NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Bortezomib for previously untreated mantle cell lymphoma

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Bortezomib is recommended, within its marketing authorisation, as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable.

2 The technology

2.1 Bortezomib is a highly selective proteasome inhibitor specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. This proteasome is a large protein complex that degrades unneeded or damaged proteins tagged with ubiquitin. The ubiquitin–proteasome pathway plays an essential role in many cellular processes, including the cell cycle. Bortezomib (Velcade, Janssen) has a marketing authorisation for treating adults with previously untreated mantle cell lymphoma for whom haematopoietic stem cell transplantation is unsuitable.

2.2 The summary of product characteristics includes the following adverse reactions for bortezomib: nausea, diarrhoea, constipation, vomiting, fatigue, fever, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased

appetite, shortness of breath, rash, shingles and muscle pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Bortezomib costs £762.38 for a 3.5 mg vial (excluding VAT; British national formulary [BNF] 70). According to the summary of product characteristics, bortezomib should be given by intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for 2 weeks on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12–21. This 3-week period is considered a treatment cycle. Six cycles are recommended, although for people with a response first documented at cycle 6, 2 additional cycles may be given. There should be at least 72 hours between doses of bortezomib. Rituximab (at 375 mg/m^2), cyclophosphamide (at 750 mg/m^2) and doxorubicin (at 50 mg/m^2) are administered on day 1 of each bortezomib 3-week treatment cycle as intravenous infusions. Prednisone is administered orally at 100 mg/m^2 for the first 5 days of each bortezomib cycle. Dose adjustment for bortezomib can be made in the event of toxicity. Full details of dose adjustments are given in the summary of product characteristics. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

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

Clinical effectiveness

3.1 The company's systematic literature review identified 1 randomised controlled trial (RCT) investigating the clinical efficacy and safety of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) in adult patients with previously untreated mantle cell lymphoma. LYM-3002 trial was a randomised, open-label,

multicentre study that compared VR-CAP against rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). The study involved 128 sites worldwide, and people were randomised in a 1:1 ratio based on the International Prognostic Index and the stage of disease at diagnosis.

3.2 In total, 487 people were randomised; 243 to bortezomib and 244 to R-CHOP. The median age was 69 years. People were given 6 to 8 cycles (18 to 24 weeks) of treatment depending upon the response documented at the cycle-6 assessment. Approximately 80% of people in both groups completed treatment. The total study duration from randomisation of the first patient until the last progression-free survival event needed for the final analysis was expected to be approximately 42 months (24 months for enrolment and 18 months for follow-up). Average treatment duration was 17.6 weeks in the bortezomib treatment group and 16.1 weeks in the R-CHOP group. Treatment discontinuation was comparable between the 2 groups (18% and 19% respectively). The majority of people had at least 6 cycles of treatment: 84% of people randomised to VR-CAP, and 83% of people randomised to R-CHOP.

3.3 The trial included 80 patients (16.4%; 38/243 in VR-CAP arm, 42/244 in R-CHOP arm) who were suitable for haematopoietic stem cell transplantation from a medical perspective but access was prevented due to availability or socio-economic reasons. The inclusion of these patients arose due to a protocol amendment part way through the LYM-3002 trial where patients who were ineligible or not considered for haematopoietic stem cell transplantation were enrolled. However concerns over the heterogeneity and interpretability of the study results resulted in a further amendment, realigning to the original eligibility criteria, and only patients who were not eligible for haematopoietic stem cell transplantation as assessed by the treating physician, were subsequently enrolled.

3.4 The primary outcome of the study was progression-free survival in the intention–to–treat (ITT) population, based on independent review

committee assessment of progression. Median progression-free survival was 751 days (24.7 months) in people randomised to VR-CAP compared with 437 days (14.4 months) in people randomised to R-CHOP (hazard ratio [HR]=0.63, p<0.001).

3.5 The company presented results for a number of secondary clinical endpoints:

- Based on independent review committee assessment of progression in the ITT population, median time to progression was 929 days (30.5 months) in people randomised to VR-CAP compared with 490 days (16.1 months) in people randomised to R-CHOP (HR=0.58; p<0.001).
- In the ITT population, median time to next anti-lymphoma treatment was 1353 days (44.5 months) for people randomised to the VR-CAP group compared with 756 days (24.8 months) for those randomised to the R-CHOP group (HR=0.50; p<0.001).
- Median treatment-free interval in the safety analysis set was 1236 days (40.6 months) for people randomised to VR-CAP compared with 624 days (20.5 months) for those randomised to R-CHOP (HR=0.50; p<0.001).
- Based on independent review committee assessment, complete response rates (complete response plus complete response unconfirmed) were 53.3% in the VR-CAP group compared with 41.7% in the R-CHOP group (odds ratio [OR]=1.688; p=0.007), and the median duration of complete response was 42.1 months compared with 18.0 months for people treated with VR-CAP. The median time to initial response based on independent review committee assessment was 42 days (1.4 months) in people randomised to VR-CAP compared with 50 days (1.6 months) in people randomised to R-CHOP (HR=1.54; p<0.001).

3.6 At the time of the company's submission, overall survival data were not mature in the LYM-3002 trial. In an interim analysis based on a median

duration of 40 months' follow-up (in which 158 deaths had been observed: 71 in the VR-CAP group [29%] and 87 in the R-CHOP group [36%]), the estimated hazard ratio for death is 0.80 (95% confidence interval [CI] 0.59 to 1.10, in favour of VR-CAP).

3.7 Three different patient-reported outcome tools were used to assess health-related quality of life in the LYM-3002 trial: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); the Brief Fatigue Inventory ; and the EuroQol Dimension Questionnaire (EQ-5D). The company reported that utility values, translated from the EQ-5D taken at day 1 of every treatment cycle and at the end-of-treatment visit, were not statistically significantly different between treatment groups at baseline and throughout the LYM-3002 treatment. The company highlighted that as the study design did not include patient-reported outcome collection after the end of treatment, it was not possible to assess the dimension of clinical benefit derived by people from the prolonged progression-free survival and prolonged disease control provided by VR-CAP. However, the company stated that such improvement in long-term prognosis would be likely to positively affect patient health-related quality of life in practice.

Subgroup analysis

3.8 In subgroup analyses based on region, the North America subgroup was combined with the European Union subgroup post hoc as the former had very few people, most of whom had a progression-free survival event (5 people with a progression-free survival event out of 8 enrolled into the R-CHOP group, and 4 people out of 6 enrolled into the VR-CAP group) that resulted in a very large CI (0.44 to 41.96) for the estimated HR (which was greater than 1).

3.9 In the pre-specified North American and Western European subgroup,: median progression-free survival for the VR-CAP group was 19.4 months compared with 14.4 months for the R-CHOP group (HR=0.77, 95% CI 0.43 to 1.38).

ERG comments on the clinical effectiveness data

3.10 The ERG highlighted that no patients from the UK were included in the LYM-3002 trial with approximately 30% of the people recruited in the European Union and North America. The other two thirds were from the 'rest of the world', in particular Russia and China. Given the different prevalence of mantle cell lymphoma depending on the geographic region and potential differences in clinical standards (for example, concomitant care), the ERG stated that this brings into question the generalisability of the trial to clinical practice in the UK.

3.11 The ERG noted that the inclusion criteria in the LYM-3002 trial were narrower than those defined in the NICE scope. The ERG noted that the population in the final scope (people with previously untreated mantle cell lymphoma, who are not going to have a stem cell transplant) might include people who would not have been eligible for inclusion in the LYM-3002 trial.

Indirect comparison

3.12 The company highlighted that the induction therapy regimens listed in the final appraisal scope (rituximab with fludarabine and cyclophosphamide [R-FC] and rituximab with bendamustine [R-bendamustine]) are not considered to be relevant comparators for VR-CAP as these are generally reserved for patients who cannot tolerate R-CHOP and, therefore, VR-CAP. However, the company did indirect comparison analyses to alternative rituximab-chemotherapy induction regimens where possible. The company emphasised the limitations of the indirect comparison and considered that these analyses are not robust because of important differences between LYM–3002 and the comparator studies. There were also methodological limitations in the comparator studies.

ERG comments

3.13 The ERG agreed with the company that the indirect analysis should be treated with caution because of the lack of similarity between the

3 included trials. The wide confidence intervals reported above could partly be explained by this heterogeneity. The ERG noted that the 3 trials included in the indirect analyses are linked to a high risk of bias.

Adverse effects of treatment

3.14 The company reported that both VR-CAP and R-CHOP induction regimens were generally well tolerated, with discontinuation rates of 8.8% and 7.0% respectively because of adverse events. Adverse-event-related deaths were 7.0% in both treatment groups. Almost all people in both treatment groups experienced a treatment-emergent adverse event, although VR-CAP was associated with a slightly higher rate of grade 3 or higher adverse events and serious adverse events. In both treatment groups, the most commonly reported grade 3 or higher adverse events were haematological (blood and lymphatic system) disorders. For adverse events of clinical interest, peripheral neuropathy was the most commonly reported and it was similar in the 2 treatment groups (30% for VR-CAP and 29% for R-CHOP).

ERG comments

3.15 The ERG agreed with the company's view that both chemotherapy induction regimens were generally well tolerated, with low rates of discontinuation because of adverse events and low rates of treatment-related deaths in both groups. However, the ERG highlighted that more serious adverse events were observed for VR-CAP (37.5%) compared to R-CHOP (29.8%) and the serious adverse events were usually of higher severity in VR-CAP. While more study drug-related discontinuations were reported for VR-CAP (7.9%) compared to R-CHOP (5.8%), there were more reported deaths related to R-CHOP (3.0%) compared to VR CAP (2.0%). The ERG highlighted that this was similar to the outcomes for the Western Europe subgroup. More comprehensive results will be available with the final analysis in 2017.

Cost effectiveness

3.16 A de novo cost-effectiveness model was developed by the company to assess the cost effectiveness of VR-CAP in England and Wales. The model included 5 states: progression-free survival from first-line treatment; progressed from first-line treatment; progression-free survival from second-line treatment; progressed from second-line treatment; and death.

3.17 The company's base-case model time horizon was 20 years. The company considered this to be essentially a lifetime time horizon for patients, given that the mean age assumed in the model was 69 years. Both costs and health outcomes were discounted at an annual rate of 3.5%. The company stated that costs were based on 2013/14 figures (NHS Reference Costs and Personal Social Services Research Unit) as these were the most recent cost data available at the time the model was developed.

3.18 The key clinical data used within the economic model were taken from the LYM-3002 trial. The ITT population of the LYM-3002 trial was used to assess the effectiveness and safety of VR-CAP compared with R-CHOP in the de novo cost-effectiveness model. Based on advice from UK haematologists, the company considered that people included in the LYM-3002 trial were similar to those expected to be seen in UK clinical practice. However, baseline demographics from only the Western European and North American subgroup were used in the model because the company considered that subgroup to be more similar to people in UK clinical practice in terms of age and weight.

3.19 Economic comparison was conducted primarily with R-CHOP because the company were of the opinion that R-CHOP induction therapy is the established standard of care for patients with previously untreated mantle cell lymphoma (for whom haematopoietic stem cell transplantation is unsuitable). The company stated that no maintenance treatment with rituximab was assumed in the model base case because it was not identified as a comparator in the decision problem. However, the company

highlighted that as R-maintenance is used in clinical practice in people with a response to induction, the potential impact of induction therapy with VR-CAP compared with R-CHOP followed by R-maintenance was investigated in exploratory analyses.

ERG comments

3.20 The ERG commented that the company's model followed a logical structure with respect to the nature of the disease. The ERG agreed that the discount rate and perspective are in line with the NICE reference case. The ERG noted that considering the average age of 69 years in the LYM–3002 trial and that the median survival is less than 5 years, a time horizon of 20 years is considered adequate and similar to a lifetime perspective. The ERG identified 2 possible concerns: the exclusion of the half-cycle correction and the exclusion of any additional treatment lines after second-line treatment. The company highlighted that it had implemented the half-cycle correction, however the ERG disagreed with how it was done. Therefore the ERG has made its own correction for the new ERG base case (see sections 3.42 to 3.46). The ERG commented that the exclusion of any additional treatment lines seemed reasonable considering the lack of evidence of treatment efficacy and the minority of patients having a third treatment line.

Model details

3.21 Instead of using the primary outcome of the LYM–3002 trial, progression-free survival assessed by an independent review committee, the company chose to use an alternative assessment (by an independent review committee member) in the base case of the model because it was felt this reflected clinical practice while retaining the blinded assessment.

3.22 The company fitted the following parametric models to estimate progression-free survival in the 2 treatment groups: exponential; Weibull; lognormal; log-logistic; gamma; and Gompertz. The company used the log-logistic model in the base case based on the goodness of fit of the progression-free survival curves (that is, using the Akaike information

criterion and the Bayesian information criterion, and visual fit and long-term fit).

Survival was modelled with parametric models fitted using the LYM 3002 patient-level data for people having VR CAP and R CHOP. However, overall survival data from the LYM–3002 trial are still immature; median overall survival for VR CAP has not been reached. Because of the a wide range of potential outcomes when attempting to fit survival curves directly to the overall survival data, the company modelled survival using progression as a surrogate marker for overall survival.

3.23 For the base case, parametric curves were fitted for 3 categories of patients: all patients who progressed from VR-CAP or R-CHOP during the trial, all patients who did not progress from VR-CAP, and all patients who did not progress from R-CHOP. This method assumed that patients who progressed had the same survival regardless of what treatment they had in first line (that is, post-progression survival was the same, regardless of the first-line therapy that had been had).

3.24 The company added non-disease-specific mortality, based on age and sex, to the model to better capture long-term survival (using UK life tables from the Office for National Statistics). It was assumed that all deaths in the pre-progression survival curves (before adjustment for background mortality) in the trial were deaths from mantle cell lymphoma.

3.25 The mean duration of second-line treatment and progression-free survival from second-line treatment were derived from the LYM-3002 trial. In the company base case, model treatment duration (90 days) and progression-free survival (231 days) were assumed to be the same for both groups, using data from both LYM-3002 trial groups combined.

3.26 The company highlighted that there were limited data available for the other comparators included in the scope. The company stated that the indirect comparison to R-bendamustine was too unreliable given the heterogeneity described previously, particularly for progression-free

survival, to be used to assess comparative efficacy within the cost-effectiveness model. Instead, the company assumed equal efficacy (progression-free survival and overall survival) to R-CHOP, which was based on clinician feedback. Similarly, the limitations of the R-FC indirect comparison meant that an assumption of equal efficacy with R-CHOP was also made for R-FC.

3.27 The company used EQ-5D data from the LYM-3002 trial for health-related quality of life estimates during and on progression from first-line treatment. Utility decrements for adverse events were included in addition to the health-state utilities while patients were on treatment, based upon LYM-3002 trial data. No long-term utility values were available from the LYM-3002 trial so instead, the company assumed equal utility while progression free during first- and second-line treatments (based on UK clinician feedback and previous non-Hodgkin's lymphoma modelling), utility associated with post-progression from second-line treatment was taken from the most relevant source related to aggressive non-Hodgkin's lymphoma, which the company stated was the most similar condition to mantle cell lymphoma in terms of expected effect on health status.

Costs

3.28 The company's model assumed that patients had only whole vials and that there was no vial sharing. On dosing regimens, cycle lengths for both VR-CAP and R-CHOP were 21 days with a maximum number of 6 cycles or 8 cycles if first response happens in cycle 6. The company also presented drug acquisition and administration costs associated with VR-CAP, R-CHOP, other comparators and second-line treatments.

3.29 In the model, the number of patients having treatment per cycle was informed by the LYM-3002 trial and reduced with each cycle going from 100% in cycle 1 down to 13.3% for VR CAP and 17.4% for R-CHOP by cycle 8.

3.30 In addition to the cost of hospital visits to treat adverse events, drug acquisition costs associated with concomitant medications were also included in the model (those used in the trial but unavailable in the UK were excluded). Costs for red blood cell and platelet transfusions were included in the company's model.

3.31 Adverse event costs were based on NHS Reference Costs 2013/14. Weekly costs attributable to adverse events produced cycle costs of £26.41 for VR-CAP and £28.81 for R-CHOP.

Company's base-case results and sensitivity analysis

3.32 In the company's base-case deterministic analysis, VR-CAP was estimated to generate 0.75 incremental life years, 0.80 incremental quality-adjusted life years (QALYs) and an incremental cost of £16,213 compared with R-CHOP, leading to an incremental cost-effectiveness ratio (ICER) of £20,362 per QALY gained. In the probabilistic analyses the ICERs for VR-CAP ranged between £13,725 (compared with R-bendamustine) and £20,264 (compared with R-CHOP) per QALY gained.

3.33 Cost-effectiveness acceptability curves (generated by the ERG from the company model) showed that R-CHOP has the highest probability of being cost-effective (51.3%) followed by VR-CAP (48.7%). The probabilities of being cost-effective for R-FC and R-bendamustine were 0.0%. VR-CAP has the highest probability (86.5%) of being cost-effective at a maximum acceptable ICER of £30,000, followed by R-CHOP (13.5%), R-FC (0.0%) and R-bendamustine (0.0%).

3.34 The ICERs were most sensitive to the survival functions used to model progression-free survival and overall survival the utility value for patients progressed from second-line treatment, intravenous administration costs and the duration of second-line treatment.

3.35 The company performed a large number of scenario analyses for the comparison between VR-CAP and R-CHOP. The most influential scenario

analyses were those incorporating different parametric distributions for progression-free survival; using Weibull, gamma and Gompertz distributions increased the ICER from £20,362 to £25,849, £27,697 and £30,452 respectively. Changing the utility value for patients progressed from second-line treatment to 0.693 (equal to patients progressing from first-line treatment) increased the ICER to £26,241 per QALY gained. Changing all health state utility values to correspond with those from Doorduijn et al. 2005 (that is, 0.61 for progression free in the first- and second-line and 0.45 for progressed patients in the first- and second-line) did increase the ICER to £28,746 per QALY gained. The company stated that cost-effectiveness results were generally robust under the sensitivity and scenario analyses conducted, with no scenarios bringing the ICER of VR-CAP compared with R-CHOP above £30,000 per QALY gained.

ERG comments

3.36 The ERG did not agree with the company using the ITT population of the LYM-3002 trial to assess the effectiveness of VR-CAP compared with R-CHOP. The ERG preferred the use of data from the European Union subgroup.

3.37 The ERG noted that the log-logistic distribution was selected for both treatment groups, for progression-free survival, based upon clinical expert opinion. However, the exponential distribution showed the best statistical fit for the VR-CAP group (based on Akaike information criterion and Bayesian information criterion). The ERG also questioned the different survival curves based on progression status and the assumption that survival for patients without progression differed between treatment groups.

3.38 The ERG agreed with the company submission that immature data may bias the extrapolation of survival data, however this was not explained further by the company. The ERG suggested that if data are too immature to model overall survival for all patients. It is questionable whether sufficient data are available to separately estimate long-term survival for

patients with and without progression. This distinction would reduce the total number of patients at risk, and may increase the uncertainty about the long-term survival. The company justified the use of different survival for patients with and without progression by referencing 1 study in mantle cell lymphoma and 1 study in non-Hodgkin's lymphoma in which better progression-free survival is associated with better overall survival. Another concern raised by the ERG on the modelling of survival was the assumption that survival for patients without progression differs between treatment groups. The ERG suggested that as a result of using immature data, it is not feasible to identify any differences in overall survival between treatment groups.

3.39 The ERG did not agree with the company using a utility value of 0.45 progression from second-line treatment because the study from which it was sourced (Doorduijn et al. 2005) was based on a small number of observations (n=26). The ERG estimated utility for progression from second-line treatment by subtracting the average disutility (from 2 different groups of people) reported in Doorduijn et al. (2005) from the baseline utility in the LYM–3002 trial for progression-free survival from first-line treatment. Therefore, the ERG used a utility of 0.624, instead of the company's value of 0.45.

3.40 The ERG did not agree with the dose reduction applied to the drug costs for VR-CAP and R-CHOP because it is questionable whether the dose reduction observed in the LYM-3002 trial is representative for UK clinical practice. Concomitant medication costs and costs for pegfilgrastim were amended for R-CHOP.

3.41 The company did not provide a subgroup analysis for the European Union or European Union/North American region subgroup. As the treatment effectiveness appears lower for the European Union subgroup, the relative treatment effect for progression-free survival was conservatively adjusted to reflect the European Union subgroup in the ERG base case.

ERG exploratory analyses

3.42 In light of a number of issues highlighted in the ERG report, the ERG made a number of amendments The ERG corrected a number of errors and changed a number of assumptions in the company's model as follows:

1. Corrected the unit prices that were different in the reference price list.
2. Corrected an error in the calculation of adverse events.
3. Corrected calculation of costs of concomitant medication.
4. Inclusion of half-cycle correction.
5. Age, weight and unit prices were made fixed instead of being stochastic (that is, instead of having distributions applied to them).
6. Proportion of patients having treatment during a cycle and proportion of patients having concomitant medication were made stochastic to reflect second order uncertainty.
7. Adjusted progression-free survival according to the HR of the European Union population
8. Start second-line treatment at time of progression.
9. Utility for progression from second-line treatment is calculated by subtracting the disutility as found in Doorduijn et al. (2005) from the baseline utility in the LYM-3002 trial for progression-free survival from first line treatment. Therefore, the ERG used a utility of 0.624, instead of the company's value of 0.45.
10. Excluded end-of-life costs.
11. Used per-protocol dosage instead of observed dosage reductions because it is unknown whether the dosage reduction is applicable to UK patients.
12. The primary assessment of progression is used instead of the alternative assessment.
13. Indirect treatment comparison is used for the effectiveness of R-FC and R-bendamustine instead of assuming equal effectiveness as R-CHOP.

14. Overall survival is not differentiated between patients with and without progression, but between treatments instead.
15. Excluded all-cause mortality as this is already incorporated in the overall survival estimate
16. The exponential distribution is used for the extrapolation of progression-free survival in the VR-CAP group and the log-logistic distribution is used for the extrapolation of progression-free survival in the R-CHOP group.

3.43 The ERG stated that the ICERs compared to R-FC and R-bendamustine were minimally influenced by the ERG changes and so the results presented focused on the comparison with R-CHOP. Including all of the ERG's amendments at the same time increased the company's base case ICER of VR-CAP compared with R-CHOP by £14,000 to £34,039 compared to the company base case. The large difference between the company base case and the ERG's ICER was caused mainly by changing the distribution for progression-free survival in the VR-CAP group to the exponential distribution, while keeping the distribution for R-CHOP progression-free survival a log-logistic distribution.

3.44 The ERG performed probabilistic sensitivity analyses for all comparators to capture the uncertainty in the estimation of input parameters in their additional analyses. The probability that VR CAP is cost effective at a threshold of £20,000 and £30,000 is smaller in the ERG analyses compared to the company's base case (11% versus 49% and 39% versus 89% for a threshold of £20,000 and £30,000, respectively). Similar to the company's base case, the probability that R FC or R bendamustine are cost effective at the usual NICE thresholds are negligible.

3.45 The ERG did some additional exploratory analyses that looked at the effect of removing some assumptions from its preferred cumulative ICER estimate of £34,039 per QALY gained. The ERG combined all their preferred assumptions together but removed the following:

- Progression-free survival adjustment for the European Union subgroup.
- Distinguish survival for patients with and without progression.
- Use the same progression-free survival distribution (log-logistic) for all treatment groups.

As survival for patients with and without progression is distinguished in this additional analysis by the ERG, all-cause mortality to survival pre-progression was included (in other words, analysis 13 was also removed). The result of removing these 4 assumptions from the ERG base case gave an ICER for VR-CAP compared with R-CHOP of £31,576 per QALY gained.

3.46 The ERG explored the effect of reverting back to the company's original utility value (0.45) and the exclusion of assumptions 7, 12-14 as in section 3.45. The result of this analysis (that is, the ERG base case excluding assumptions 7, 9, 12, 13 and 14) gave an ICER of £26,647 per QALY gained for VR-CAP compared with R-CHOP.

3.47 Full details of all the evidence are in the Committee papers. [Editors to add unique identifier from website in-development page to complete hyperlink].

4 Consideration of the evidence

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

4.1 The Committee heard from the clinical and patient experts that mantle cell lymphoma is associated with short survival, and a new treatment that improves survival would be very valuable for people with this condition.

The Committee also heard that although good quality of life with minimal treatment side effects was important to people with mantle cell lymphoma, they are often willing to accept more severe side effects if the treatment is also more effective. The clinical expert highlighted that the treatment of mantle cell lymphoma has changed in recent years as more evidence has emerged about the effectiveness of the different treatment regimens. The Committee understood from the clinical expert that rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is currently the standard of care in England for people with untreated mantle cell lymphoma for whom haematopoietic stem cell transplant is unsuitable, and that in clinical practice this is the most appropriate comparator for bortezomib combination therapy. Rituximab plus bendamustine is sometimes used, and to a lesser extent rituximab with fludarabine and cyclophosphamide, but these regimens are usually reserved for people who have already tried R-CHOP, or are not fit enough to tolerate it. The Committee also heard that maintenance therapy with rituximab is now routinely given in clinical practice, and is thought to substantially improve outcomes. The Committee concluded that R-CHOP was the current standard of care for those who could tolerate it, and should be considered the main comparator for bortezomib in people with untreated mantle cell lymphoma for whom haematopoietic stem cell transplant is unsuitable.

Clinical effectiveness

4.2 The Committee considered the LYM-3002 trial, which compared bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP), with rituximab in combination with cyclophosphamide, doxorubicin, prednisone and vincristine (R-CHOP). The Committee noted that the age and other baseline characteristics of participants in the trial were broadly generalisable to people in England with this disease. It was aware that no patients from the UK were included in the trial, although 28% were recruited from the EU. The Committee acknowledged that although standard of care might differ between England, the rest of the EU, and the rest of the world; there was no

reason to suggest that the course of the disease, or response to treatment would be different. The Committee therefore agreed that the results from the whole intention-to-treat (ITT) population were suitable for evaluating clinical effectiveness. The Committee considered that a strength of the LYM-3002 trial was the direct comparison with R-CHOP, which is current standard of care in England. However, it noted that the trial did not include maintenance therapy with rituximab, which is now part of routine practice. The Committee acknowledged that although this made the generalisability of the results more uncertain, rituximuab maintenance was not included in either treatment group. The Committee heard from the clinical expert that it was assumed that rituximab maintenance therapy following VR-CAP should provide the same benefit as is seen when rituximab maintenance is given subsequently to R-CHOP. It accepted that there was no positive evidence that rituximab maintenance would affect the relative effectiveness of VR-CAP compared with R-CHOP as demonstrated in the trial. The Committee also noted that the trial included a number of people (16.4%) for whom haematopoietic stem cell transplant was suitable, which is outside the marketing authorisation, but as these were balanced between the 2 treatment groups, it agreed with the Evidence Review Group (ERG) that that this would not have affected the results. The Committee concluded that the population included in the LYM-3002 trial was generalisable to practice in England.

4.3 The Committee considered the results of the LYM-3002 trial. It noted that the primary trial outcome of progression-free survival was statistically significantly better for VR-CAP compared with R-CHOP (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.50 to 0.79), based on independent review. It heard from the clinical expert that mantle cell lymphoma is an aggressive disease which becomes symptomatic when it recurs, and in this country clinicians may not routinely follow up patients with scans, as was done in the trial, but only scan when they develop symptoms in order to confirm progression before starting treatment. The Committee acknowledged that measuring disease progression on scans, as done in

the trial, is a more objective indicator of disease progression than time to starting next treatment.

4.4 The Committee considered the secondary outcomes in the trial. It noted that overall survival data from the LYM-3002 trial were immature, as the median was not reached in the VR-CAP group. It heard from the clinical expert that there is 6-year follow-up data from a trial in people with lymphoma (not specifically mantle cell lymphoma), showing that longer progression-free survival results in longer overall survival. The Committee agreed that it was not unreasonable to assume that an overall survival benefit would result from an improvement in progression-free survival. The Committee concluded that VR-CAP provides improved progression-free survival compared with R-CHOP, and is likely to improve overall survival.

4.5 The Committee considered the other secondary outcomes in the LYM-3002 trial. It noted that 3 of these showed statistically significant benefits for VR-CAP compared with R-CHOP (time to next treatment, treatment-free interval and duration of response; see section 3.5). The Committee heard from the patient expert that treatment-free interval is of particular importance to people with mantle cell lymphoma because they would not have to tolerate the side effects of chemotherapy during that time. It noted that the difference in treatment-free interval between VR-CAP and R-CHOP was almost 20 months (40.6 months compared with 20.5 months respectively, HR 0.50, p value <0.001). The Committee concluded that bortezomib, within its marketing authorisation, is a clinically effective treatment for untreated mantle cell lymphoma in people for whom haematopoietic stem cell transplant is unsuitable.

4.6 The Committee considered the adverse events reported in the LYM-3002 trial. It noted that for the safety analysis data set, both VR-CAP and R-CHOP appeared to be generally well tolerated with low rates of discontinuation because of adverse events, and low fatality rates in both groups. The Committee was aware that some side effects occurred more

frequently with VR-CAP than R-CHOP, (for example, diarrhoea, 30.4% compared with 9.1%; fever 29.2% compared with 15.3%; and thrombocytopenia 72.1% compared with 19.0% respectively). However, it acknowledged the comments from the clinical and patient experts that people with mantle cell lymphoma are sometimes willing to tolerate more side effects if a treatment is more effective. The Committee noted that the trial was conducted using intravenously administered VR-CAP, but heard from the company and the clinical expert that it is likely to be given subcutaneously in clinical practice. It heard from the clinical expert that subcutaneous administration of bortezomib should result in a lower incidence of peripheral neuropathy and other adverse events because peaks in the concentration of bortezomib in the blood would be avoided. The Committee concluded that although bortezomib was associated with an increased adverse event profile, it is a generally well-tolerated treatment.

4.7 The Committee discussed the company's indirect comparison, which aimed to compare bortezomib (VR-CAP) with the comparators listed in the scope (R-CHOP, rituximab with fludarabine and cyclophosphamide , and rituximab with bendamustine). It noted the concerns of both the company and the ERG about the heterogeneity of the trials included in the indirect comparison network. The Committee noted that the company did not use the network to inform its economic model. The Committee agreed that the indirect comparison was unlikely to be robust and concluded that because R-CHOP was indeed the most relevant comparator to be considered, the direct evidence from LYM-3002 trial was sufficient to enable the Committee to make a decision on the effectiveness of VR-CAP in people with mantle cell lymphoma.

Cost effectiveness

4.8 The Committee considered the company's economic model. It noted that the model used a 20-year time horizon, and agreed with the company and the ERG that this was reasonable given that the average age of people in

the trial was 69 years and that median survival was less than 5 years. The model included 5 states, including 2 lines of therapy and a treatment free interval; the Committee noted that the company's economic model was primarily focused on the comparison between V-CAP and R-CHOP because it was considered that R-CHOP is the most appropriate comparator. The Committee concluded that the company's model followed a logical approach, and agreed that the principal comparator is R-CHOP.

4.9 The Committee considered the company's approach to estimating progression-free survival in the economic model. It noted that the company used the same parametric curves (log-logistic) for both treatment groups, in line with guidance from Decision Support Unit. The Committee also noted the opinion expressed by the ERG that an exponential distribution was a better fit for the VR-CAP group; and that the ERG had explored this approach in its exploratory analyses (see sections 3.42–3.46, and 4.14). The ERG's preferred method, using different parametric curves for the 2 treatments, had a substantial effect on the cost-effectiveness estimate, increasing the company's base-case incremental cost-effectiveness ratio (ICER) of £20,300 to £33,100 per quality-adjusted life year (QALY) gained. The Committee discussed the guidance published by the Decision Support Unit, and concluded that the same distribution should be used for both treatment groups unless there is a clinically plausible reason to do otherwise. The Committee concluded that the company's approach, using log-logistic distributions for both treatment groups was appropriate in this case.

4.10 The Committee considered the clinical effectiveness estimates used in the company's model. It noted that for the comparison of VR-CAP with R-CHOP, the company had used direct evidence from the ITT population in the LYM-3002 trial. The Committee was aware of the ERG's concerns that no patients from the UK were included in the LYM-3002 trial, and that the results might not be generalisable to clinical practice in the UK. The ERG's preference was to use data from the European Union subgroup

rather than the whole trial population. However, the Committee also noted the ERG's concerns that all outcomes for this subgroup were likely to be underpowered. In the absence of a test for interaction showing a different effect of VR-CAP in different regions, the Committee concluded that it was appropriate to use data from the ITT population of the LYM-3002 trial in the economic model.

4.11 The Committee considered the way in which overall survival had been extrapolated in the company's model. It was aware that because overall survival data were immature, a number of different approaches could potentially be used to estimate survival beyond the end of the trial (see sections 3.22 to 3.24). The Committee noted that the survival estimates for everyone in the model appeared implausibly long, but that the company had tried to remedy this by applying an adjustment for all cause-mortality. The Company also estimated overall survival differently depending on whether or not people's disease had progressed. The Committee noted the ERG's comment that because the data is immature it may not be possible to identify any differences in overall survival between the treatment groups, and the suggestion that a more conservative approach would be to assume no effect on overall survival, only on progression-free survival. The Committee appreciated the difficulty of predicting survival in absolute terms, but was aware that it was the difference in overall survival between VR-CAP and R-CHOP, which was the most relevant to its assessment of cost effectiveness. It concluded that the overall survival benefit as predicted in the company's model was not unreasonable, given the progression free survival benefit demonstrated in the trial.

4.12 The Committee considered the utility values used in the model. It was aware that the ERG did not agree with the company's value of 0.45 for 'progressed disease from second-line treatment'. This was because it was based on a study in aggressive non-Hodgkin's lymphoma, and was conducted in a small patient population. The Committee noted that both the company and the ERG had explored the effect of using alternative

values (0.693 and 0.624 respectively). It heard from the clinical expert that after second-line treatment, further treatment tends not to work very well, and may result in more toxicity than benefit, with a negative effect on quality of life. The expert highlighted that after 2 lines of therapy, people would be unlikely to regain the same or similar utility as those having first-line treatment. The Committee concluded that the company's choice of a lower utility of 0.45 for its base-case was reasonable.

4.13 The Committee considered the costs used in the company's economic model. It was aware that the clinical trials were all conducted using intravenously administered bortezomib, and it noted that this was also assumed in the company's economic model. The Committee was aware that bortezomib is available as a subcutaneous formulation and is likely to be the preferred method of administration in clinical practice. The Committee heard from the clinical expert that the subcutaneous formulation could reduce the risk of peripheral neuropathy and also the need for thromboprophylaxis, as well as being associated with lower costs of administration. The Committee concluded that subcutaneous administration would be used in clinical practice, and the costs would, therefore, likely be lower than those used in the company's model.

4.14 The Committee considered the company's base-case cost-effectiveness results, and the ERG's exploratory analyses. It noted that the company's base case deterministic and probabilistic ICERs for VR-CAP compared with R-CHOP were £20,400 and £20,300 per QALY gained. The Committee considered the ERG's exploratory analyses, which amended 16 assumptions compared with the company's model (see section 3.42). It noted that the ERG's combined analyses resulted in an ICER of £34,000 per QALY gained. The Committee agreed with the majority of the ERG's amendments but noted 5 amendments in particular, which it questioned:

- The ERG's suggestion of using the hazard ratio for progression-free survival from the European Union subgroup (see section 4.7).

- The utility on progression from second-line treatment, where the ERG used a utility of 0.624 instead of the company's 0.45 value (see section 4.10).
- Overall survival not being distinguished between people with and without progression, (see section 4.8).
- The ERG's exclusion of all-cause mortality (see section 4.8).
- The ERG's use of an exponential curve for the extrapolation of progression-free survival in the VR-CAP group and a log-logistic distribution for the R-CHOP group (see section 4.9).

The Committee considered the cost-effectiveness results excluding these amendments from the ERG's combined exploratory analyses (for the reasons highlighted in sections 4.7 to 4.10). The Committee noted that when these analyses were removed, the ERG's estimate of the ICER decreased to £26,700 per QALY gained. The Committee agreed that this may be a conservative estimate of the ICER because the subcutaneous administration of bortezomib would be likely to reduce costs further. The Committee also considered that the ERG's assumption of using per-protocol dosage rather the mean dosage from the LYM-3002 trial was overly conservative because the mean dosage given in the trial would be similar to the actual dosage given in clinical practice. It agreed that these assumptions would be likely to reduce the ICER further. The Committee concluded that although there was significant uncertainty in the modelling of long-term survival, the most plausible ICER for VR-CAP compared with R-CHOP was likely to be in the range of £20,300 to £26,700 per QALY gained, and therefore VR-CAP represented a cost-effective use of NHS resources.

4.15 The Committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when appraising bortezomib. It 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 heard nothing to suggest that there is any basis for taking a different view on the relevance of the PPRS to this appraisal of bortezomib. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the cost effectiveness of bortezomib.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Bortezomib is recommended, within its marketing authorisation, as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable.		1.1
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical and patient experts that mantle cell lymphoma is associated with short survival, and a new treatment which improved survival would be very valuable for people with this condition. It concluded that rituximab in combination with cyclophosphamide, doxorubicin, prednisone and vincristine (R-CHOP) was the current standard of care for those who could tolerate it, and should be considered the main comparator for bortezomib in people with untreated mantle cell lymphoma for whom haematopoietic stem cell transplant is unsuitable.	4.1
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 primary trial outcome of progression-free survival was statistically significantly better for VR-CAP compared with R-CHOP (HR 0.63, 95% CI 0.50 to 0.79), based on an independent review.	4.3
What is the position of the treatment in the pathway of care for the condition?	The Committee concluded that R-CHOP was the current standard of care for those who could tolerate it, and should be considered the main comparator for bortezomib in people with untreated mantle cell lymphoma for whom haematopoietic stem cell transplant is unsuitable.	4.1
Adverse reactions	The Committee concluded that although bortezomib was associated with an increased side effect profile, it is a generally well-tolerated treatment.	4.6
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee considered the LYM-3002 trial, which compared bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP), with R-CHOP. The Committee noted that the age and other baseline characteristics of participants in the trial were broadly generalisable to people in	4.2,

	England with this disease. It was aware that no patients from the UK were included in the trial, although 28% were recruited from the EU.	
Relevance to general clinical practice in the NHS	The Committee considered that a strength of the LYM-3002 trial was the direct comparison with R-CHOP, which is current standard of care in England. However, it noted that the trial did not include maintenance therapy with rituximab, which is now part of routine practice. The Committee acknowledged that although standard of care might differ between England, the rest of the EU, and the rest of the world; there was no reason to suggest that the course of the disease, or response to treatment would be different. The Committee concluded that the population included in the LYM-3002 trial was generalisable to practice in England.	4.2
Uncertainties generated by the evidence	Overall survival data from the LYM-3002 trial was immature, as the median was not reached in the VR-CAP group.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable.	

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The primary trial outcome of progression-free survival was statistically significantly better for VR-CAP compared with R-CHOP (HR 0.63, 95% CI 0.50 - 0.79), based on independent review.	4.3
For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations?	Not applicable	
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee concluded that the company's model followed a logical approach, and agreed that the principal comparator is R-CHOP. The Committee agreed that the company's approach, using log-logistic distributions for both treatment groups was appropriate in this case. In the absence of a test for interaction demonstrating a different effect of VR-CAP in different regions, the Committee concluded that it was appropriate to use data from the ITT population of the LYM-3002 trial in the economic model.	4.8, 4.9, 4.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the survival estimates for everyone in the model appeared implausibly long, but that the company had tried to remedy this by applying an adjustment for all cause-mortality. The Committee appreciated the difficulty of predicting survival in absolute terms, but was aware that it was the difference in overall survival between VR-CAP and R-CHOP, which was the most relevant to its assessment of cost effectiveness. It accepted that the overall survival benefit as predicted in the company's model was not unreasonable, given the progression free survival benefit demonstrated in the trial	4.11

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 agreed with the clinical expert and the company that after 2 lines of therapy, people would be unlikely to regain the same or similar utility as those having first-line treatment and so the company's choice of a lower utility of 0.45 in this case was reasonable. No.	4.13
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable	
What are the key drivers of cost effectiveness?	The choice of curve used to extrapolate progression-free survival and overall survival. The ERG explored this by using an exponential distribution in the VR-CAP group and a log-logistic distribution for the R-CHOP group (see section 4.9). This amendment increased the base-case ICER from £20,300 to £33,100 per QALY gained.	4.14

Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that although there was significant uncertainty in the modelling of long-term survival, the most plausible ICER for VR-CAP compared with R-CHOP was likely to be in the range of £20,300 to £26,700 per QALY gained.	4.14
For reviews (except rapid reviews): How has the new cost-effectiveness evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations?	Not applicable	-
Additional factors taken into account		
Patient access schemes (PPRS)	The Committee concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the cost effectiveness of bortezomib.	4.15
End-of-life considerations	Not applicable.	-
Equalities considerations and social value judgements	No equality issues were identified.	-

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has mantle cell lymphoma and the doctor responsible for their care thinks that bortezomib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 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.
- 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 the final appraisal determination goes out for appeal and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- None

Under development

- Non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma. NICE clinical guideline, publication expected December 2015
- Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma. . NICE technology appraisal guidance, publication expected TBC.
- Ibrutinib for the treatment of relapsed or refractory mantle cell lymphoma. NICE technology appraisal guidance, publication expected TBC.

7 Review of guidance

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

Dr Jane Adam
Chair, Appraisal Committee
October 2015

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.

Dr Jane Adam (Chair)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant
GP, Swadlincote, Derbyshire

Dr Andrew England
Senior Lecturer, Directorate of Radiography, University of Salford

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Mohit Misra

GP, Queen Elizabeth Hospital, London

Ms Pamela Rees

Lay Member

Mr Stephen Sharp

Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

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.

Christian Griffiths
Technical Lead

Joanna Richardson
Technical Adviser

Bijal Joshi
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews:

- Wolff R, Ramaekers B, van Dongen-Leunis A, et al., Bortezomib for previously untreated mantle cell lymphoma: a Single Technology Appraisal, September 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. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on bortezomib by making a submission to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I. Company

- Janssen (bortezomib)

II. Professional/expert and patient/carer groups:

- British Society for Haematology
- Cancer Research UK
- Leukaemia CARE
- Lymphoma Association
- Royal College of Pathologists
- Royal College of Physicians
- UK Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS England
- 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
- National Collaborating Centre for Cancer
- Roche Products (rituximab)

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 bortezomib by providing oral evidence to the Committee.

- Professor Simon Rule, Consultant Haematologist / Professor of Clinical Haematology, nominated by organisation representing Janssen and Royal College of Physicians – clinical expert
- Ms Katharine Robinson, nominated by organisation representing Lymphoma Association – 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.

- Janssen