the model.

4.12   The Committee also discussed the costs in the model for treatment after panobinostat plus bortezomib and dexamethasone or lenalidomide and dexamethasone. The Committee agreed that removing the costs of subsequent treatment included in the company's model (pomalidomide plus dexamethasone with best supportive care, other active treatments with best supportive care, or best supportive care alone) would have an unknown effect. The Committee concluded that it would have been helpful to see the effect of removing subsequent treatments on accrual of discounted costs, and the resulting incremental cost-effectiveness ratios (ICERs).

4.13   The Committee considered whether panobinostat could be considered a cost-effective use of NHS resources. It noted that

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when including the patient access scheme (PAS), the company's base-case ICER for panobinostat plus bortezomib and dexamethasone (incorporating subcutaneous bortezomib), dominated that of lenalidomide plus dexamethasone (that is, it both cost less and was more effective). However, when using the ERG's adjustments to the model (see section 3.28) and the matching adjusted indirect treatment comparison method (MAIC), the probabilistic base-case ICER including the PAS was £99,880 per quality-adjusted life year (QALY) gained. The Committee considered that addressing its concerns about the method of indirect comparison used, the company's use of the proportional hazards assumption (see sections 4.7 and 4.8), removing the cost of subsequent treatment (see section 4.12) and comparing panobinostat plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone (see section 4.10) were unlikely to result in ICERs within the range normally considered a cost-effective use of NHS resources. It concluded that it was not possible to determine the most plausible ICER, because the appropriate analyses had not been presented. However, considering all the evidence available for the comparison with lenalidomide plus dexamethasone and noting its preferred assumptions the Committee concluded that the ICER was likely to be over the range that would normally be considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

4.14 The Committee discussed whether panobinostat could be considered innovative. It heard from the clinical and patient experts that panobinostat may provide an additional treatment option for patients because of its different mode of action to existing treatments. However, given its previous conclusion on clinical efficacy (see section 4.3 and 4.5), the Committee considered that

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panobinostat was not a step-change in treatment. The Committee concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations, and that there was no need to change its conclusions on that basis.

4.15   The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.16   The Committee considered the criterion for short life expectancy. The Committee noted comments from clinical specialists that patients having lenalidomide plus dexamethasone after 2 previous treatments have a life expectancy of approximately 30 months. The Committee concluded that patients having the current standard of care in the NHS would have an expected survival of more than 24 months and that panobinostat plus bortezomib and dexamethasone does not fulfil the criterion for short life expectancy.

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4.17   The Committee considered the criterion for extension to life. The Committee noted that when the company carried out a scenario analysis using the matching adjusted indirect treatment comparison method, the resulting life years gained was 0.071 (approximately 26 days). The Committee concluded that panobinostat plus bortezomib and dexamethasone did not produce an additional survival advantage of at least 3 months, so does not fulfil the criterion for extension to life.

4.18   The Committee considered the criterion for small patient populations. The Committee noted that the company provided a figure of 1300 people in England and Wales eligible for panobinostat in combination with bortezomib and dexamethasone for the full population but did not provide data for the subgroup. The Committee concluded it was not possible to make a conclusion on the population size. On the basis of the considerations in sections 4.16, 4.17 and 4.18, the Committee agreed that panobinostat did not fulfil the criteria for special consideration under the supplementary advice from NICE. The Committee concluded that panobinostat in combination with bortezomib and dexamethasone does not represent a cost-effective use of NHS resources and that it was not recommended for treating multiple myeloma in people who have had at least 2 previous therapies including bortezomib and an immunomodulatory agent.

4.19   The Committee considered whether it should take into account the consequences of the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and in particular the PPRS Payment Mechanism, when appraising panobinostat. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee

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heard nothing to suggest that there was any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of panobinostat. It therefore concluded that the PPRS Payment Mechanism was not applicable for the consideration of cost effectiveness of panobinostat.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Panobinostat plus bortezomib and dexamethasone is not recommended within its marketing authorisation for treating multiple myeloma, that is, 'for adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent'.		1.1
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard that the pathway of treatment is heterogeneous and people could have either thalidomide or bortezomib, plus an alkylating agent and a corticosteroid, as first-line treatment as recommended in NICE and this may be followed by bortezomib and then lenalidomide.	4.1
	The Committee heard that multiple myeloma is a life-long condition that has a serious effect on quality of life and that patient desired treatment outcomes are about both survival and quality of life.	4.2

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the clinical and patient experts that panobinostat may provide an additional treatment option for patients because of its different mode of action when compared with existing treatments but did not considered it a step-change in treatment.	4.14
What is the position of the treatment in the pathway of care for the condition?	The Committee noted that panobinostat had received a marketing authorisation (that is, people with relapsed and refractory multiple myeloma who have had at least 2 treatments including an immunomodulatory treatment and bortezomib). The Committee concluded that although lenalidomide plus dexamethasone was the main comparator it would have liked the company to also provide a compairson with bortezomib and dexamethasone.	4.3 4.4
Adverse reactions	The Committee concluded that although there were some adverse events associated with panobinostat plus bortezomib and dexamethasone treatment, they were manageable in clinical practice.	4.5
Evidence for clinical effectiveness		

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Availability, nature and quality of evidence	The Committee noted that the main source of evidence was the PANORAMA-1 trial that compared panobinostat plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone in patients who had relapsed or relapsed and refractory multiple myeloma and had received 1–3 previous treatments.	4.3
	The Committee also considered the company's indirect comparison of panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone. The Committee concluded that although lenalidomide plus dexamethasone was the main comparator, it would have liked the company to also provide a comparison with bortezomib and dexamethasone for the subgroup of interest given its use in established practice in the NHS.	4.4
Relevance to general clinical practice in the NHS	The Committee accepted that the results from the PANORAMA-1 trial used in the post hoc subgroup analysis were relevant and generalisable to patients who have had at least 2 previous treatments in UK clinical practice	4.3

Uncertainties generated by the evidence	The Committee heard from the clinical experts that comparing the lenalidomide trials MM-009 and MM-010 with the PANORAMA-1 trial in the indirect comparison was difficult because the baseline characteristics of the patients were very different. The Committee also heard from the company that it had not compared panobinostat plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone for this subgroup, because bortezomb had been removed from the Cancer Drugs Fund for this indication. However, the clinical experts indicated that for some patients re-treatment with bortezomib is useful.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	NA	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee considered the criterion for short life expectancy and noted comments that patients having lenalidomide plus dexamethasone after 2 previous treatments have a life expectancy of approximately 30 months. It concluded that patients having the current standard of care in the NHS would have an expected survival of more than 24 months and that panobinostat plus	4.16

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	bortezomib and dexamethasone does not fulfil the criterion for short life expectancy.	
	The Committee considered the criterion for extension to life. The Committee noted that when the company carried out a scenario analysis using the matching adjusted indirect treatment comparison method, the resulting life years gained was 0.071 (approximately 26 days). The Committee concluded that panobinostat plus bortezomib and dexamethasone did not produce an additional survival advantage of at least 3 months, so does not fulfil the criterion for extension to life.	4.17
	The Committee considered the criterion for small patient populations. The Committee noted that the company provided a figure of 1300 people in England and Wales eligible for panobinostat in combination with bortezomib and dexamethasone for the full population but did not provide data for the subgroup.	4.18
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee noted that the company had calculated hazard ratios for progression-free survival and overall survival for lenalidomide plus dexamethasone compared with panobinostat plus bortezomib and dexamethasone using 3 indirect comparison methods (naïve comparison, unadjusted Cox regression and matching adjusted indirect treatment comparison).	4.7
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee heard from the ERG that unadjusted Cox regression was not suitable to calculate a hazard ratio for progression-free survival.	4.7
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that the company had measured health-related quality of life in the PANORAMA-1 trial to provide utility values for the pre-progression with panobinostat treatment health state. It also noted that EQ-5D data were not available for lenalidomide plus dexamethasone and that the company used 2 scenarios for the utility value for pre-progression patients having lenalidomide. The Committee also noted that disutilities had not been incorporated in the model. However, because health-related quality of life data were collected in the PANORAMA-1 trial, these values would have included chronic adverse events. The Committee concluded that the utility values used by the company	4.9

	were appropriate. The Committee concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations, and that there was no need to change its conclusions on that basis.	4.14
Are there specific groups of people for whom the technology is particularly cost effective?	N/A	-
What are the key drivers of cost effectiveness?	The Committee would have liked the company to have preferred independently fitted parametric curves to be fitted to the panobinostat and lenalidomide data, to determine how sensitive the ICER was to the assumptions, and to have provided a plot of log (cumulative hazard) against log (time). The Committee concluded for these data it was inappropriate for the company to use the proportional hazards assumption. The Committee would have preferred survival curves fitted independently to the lenalidomide and panobinostat data and concluded that an alternative approach, such as this, should have been applied to the matched adjusted indirect treatment comparison adjusted data used.	4.7 4.8

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	The Committee heard from the clinical experts that almost all patients have bortezomib by subcutaneous administration and so it concluded this to be the most appropriate bortezomib cost to be included in the model.	4.11
	The Committee agreed that removing the costs of subsequent treatment included in the company's model and concluded that it would have been helpful to see the effect on the resulting incremental cost-effectiveness ratios (ICERs).	4.12
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that it was not possible to determine the most plausible ICER, because the appropriate analyses had not been presented.	4.13
Additional factors taken into account		
Patient access schemes (PAS)	The company has agreed a patient access scheme with the Department of Health. If panobinostat had been recommended, this scheme would provide a simple discount to the list price of panobinostat with the discount applied at the point of purchase or invoice.	2.3

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End-of-life considerations	The Committee considered that panobinostat did not meet the short life expectancy, extension to life criteria and could not conclude on the population size. The Committee therefore agreed that panobinostat in combination with bortezomib and dexamethasone did not fulfil the criteria for special consideration under the supplementary advice from NICE.	4.16, 4.17, 4.18
Equalities considerations and social value judgements	No equalities issues were identified during the scoping exercise or appraisal process.	-

5   Implementation

5.1   The Department of Health and Novartis have agreed that panobinostat will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

5.2   NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.

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- Costing template and report to estimate the national and local savings and costs associated with implementation.

- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.

- A costing statement explaining the resource impact of this guidance.

- Audit support for monitoring local practice.

6   Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy](#). NICE technology appraisal guidance 171 (2009).
- [Bortezomib monotherapy for relapsed multiple myeloma.](#) NICE technology appraisal guidance 129 (2007).

7   Proposed date for review of guidance

7.1   NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

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Andrew Stevens

Chair, Appraisal Committee

September 2015

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8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Mr David Chandler
Lay Member

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Dept of Primary Care and Population Health, University College London

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Dr Nigel Langford
Consultant in Clinical Pharmacology and Therapeutics and Acute Physician,

Leicester Royal Infirmary

Dr Patrick McKiernan
Consultant Paediatrician, Birmingham Children's Hospital

Dr Iain Miller
Founder & CEO, Health Strategies Group

Dr Anna O'Neill
Deputy Head of Nursing & Healthcare School / Senior Clinical University

Teacher, University of Glasgow

Dr Claire Rothery
Research Fellow in Health Economics, University of York

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS

Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of

Sheffield

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related

Research, University of Sheffield

Professor Robert Walton
Clinical Professor of Primary Medical Care, Barts and The London School of

Medicine & Dentistry

Dr Judith Wardle
Lay member

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NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Caroline Hall
Technical Lead

Dr Sally Doss
Technical Adviser

Lori Farrar
Project Manager

9   Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group:

- Durand A, Rtveladze K, Pritchard C, Cooper C, Mujica-Mota R. The clinical and cost-effectiveness of panobinostat for treating multiple myeloma in people received at least one prior therapy. Single Technology Appraisal NIHR HTA Programme, Optimity Advisors and Peninsula Technology Assessment Group, 2015.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

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- Novartis

II. Professional/expert and patient/carer groups:

- Leukaemia CARE
- Myeloma UK
- Association of Cancer Physicians
- British Society for Haematology
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- UK Myeloma Forum

III. Other consultees:

- Department of Health
- NHS Canterbury and Coastal CCG
- NHS England
- NHS Isle of Wight CCG
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- The Institute of Cancer Research
- Peninsula Technology Assessment Group, University of Exeter (PenTAG)
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

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C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Panobinostat for treating multiple myeloma in people who have received at least one prior therapy by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Guy Pratt, Consultant Haematologist, nominated by Novartis pharmaceuticals – clinical expert
- Professor Jamie Cavenagh, professor of Haemato-oncology, nominated by UK Myeloma Forum - clinical expert
- Eric Low, Chief Executive, nominated by Myeloma UK – patient expert
- Stuart Fullerton, nominated by Myeloma UK – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis Pharmaceuticals

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