NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Bendamustine for the treatment of chronic lymphocytic leukaemia

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group's (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:

- **Clarify the progression-free survival probabilities.**
- **Provide updated overall survival data, including Kaplan–Meier estimates and numbers at risk.**
- **Provide baseline information for the additional need-to-treat criteria specified.**
- **Provide details of quality-of-life data as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) criteria from study 02CLLIII.**
- **Clarify how progression within the first 3 months of the trial (leading to exclusion from the trial) was dealt with in the model.**
- **Clarify the number of retreatment cycles permitted in the model before subsequent treatments were given.**
- **Explain how mortality for patients in the 'best supportive care' state was dealt with in the model.**
- **Describe how background mortality (for example, death from stroke), was dealt with in the model.**
- **Explain the basis of the assumptions used in the economic model for allocating patients to second line care.**
- **Provide plots for alternative survival functions and associated results from statistical tests.**
- **Explain how utilities were handled in relation to the utilities from the general public.**
- **Provide health-state descriptions for the utility study.**

Licensed indication

Bendamustine (Levact, Napp) was granted a UK marketing authorisation by the Medicines and Healthcare Product Regulatory Agency (MHRA) in August 2010. It is licensed for first-line treatment of chronic lymphocytic leukaemia (CLL), of Binet stage B or C, in patients for whom fludarabine combination chemotherapy is not appropriate.

Key issues for consideration

Clinical effectiveness

- Are participants in the 02CLLIII study representative of people with CLL (Binet stage B or C) for whom fludarabine combination chemotherapy is not appropriate in routine NHS clinical practice?
- Is the lack of any formal criteria for identifying people for whom fludarabine combination chemotherapy is not appropriate an issue? The decision about first-line treatment in the 'real-world' setting is currently a matter of physician's (and patient's) judgement.
- Do the subgroups in the submission show differential effectiveness of bendamustine (subgroups of Binet stage, age and WHO status)?
- Will the subgroup of people with TP53 deletions be considered for treatment with bendamustine? During consultation, several comments were received about this subgroup responding differently to treatment with bendamustine, compared with people not in this subgroup.

Cost effectiveness

- Are the costs and utilities used in the manufacturer's model appropriate?
- Does the manufacturer's model use the correct assumptions for frequency of blood transfusion, overall survival, dose intensities and frequency of visits to a haematologist? The ERG's revised assumptions were: frequency of blood transfusion from every 3 weeks to every 4 weeks for the last 6 months of life; the hazard ratio for overall survival from 1.66 to 1.30; dose intensities from 100% to 90% for bendamustine and from 100% to 95% for chlorambucil; and frequency of visits to a haematologist from three per month to two per month. This led to a change in the incremental cost-

effectiveness ratio (ICER) from £12,000 in the manufacturer's submission to £9400 in the ERG report.

- Does the manufacturer's model handle second-line treatment in the correct way? The ERG suggested two alternative ways to model second-line treatment: calculating the cost of all second-line drugs received in each treatment arm in the randomised controlled trial (RCT) and modelling the actual, unadjusted overall survival from the RCT; and estimating overall survival for each treatment arm assuming no second-line drug treatment. This reduced the ICER further from £9400 to less than £8700 per QALY gained.

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	People with previously untreated CLL (Binet stage B or C) for whom fludarabine combination chemotherapy is not appropriate
Intervention	Bendamustine
Comparator	Chlorambucil
Outcomes	Progression-free survival, response rates, overall survival, adverse effects of treatment and health-related quality of life
Economic evaluation	The cost-effectiveness of bendamustine was expressed as a cost per QALY. A lifetime time horizon was used. Costs were considered from an NHS and PSS perspective.
Subgroups	A sensitivity analysis was presented based on patients' WHO performance status. Response rates and progression-free survival were presented for patients according to disease stage and an analysis was presented based on patients' age, as a proxy for comorbidities.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG confirmed that the population was defined appropriately as 'people with previously untreated CLL (Binet stage B or C) for whom fludarabine combination chemotherapy is not appropriate'. The ERG acknowledged the lack of definitive criteria for determining in which patients fludarabine

combination therapy is not suitable, (as discussed in section 2.5, page 27, of the manufacturer's submission). The ERG noted that the group of patients with CLL who are currently treated with chlorambucil in the UK is heterogeneous with regard to performance status, age and comorbidities.

The ERG noted that the Binet staging system is frequently used in Europe to determine prognosis. The ERG highlighted that patients with stage A disease generally survive for at least 10 years. For patients with stage B disease, the median survival time is 5–8 years, and for those with stage C disease, it is 1–3 years.

1.2.2 Intervention

The ERG did not comment on appropriateness, but the intervention matched the scope and was consistent with the marketing authorisation.

1.2.3 Comparators

The ERG considered that the choice of comparator was in line with the final NICE scope. Chlorambucil is the current standard first-line therapy for patients for whom a fludarabine-containing regimen is not suitable. The Phase III study provided a direct comparison of bendamustine with chlorambucil.

1.2.4 Outcomes

The ERG considered that the outcomes were in line with those in the final NICE scope and are valid outcomes in oncology trials. Response rate is generally considered clear evidence of anti-tumour activity and as such is an appropriate indicator of clinical benefit.

1.2.5 Economic evaluation

The ERG confirmed that the cost effectiveness of bendamustine was expressed as the cost to achieve an additional quality-adjusted life year (QALY) from treatment. The ERG considered that the lifetime horizon of 35 years used for the economic evaluation was appropriate.

1.3 Statements from professional/patient groups and nominated experts

Six statements were received from professional and patient groups. Patient and professional groups confirmed that chlorambucil oral chemotherapy is considered the standard treatment for this group of patients. They stated that bendamustine would provide an additional treatment option in patients for whom fludarabine based treatment is not suitable, improving the treatment options for this group of patients.

Statements from patient and professional groups identified a number of subgroups of interest: people with Binet stage C disease who have significantly compromised bone marrow function making them ineligible for treatment with fludarabine; people with compromised kidney function who are ineligible for fludarabine treatment because fludarabine is eliminated via the kidneys; and people who will be ineligible for fludarabine therapies because of advanced age and frailty. Four of the six statements received from patient and professional groups highlighted a subgroup of people with tumour protein 53 (TP53) deletions. This was described as a relatively uncommon subgroup (less than 10% of patients) in practice. Professional groups highlighted that no convincing data suggest that bendamustine will have a particular role in this subgroup of patients. One clinician commented that because TP53 defects are strongly predictive of resistance to a range of chemotherapeutic agents including bendamustine, patients with TP53 defects should be offered alternative therapy that is more likely to be effective. By contrast, a patient's statement suggested that bendamustine has demonstrated effectiveness in this group of people and may offer an effective treatment option for people who have few other treatment options.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

One trial was identified by the manufacturer for inclusion in its submission to NICE. Trial 02CLLIII compared bendamustine with chlorambucil in 319 people

with previously untreated CLL, for whom fludarabine based therapy was not considered appropriate. The study was a Phase III, open-label (due to the method of administration), multicentre parallel group international study comparing initial treatment of patients with Binet stage B or C CLL needing treatment. This study was carried out at 45 sites across Europe, including one centre in the UK. Recruitment started in November 2002 and the last patient completed follow-up in June 2008. The follow-up period ended 1-year after the last enrolled patient completed treatment.

The manufacturer considered that patients in trial 02CLLIII were representative of the group of patients in the UK who would usually be treated with chlorambucil, that is, people for whom fludarabine based therapy was not considered appropriate. The manufacturer stated that the group of patients currently treated with chlorambucil in the UK is heterogeneous with respect to performance status, age and comorbidities. In study 02CLLIII, 51% of patients were aged below 65 years and 49% were aged 65 years or above. Patients also had a range of WHO performance status scores: 67% with WHO 0, 28% with WHO 1 and 3% with WHO 2. Additionally, the manufacturer highlighted that a study of fludarabine combination therapy (trial CLL8) was recruiting at the same time as trial 02CLLIII. Therefore, physicians nominating their patients for participation in a clinical trial would have judged their suitability for fludarabine-based therapy and put them forward for the most appropriate treatment.

Patients were randomised 1:1 to receive either intravenous bendamustine or oral chlorambucil (stratified by centre and Binet stage). In the bendamustine group, participants received 100 mg/m²/day intravenously over 30 minutes on days 1 and 2 of a 28-day treatment cycle. The next cycle started on day 29. In the chlorambucil group, patients were administered 0.8 mg/kg (Broca's normalised weight) orally on days 1 and 15 or of a 28-day treatment cycle. The next cycle started on day 29. Patients were followed-up every 3 months. Patients' response to treatment was assessed after three cycles and at the end of treatment.

Baseline demographics of the patient population are set out in table 1 below and are described by the manufacturer to be 'well balanced between the groups'. The median number of treatment cycles per patient was six in both groups. The mean number of treatment cycles per patient was 4.9 (standard deviation [SD] = 1.7) in both groups. Patients receiving chlorambucil could be retreated after the first course of therapy, and 63.1% received one or more retreatment cycles. The mean number of cycles for those patients who were retreated was 1.13.

Table 1 Baseline demographics from study 02CLLIII

	Bendamustine (n = 162)	**Chlorambucil (n = 157)**
Number of female participants	60 (37%)	62 (39%)
WHO performance status (number of people)		
Missing	3 (2%)	5 (3%)
WHO 0	113 (70%)	102 (65%)
WHO 1	43 (26%)	45 (29%)
WHO 2	3 (2%)	5 (3%)
Mean age, years (SD)	63.0 (7.5)	63.6 (8.8)
Age range, years	45.0–77.0	35.0–78.0
Median age, years	63.0	66.0
Number of participants at Binet stage B	116 (72%)	111 (71%)
Adapted from table 5.4 of the manufacturer's submission. WHO 0 = asymptomatic. WHO 1 = symptomatic but completely ambulatory. WHO 2 = symptomatic, in bed for less than 50% of the day. SD = standard deviation.		

Results

There were two primary outcomes: overall response rate; which included complete response, nodular partial response and partial response; and progression-free survival (the time from randomisation to first progressive disease or relapse after intercurrent remission or death owing to any cause, whichever occurred first). See section 5.3.5 of the manufacturer's submission for details of the different types of response.

There were five secondary outcomes: time to progression of disease, or relapse, or death; duration of response or remission; overall survival; quality of life (assessed using EORTC criteria); and adverse events (toxicities). See section 5.5 of the manufacturer's submission for full results for the secondary outcomes.

Response rates

Results for the primary outcome of overall response rate are shown in table 2. Bendamustine was associated with a significantly higher overall response rate compared with chlorambucil (68% of participants compared with 31%, relative risk [RR] = 2.22, 95% confidence interval [CI] 1.76 to 2.81), a higher likelihood of achieving a complete response (31% of participants compared with 2%, RR = 16.15, 95% CI 7.36 to 35.46) and a higher likelihood of achieving a nodular partial response (11% of participants compared with 3%, RR = 4.12, 95% CI 1.56 to 10.88). There was no statistically significant difference between treatments for partial response.

Table 2 Response rates (intent-to-treat population)

	Bendamustine (n = 162)	**Chlorambucil (n = 157)**	**Relative risk (95% CI)**	**p value**
Complete response	50 (30.9%)	3 (1.9%)	16.15 (7.36 to 35.46)	0.0000[a]
Nodular partial response	17 (10.5%)	4 (2.5%)	4.12 (1.56 to 10.88)	0.0043[a]
Partial response	43 (26.5%)	41 (26.1%)	1.02 (0.70 to 1.47)	0.9309
Overall response	110 (67.9%)	48 (30.6%)	2.22 (1.76 to 2.81)	0.0000[a]

Adapted from table 5.5 of the manufacturer's submission. Data show number of people achieving each type of response. [a] Shows statistically significant results ($p < 0.05$). CI = confidence interval.

Regardless of Binet stage, patients showed a higher likelihood of overall response and of complete response with bendamustine compared with chlorambucil. The manufacturer highlighted that the differences in response rates between the treatment groups were maintained regardless of age, but that variation by age group was greater in the results for the bendamustine group: the overall response rate for the bendamustine arm was 72% for people aged below 65 years and 64% for those aged 65 years or older ($p > 0.3$). This compares with 28% and 33%, respectively, within the chlorambucil arm ($p > 0.6$). Further results by age are presented in table 5.6, page 56, of the manufacturer's submission.

Survival

Figure 5.5 in the manufacturer's submission shows the primary outcome of progression-free survival within the two arms of the trial. Median progression-free survival was 21.6 months in the bendamustine arm compared with 8.3 months in the chlorambucil arm, hazard ratio = 4.37 (95% CI 3.14 to 6.07, $p < 0.0001$). This difference between the treatment groups was evident in patients with Binet stage B disease (21.4 months versus 9.0 months) and for stage C disease (25.4 months versus 6.3 months).

In terms of overall survival after 35-months of follow up, 72 of the trial patients had died, 31 in the bendamustine group and 41 in the chlorambucil group (HR = 1.45, 95% CI 0.91 to 2.3, $p = 0.1623$). Death due to CLL was reported for 13 patients in the bendamustine group and 21 patients in the chlorambucil group. The manufacturer stated that an estimation of median overall survival was possible only for patients in the chlorambucil group (65.4 months).

The manufacturer presented a breakdown of overall survival according to response rate. The manufacturer suggested that the numbers of patients achieving a complete response and nodular partial response drive the overall survival advantage, and that this is in line with the published literature, which contains increasing evidence that a meaningful remission is needed, particularly a complete remission, to gain an improvement in overall survival from therapy. The breakdown of the survival data by response can be seen in Figure 5.8 on page 54 of the manufacturer's submission.

The manufacturer reported on an unpublished abstract that described results after a median observation time of 54 months. The results from this study show that bendamustine offers significantly greater response rates and progression-free survival and a much longer time to next treatment than chlorambucil. The manufacturer commented that this confirms the overall survival benefit for bendamustine compared with chlorambucil but that the result was not statistically significant (hazard ratio = 1.3 in favour of bendamustine, $p = 0.24$).

Quality of life

During the treatment period, patients' quality of life was assessed using EORTC quality-of-life questionnaires. Patients' overall quality of life was modestly improved in both groups during treatment with no significant differences between the groups. The manufacturer explains within its submission that the quality-of-life data collected during the trial reflected the scenario in which patients receiving a more effective therapy (bendamustine) experienced a greater number of adverse events during the treatment period leading to a quality of life detriment in some health dimensions.

Adverse events

The manufacturer's submission reported that most adverse events in study 02CLLIII were haematological, that these were generally higher in the bendamustine group than in the chlorambucil group, and that they were usually manageable and of short duration. Overall, adverse events were reported in 89% (n = 143) of the bendamustine group and 81% (n = 122) of the chlorambucil group. Table 3 contains a summary of the adverse events recorded in the trial. Statistically significant differences in adverse event rates were seen for: neutropenia/granulocytopenia, leukopenia, lymphopenia, vomiting, diarrhoea, pyrexia, chills, infection and hyperuricaemia. Of these, the highest incidence was for neutropenia, affecting 44 people in the bendamustine group compared with 21 people in the chlorambucil group. There were no statistically significant differences between the treatment groups for thrombocytopenia, anaemia, nausea, asthenia, fatigue, hypersensitivity, nasopharyngitis, weight decrease, cough, rash and pruritus.

Table 3 Summary of adverse events occurring in at least 5% of patients, all grades

	Bendamustine (n = 161)	Chlorambucil (n = 151)	Relative risk (95%CI)	p value
Blood and lymphatic system disorders				
Neutropenia/granulocytopenia	44 (27%)	21 (14%)	1.97 (1.25 to 3.10)	0.0036[a]
Thrombocytopenia	40 (25%)	31 (21%)	1.21 (0.80 to 1.83)	0.3644
Anaemia	35 (22%)	21 (14%)	1.56 (0.96 to 2.54)	0.0721
Leukopenia	28 (17%)	4 (3%)	5.25 (2.35 to 11.76)	0.0001[a]
Lymphopenia	10 (6%)	1 (1%)	9.38 (1.79 to 49.06)	0.0080[a]
Gastrointestinal disorders				
Nausea	31 (19%)	21 (14%)	1.38 (0.84 to 2.29)	0.2060
Vomiting	25 (16%)	10 (7%)	2.34 (1.20 to 4.59)	0.0129[a]
Diarrhoea	16 (10%)	6 (4%)	2.50 (1.04 to 6.00)	0.0401[a]
General disorders and administration-site conditions				
Pyrexia	40 (25%)	8 (5%)	4.69 (2.49 to 8.84)	0.0000[a]
Asthenia	14 (9%)	7 (5%)	1.88 (0.79 to 4.45)	0.1533
Fatigue	14 (9%)	7 (5%)	1.88 (0.79 to 4.45)	0.1533
Chills	9 (6%)	2 (1%)	4.22 (1.06 to 16.85)	0.0415[a]
Immune system disorders				
Hypersensitivity	8 (5%)	3 (2%)	2.50 (0.71 to 8.82)	0.1541
Infections and infestations				
Nasopharyngitis	11 (7%)	11 (7%)	0.94 (2.10 to 0.42)	0.8762
Infection	10 (6%)	2 (1%)	4.69 (1.21 to 18.13)	0.0251[a]
Investigations				
Weight decreased	9 (6%)	5 (3%)	1.69 (0.59 to 4.86)	0.3320
Metabolism and nutrition disorders				
Hyperuricaemia	12 (7%)	2 (1%)	5.63 (1.54 to 20.60)	0.0091[a]
Respiratory, thoracic and mediastinal disorders				
Cough	10 (6%)	7 (5%)	1.34 (0.52 to 3.42)	0.5407
Skin and subcutaneous tissue disorders				
Rash	15 (9%)	7 (5%)	2.01 (0.86 to 4.70)	0.1071
Pruritus	8 (5%)	4 (3%)	1.88 (0.59 to 5.98)	0.2877

Data shows number of people who had specified adverse events. [a] Shows statistically significant results ($p < 0.05$). CI = confidence interval.

Fifty patients had serious adverse events: 31 (19%) in the bendamustine group and 19 (13%) in the chlorambucil group. The most common serious adverse events in the bendamustine group were hypersensitivity, pneumonia, anaemia, vomiting, pyrexia and tumour-lysis syndrome. The most common serious adverse event in the chlorambucil group was herpes zoster.

Overall, 54 (34%) of patients in the bendamustine group and 46 (31%) in the chlorambucil group required at least one dose reduction. The most common reasons for dose reduction in both groups were neutropenia and thrombocytopenia. Of the trial population, 23 were withdrawn from the study due to unacceptable toxicity or because the risk/benefit assessment was no longer considered acceptable by the investigator (18 in the bendamustine group and five in the chlorambucil group). The most frequent adverse events leading to withdrawal from the study were hypersensitivity reactions including skin and subcutaneous tissue (nine patients treated with bendamustine and two treated with chlorambucil).

2.2 Evidence Review Group comments

The ERG commented that the manufacturer's submission contained all the relevant studies and the relevant data within those studies, and that the submitted evidence in the manufacturer's submission adequately reflects the decision problem. The ERG found that the searches conducted by the manufacturer were appropriate and included all relevant studies.

The ERG noted that the evidence base for this appraisal comprised only one RCT. Nevertheless, the ERG found that study 02CLLLIII was of good quality and reflects UK clinical practice. The ERG noted that study 02CLLIII was an open-label study and, therefore, lacked blinding for both participants and investigators, which introduced the potential for bias. However, outcomes were reviewed by an independent review team according to criteria defined by the National Cancer Institute Working Group on CLL. Study 02CLLIII was an international study, employing 45 centres across Europe, one of which was in the UK. The ERG noted that no further details were reported regarding other sites involved, or number of patients recruited in the UK. Additionally, no analysis by country was performed. Since any multicentre trial may have inherent variations in disease management, knowing the proportion of trial participants based in the UK may improve confidence regarding applicability of trial results in this country.

The ERG highlighted that patients for whom fludarabine was unsuitable were noted in the manufacturer's submission (section 2.1, page 21) to be: more

elderly with comorbidities and lower performance status. Therefore the ERG questioned whether the 65–70% of patients in study 02CLLIII with a WHO performance status of 0, coupled with a relatively young mean age of 63–64, were representative of the target population.

The ERG pointed out that maximum follow-up was approximately 5 years and that median survival was 2–7 years in the population of interest. As such, a longer follow-up would increase validity.

The ERG noted that because the quality-of-life data were collected only during the treatment period, it was inadequate to capture the long-term effects of bendamustine or chlorambucil. Also, patients who discontinued therapy were not followed-up, introducing the possibility of attrition bias.

The ERG noted that the dosage regimen used for bendamustine was the same as that proposed in the summary of product characteristics, but that the dosage regimen for chlorambucil varies in clinical practice. However, the ERG considered that the course of therapy used in Study 02CLLLIII was broadly consistent with UK clinical practice and so this should be considered a relatively minor issue.

2.3 Statements from professional/patient groups and nominated experts

The patient and professional groups agreed that bendamustine offers a superior initial treatment for the significant numbers of people with CLL who cannot tolerate treatment with fludarabine. Patient and professional groups stated that benefits of treatment include relief from symptoms of the disease, longer time in remission and improved quality of life, including: improvements in pain, fatigue, anaemia, mobility, benefits to mental health, and more capacity to enjoy life, to care for oneself, to work and to fulfil other personal responsibilities. When people are in remission, the burden to the NHS and carers will be reduced.

Possible side effects of bendamustine are more unpleasant than those of oral chlorambucil, which usually has few side effects. However, the patient and

professional groups stated that patients are likely to prefer the clinically more effective treatment in spite of increased risk of side effects. In practice, relatively few people find the side effects of bendamustine intolerable and all are of short duration, the main one being neutropenia. Infection of grade 3 and above is the most important toxicity in CLL trials. One patient group considered that the rate of such infections in the bendamustine arm of the trial reported in Knauf et al (2009) was acceptable (8%) and comparable to that of the chlorambucil arm (3%).

Patient and professional groups highlighted that bendamustine is more cumbersome to administer than oral chlorambucil, needing additional pharmacy input and day-unit capacity, and may also need more (but minimal) supportive care (for example, blood transfusion, antibiotics and hospital admissions). Bendamustine is given in a hospital environment by injection, and patients need to attend hospital for 2 days every 4 weeks. Training requirements should not be significant because both pharmacists and nurses will already be familiar with administering other types of chemotherapy, and bendamustine has no particular difficulties in preparation or administration.

Comments about the injection versus oral administration include: ‘I have asked several CLL patients if they feel that the extra hospital visits and discomfort of this form of treatment would put them off using bendamustine given the possible advantages of the drug, and the answer has resoundingly been that they would willingly tolerate the difficulties and ‘this inconvenience is likely to be tolerable for patients because they will opt for the therapy with proven superiority. The clinical benefits will outweigh the practical inconveniences’.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer’s submission

The manufacturer did not identify any cost-effectiveness studies of bendamustine in CLL. The manufacturer developed a de novo economic model using a Markov framework to estimate the cost-effectiveness of bendamustine compared with chlorambucil for the first-line treatment of CLL

in patients for whom fludarabine-based therapies were considered inappropriate. The model used a lifetime time horizon, which was assumed to be 35 years, and a cycle length of 3 months. The model starts with the patient entering a course of first-line treatment with either bendamustine or chlorambucil. Patients who remain progression-free on chlorambucil for at least 12 months are retreated with chlorambucil, whilst the base-case analysis assumes that patients can be treated with bendamustine only once. All patients begin treatment in the stable disease health state. In the next model cycle they move to the state representing their best overall response: stable disease, partial response, complete response, progressive disease or death. The patient moves around the model according to transition probabilities, derived from study 02CLLIII, until death, or if the patient enters the progressive state they can move to a second stage of the model, in which they have equal chance of being offered treatment with fludarabine plus cyclophosphamide or best supportive care.

If the patient enters the fludarabine plus cyclophosphamide treatment option, they are modelled as receiving treatment, then following treatment they can move into any of the states: stable disease, partial response, complete response, progressive disease or death. In this part of the model, if the patient moves into the progressive disease stage they may move into supportive care, or enter the death state. At the supportive care stage, the patient receives best supportive care until death. In total, 39 health states are modelled.

The costs used were from the perspective of the NHS and PSS and are for drug acquisition, drug administration, disease management (such as visits to the haematologist, blood tests and blood transfusions), and for adverse events. Napp commissioned an advisory board of five UK haematologists to investigate treatment pathways and estimate resource use for other costs of CLL while on treatment. Resource use when not on drug treatment (first or second line), including for adverse events, was informed by clinical experts, and was assumed to be independent of treatment arm.

The mean cost of bendamustine per person was £4741.54 assuming a body surface area of 1.72 m2 and an average treatment course of 4.9 cycles (including product wastage), based on unit costs of: 25mg vials in packs of 5 and 20 of £347.26 and £1379.04 respectively, and 100mg vials in packs of 5 of £1379.04 (Trade Price List, Napp, September 2010). The mean cost of chlorambucil was £91.76 based on a Broca's weight of 68.73kg for 4.9 treatment cycles (2mg x 25 tab pack = £8.36, taken from BNF 59). Total costs (including cost of therapy and other costs: the cost of: infusion; haematologist outpatient visit; blood count; biochemistry and antiemetic cost per cycle) were £7673.00 and £1136.60 respectively (as shown in table 6.19 of the manufacturer's submission).

Utilities in the model were derived using two different methods. The first method used a mapping equation to derive utility estimates from the EORTC-C30, (measured during the trial) to EQ-5D utility. The mapping equation was developed using a dataset of 199 patients with inoperable oesophageal cancer, in which the EORTC-C30 and the EQ-5D were both collected. The second method of deriving utilities for the model was to estimate utility using vignettes. The vignettes described various disease-specific health states and participants from the UK general population were asked to value these health states using the standard gamble method (Beusterien et al, 2010*)*. Utility values were assigned to health states according to Beusterien et al (2010), with the exception of the treatment period, which was based on the quality of life data collected in study 02CLLIII. The mapping was used for baseline utility only. The utilities derived by the standard gamble method were applied to the disease states within the model.

For the bendamustine and chlorambucil treatment period (about 4.9 months), utility was set to 0.70 in both groups, which was the value elicited from study 02CLLIII using the mapping algorithm. Utility decrements associated with adverse events (taken from Beusterien et al, 2010) were also applied during this period. Table 4 contains details of some of the raw utilities used in the model, including utilities for the states: complete response (0.91); a partial response (0.84); no change (0.78); and progressive disease (0.68). See

section 5.1.6 of the ERG report for details of how these utilities were adjusted for use in the model. Table 4 also provides raw utilities for adverse events included within the model, for: nausea, vomiting, diarrhoea, anaemia, pyrexia and pneumonia. Pneumonia was seen to cause the greatest drop in utility (0.20), whereas the adverse event of nausea or nausea and vomiting led to the smallest drop in utility (0.05). Patients with an adverse event experienced a utility decrement equal to the difference between the 'no change plus adverse event' valuation and the 'no change' valuation (from Beusterien et al, 2010), regardless of their health state.

Table 4 Raw utilities before adjustment

Health state	Mean (SD)	95% CI
Baseline utility (used for both treatments during active treatment (0–4.9 months); used as baseline utility throughout model)	0.70 (0.22)	0.67 to 0.73
Complete response	0.91 (0.11)	0.88 to 0.93
Partial response	0.84 (0.14)	0.81 to 0.87
No change	0.78 (0.14)	0.75 to 0.82
Progressive disease	0.68 (0.20)	0.64 to 0.72
No change + grade 1–2 nausea	0.73 (0.17)	0.69 to 0.76
No change + grade 1–2 nausea and vomiting	0.73 (0.16)	0.69 to 0.76
No change + grade 1–2 diarrhoea	0.70 (0.19)	0.66 to 0.74
No change + grade 3–4 anaemia	0.69 (0.18)	0.65 to 0.72
No change + grade 3–4 pyrexia	0.67 (0.17)	0.63 to 0.70
No change + grade 3–4 pneumonia	0.58 (0.19)	0.54 to 0.62
No change + second-line treatment	0.71 (0.17)	0.68 to 0.75
Adapted from table 6.18 in the manufacturer's submission. Baseline utility was estimated from trial 02CLLIII using mapping equation from EORTC QLQ-C30. All other utilities were taken from Beusterien et al, 2010. Numbers refer to grade of adverse event. SD = standard deviation. CI = confidence interval.		

Results

Table 5 contains the base-case results from the economic analysis. The results of the model give a total cost of £49,000 and £33,821 respectively. Bendamustine was associated with more QALYs than chlorambucil: 4.82 QALYs compared with 3.55 QALYs, resulting in a cost per QALY gained of £11,960. Treatment with bendamustine is predicted to yield a mean of 1.27 extra QALYs compared with chlorambucil, of which 0.98 are gained in progression-free survival and 0.29 in progressive disease. Treatment with

bendamustine is expected to cost £15,200 more per person than chlorambucil. This difference is largely explained by the greater costs associated with bendamustine in the following: per person acquisition cost compared with chlorambucil (+£4600), first line drug administration (+£1200), blood transfusion (+£6300), and haematologist visits in progressive disease (+£2400).

Table 5 Base-case cost-effectiveness results

		Bendamustine	Chlorambucil	Difference[a]
QALYs	**progression-free survival**	1.52	0.54	0.98
	progressive disease	3.30	3.01	0.29
	Total	4.82	3.55	1.27
First-line drug acquisition cost		£4726	£150	£4576
First-line drug administration cost		£2922	£1706	£1216
Second-line FC drug acquisition cost		£437[b]	£332[b]	£105[b]
Second-line FC administration and monitoring cost		£343[b]	£260[b]	£83[b]
Adverse events (first-line)		£375	£190	£185
Adverse events (second-line)		£155	£117	£37
Blood transfusions		£28,007[b]	£21,708[b]	£6299[b]
Haematologist visits in progressive disease		£10,579[b]	£8200[b]	£2379[b]
Other costs[c]		£1456[b]	£1158[b]	£299[b]
Total costs		£49,000	£33,821	£15,179
ICER		£12,000	–	–

Adapted from the ERG report, table 19. [a]Difference is bendamustine minus chlorambucil [b]Calculated by the ERG; all other values taken from the submission. [c]Comprises blood count and biochemistry in all health states when not on treatment, and haematologist visits (for stable disease, partial response, and complete response, but not progressive disease) when not on treatment. QALY = quality-adjusted life years. FC = fludarabine + cyclophosphamide. ICER = incremental cost-effectiveness ratio.

Estimates of cost-effectiveness were presented for three subgroups: people aged 65 years or older; people with a WHO physical status of 1 or higher; and people aged 65 years or older who also had a WHO physical status of 1 or higher). The data suggest that the treatment effect of bendamustine was maintained across these subgroups, although uncertainty around the treatment effects is high due to the smaller sample sizes. As shown in table 6, ICERs were lower than £15,000 regardless of subgroup.

Table 6 Subgroup cost-effectiveness results

	Drug	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Age ≥ 65	Bendamustine	£40,451	4.09	£12,771	1.01	£12,617
	Chlorambucil	£27,680	3.08	–	–	–
WHO ≥ 1	Bendamustine	£42,924	3.97	£13,921	1.03	£13,452
	Chlorambucil	£29,002	2.94	–	–	–
Age ≥ 65 and WHO ≥ 1	Bendamustine	£37,292	3.53	£12,948	0.95	£13,567
	Chlorambucil	£24,344	2.57	–	–	–

QALYs = quality-adjusted life years. ICER = incremental cost-effectiveness ratio. WHO performance status ≥ 1 corresponds to patients with symptoms.

Univariate sensitivity analyses were conducted around inputs into the model including: treatment effects; survival distributions; treatment pathway after first-line therapy; data sources for subsequent line therapies; utilities; discount rate, patient's body surface area; time to retreatment; response rates; costs. The results of these analyses are presented in table 6.31 of the manufacturer's submission and are summarised in table 7 below. The results show that conducting one-way sensitivity analysis had little effect on the cost effectiveness of bendamustine relative to chlorambucil, with results of the cost per QALY gained ranging from £4886 to £13,375.

Table 7. Results of sensitivity analyses, adapted from table 6.31 of the manufacturer's submission

	Variable	Base case	Sensitivity analysis	ICER
Distribution used for survival analysis	Overall survival	Weibull	Exponential	£12,858
			Log logistic	£12,295
			Log normal	£12,603
			Weibull separate [a]	£12,535
First-line response	Chlorambucil OR	Base case	Upper CI	£12,599
			Lower CI	£11,362
	Bendamustine OR	Base case	Upper CI	£11,103
			Lower CI	£12,950
Costs	Patient's body surface area	1.51–1.75m²	1.26–1.50	£11,412
			1.76–2.00	£12,492
			2.01–2.25	£13,041
	Health state	Include	Exclude	£4,886
			+20%	£13,375
			−20%	£10,545
	Cost of bendamustine administration	Base case	+20%	£12,851
			−20%	£11,069
Utilities	Source	Beusterien	Fludarabine[b]	£11,024
			Rituximab[c]	£10,607
	Remove benefit in treatment period	Yes	No	£11,803
	Adverse event utilities (subsequent therapies)	Include	Exclude	£11,931
			+20%	£11,966
			−20%	£11,954
Decision maker	Discount rate (costs/outcomes)	3.5%	0%	£12,256
			6%	£11,842

[a] separate survival curves fitted to each arm. [b]Data taken from 'Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia' (NICE technology appraisal guidance 119). [c] Data taken from 'Rituximab for the first-line treatment of chronic lymphocytic leukaemia' (NICE technology appraisal guidance 174). OR = odds ratio. CI = confidence interval

The manufacturer estimated the probability of the two treatments being cost effective at given thresholds. The probabilities of bendamustine being cost effective were 90% at a threshold of £20,000 per QALY gained, 96% at £25,000 and 98% at £30,000 (see table 6.32 in the manufacturer's submission).

3.2 Evidence Review Group comments

The ERG identified a recent poster reporting a cost-effectiveness study of bendamustine versus alemtuzumab and chlorambucil for CLL, presented at

the 15th International Society for Pharmacoeconomics and Outcomes Research meeting in 2010. Using a discrete event simulation, taking a US payer perspective, the ICER for bendamustine versus chlorambucil was $50,800 per QALY, or about £33,000 per QALY. The ERG highlighted that the submission base-case ICER of £12,000 per QALY is substantially lower than this US study. The ERG explained this by the fact that the US study predicts a far lower life expectancy on bendamustine (median overall survival 6.1 years for US study vs. 8.3 years for this submission) and highlighted the influence of overall survival gains in determining the cost effectiveness of bendamustine.

Overall, the ERG considered that the manufacturer's economic model was of high quality and contained no logical errors. The ERG found the structure of the model to be typical of models for cancer in that the health states progression-free survival and progressive disease were modelled. The ERG considered the model to be more sophisticated than some models for the following two reasons:

- Progression-free survival was split according to response: complete response, partial response or stable disease. The depth of response influences the utilities (better responses having higher utility) and the disease-management costs (better responses carrying lower costs).
- Retreatment with first-line therapy and subsequent second-line fludarabine combination therapy was modelled. This reflects the reality of management, in which a patient's improvement on initial therapy may permit subsequent use of fludarabine combination therapy.

The ERG commented that the utility data to inform the cost effectiveness modelling were sparse, however they considered that this was an issue for all economic evaluations in this condition. The ERG believed that it was appropriate to use the baseline utility of 0.70 estimated from the data collected during the main RCT. Although this approach was based on mapping between EORTC and EQ-5D, rather than on EQ-5D data collected in the trial, it is supported within the NICE reference case. The submission bases the utilities for patients after treatment on data from Beusterien et al (2010), a study commissioned by the manufacturer. The ERG was generally

satisfied with the use of these data for the cost-effectiveness model, given the absence of clearly superior alternative data. Furthermore, the cost-effectiveness of bendamustine was found to be relatively insensitive to the source of the utilities.

The ERG was broadly satisfied with the costs used in the model. The ERG found that the modelled dosing schedules of bendamustine and of chlorambucil and that the assumption of a mean of 4.9 treatment cycles per patient (as experienced in the RCT), were appropriate. The ERG confirmed that the prices of the treatments were accurate. Although there is no consensus on the appropriate dosing of chlorambucil, the ERG considered that differences in dosing between that costed in the model and that realised in practice will have a negligible effect on the cost-effectiveness of bendamustine, because chlorambucil has a low acquisition cost. The ERG was satisfied with the assumptions regarding the costs of administration of bendamustine. The ERG considered that the cost for a bendamustine patient per visit should be £270 not £131, however the effect of this on the ICER was marginal.

The manufacturer extrapolated survival over many years within the model. The ERG cautioned that while the extrapolation in the model was considered to be reasonable, the extrapolation introduces uncertainty to the modelled overall survival, and hence to the cost-effectiveness of bendamustine.

The manufacturer’s base-case ICER for bendamustine versus chlorambucil was £12,000 per QALY gained. The ERG disagreed with the assumptions used in the manufacturer’s model on three main points, however when the ERG amended the manufacturer’s model with revised figures, the resulting ICERs were lower than the base-case ICER in all instances:

The ERG disagreed with the assumption in the economic evaluation that patients with progressive disease have a blood transfusion every 3 weeks. Instead, the ERG believed a more appropriate assumption was that patients receive a blood transfusion every 4 weeks for the last 6 months of life, in both

treatment arms. Under this revised assumption, the base-case ICER fell from £12,000 to £7,000 per QALY gained.

The ERG believed that the modelled treatment effect in terms of the hazard ratio for overall survival was too high, biasing the cost effectiveness in favour of bendamustine. The submitted model assumed a hazard ratio of 1.66, whereas the most mature data provided by the manufacturer indicates a hazard ratio of 1.30. In this case, the manufacturer's base-case ICER decreased from £12,000 to £11,700 per QALY gained. When the ERG applied the updated hazard ratio and the revised assumptions for blood transfusion costs, the ICER increased from £7000 to £9700 per QALY. The ERG explains this paradox as follows: when the hazard ratio is reduced the incremental discounted QALYs fall substantially, from 1.27 to 0.70. However, the base-case incremental blood transfusion costs also decrease substantially, from £6,300 to £1,400. The net effect is to leave the base-case ICER virtually unchanged. On the other hand, starting with the assumption of no incremental blood transfusion costs, although incremental QALYs again fall substantially, the incremental blood transfusion costs remain at zero when the hazard ratio reduces. Therefore, the ICER increases substantially, from £7,000 to £9,700 per QALY.

The ERG disagreed with the assumptions regarding dose intensities for bendamustine and chlorambucil and assumed frequencies of visits to a haematologist when not treated. Updating the assumption for dose intensities (from 100% to the intensities seen in the RCT: 90% for bendamustine and 95% for chlorambucil) the manufacturer's base-case ICER decreases from £12,000 to £11,600 per QALY. Updating the assumption for the frequency of visits to a haematologist when not treated (from three per month to two per month), the ICER decreases from £12,000 to £11,500 per QALY gained. When the ERG updated the manufacturer's model with assumptions outlined above for blood transfusions, the hazard ratio for overall survival, dose intensities and frequency of visits to a haematologist, the ICER decreased from £12,000 to £9,400 per QALY gained (see table 20 of the ERG report).

The ERG stated that confirming the ICERs in the subgroups (patient's age ≥ 65 years; WHO status ≥ 1; and patient's age ≥ 65 years plus WHO status ≥ 1) was not possible because there was no independent source with which to check the subgroup-specific response data and survival curves. Additionally, the ERG stated that it did not explore alternative ICERs for the subgroups because it did not have updated estimates for the hazard ratios by subgroup for overall survival.

In the RCT, a higher proportion of patients in the chlorambucil arm were given second-line drugs compared with patients in the bendamustine arm. The ERG was broadly satisfied with the submission's approach to incorporating second-line drug costs, but explored two alternative methods within its submission. In the first method, the ERG costed all second-line drugs received in each treatment arm in the RCT and modelled the actual, unadjusted overall survival from the RCT, the result of this was that the manufacturer's base-case ICER fell from £12,000 to less than £10,900 per QALY, and the ERG proposed base-case ICER of £9,400 falls to less than £8,700 per QALY. In the second method, when the ERG do not cost the second-line drugs received in the RCT, but estimate overall survival for each treatment arm assuming no second-line drug treatment, the ICERs fall in the same way.

3.3 Further considerations following premeeting briefing teleconference

In response to statements received from professional and patient groups, the ERG commented that the subgroup of people with TP53 deletions would be considered for treatment with bendamustine. The ERG explained that although there are no treatments that show benefit, the capacity for benefit is there but the likelihood for benefit is rare. Patients presenting with a sizable TP53 subclone are less likely to derive any benefit from chemotherapy treatment including bendamustine; this subgroup is only representative of a small number of patients.

4 Equalities issues

This technology will not be suitable for patients who do not want to be treated by injection or infusion.

5 Authors

Dr Helen Starkie and Zoe Charles, with input from the Lead Team (Dr Wasim Hanif, Richard Devereaux-Phillips and Dr Judith Wardle).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

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

- Hoyle M, Crathorne L, Jones-Hughes T et al. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp (October, 2010).

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Napp Pharmaceuticals Limited

II Professional/specialist, patient/carer and other groups:

- British Society for Haematology and Royal College of Pathologists (joint submission)
- Chronic Lymphocytic Leukaemia Support Association
- Leukaemia CARE
- Lymphoma Association
- Royal College of Physicians/NCRI/RCR/ACP/JCCO
- United Kingdom Chronic Lymphocytic Leukaemia Forum

C Additional references used:

Beusterien KM, Davies J, Leach M et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health and Quality of Life Outcomes 2010; 8: 50