

Bendamustine for the first- line treatment of chronic lymphocytic leukaemia

Technology appraisal guidance

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1 Guidance

- 1.1 Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

2 The technology

- 2.1 Bendamustine (Levact, Napp Pharmaceuticals) is an alkylating anti-tumour agent. It has a UK marketing authorisation for the 'first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate'.
- 2.2 The most common adverse reactions with bendamustine hydrochloride are haematological adverse reactions (leukopenia, thrombocytopenia), dermatological toxicities (allergic reactions), constitutional symptoms (fever) and gastrointestinal symptoms (nausea, vomiting). For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 Bendamustine is administered by intravenous infusion, over 30–60 minutes on days 1 and 2, every 4 weeks. Dose depends on body surface area (100 mg/m²). Bendamustine is available as 25-mg vials in packs of 5 and 20 for £347.26 and £1379.04 respectively, and 100-mg vials in packs of 5 for £1379.04 (excluding VAT; 'Monthly index of medical specialities' [MIMS], November 2010). The mean cost of bendamustine per person taken from the manufacturer's submission is £4741.54, assuming a body surface area of 1.72 m² and an average treatment course of 4.9 cycles (including product wastage). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of bendamustine and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

Clinical effectiveness

- 3.1 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 chronic lymphocytic leukaemia, for whom fludarabine-based therapy was not considered appropriate. It was a phase III, open-label (because of the method of administration), multicentre parallel group international study comparing initial treatment of patients with Binet stage B or C chronic lymphocytic leukaemia. This study was carried out at 45 sites across Europe, including one centre in the UK. Recruitment started in November 2002 and follow-up was completed in June 2008, 1 year after the last enrolled patient completed treatment.
- 3.2 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 World Health Organization (WHO) performance status scores: 67% with WHO 0, 28% with WHO 1 and 3% with WHO 2. The manufacturer also highlighted that a study of fludarabine combination therapy (trial CLL8) was recruiting at the same time as trial 02CLLIII. Therefore, clinicians nominating their patients for a clinical trial would have judged the suitability of fludarabine-based therapy for them and put them forward for the most appropriate treatment.

- 3.3 Patients in trial 02CLLIII 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 in kg = height in cm minus 100) orally on days 1 and 15 or, if necessary, given as divided doses on days 1-2 and days 15-16 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 treatment cycles and at the end of treatment. 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 = 1.7) in both groups. Following first-line treatment with chlorambucil, patients who remained progression-free for at least 12 months could be re-treated with chlorambucil. 63.1% received one or more re-treatment cycles. The mean number of cycles for those patients who were re-treated was 1.13.
- 3.4 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). 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 European Organisation for Research and Treatment of Cancer [EORTC] criteria); and adverse events (toxicities).

Response rates

- 3.5 Bendamustine was associated with a significantly higher overall response rate compared with chlorambucil (68% of participants compared with 31% respectively, 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% respectively, 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%

respectively, RR = 4.12, 95% CI 1.56 to 10.88). There was no statistically significant difference between treatments for partial response.

- 3.6 Regardless of Binet stage, there was 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 compared with 28% and 33% respectively within the chlorambucil arm ($p > 0.6$).

Survival

- 3.7 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).
- 3.8 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 (hazard ratio = 1.45, 95% CI 0.91 to 2.31, $p = 0.1623$). Death due to chronic lymphocytic leukaemia 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).
- 3.9 The manufacturer presented a breakdown of overall survival according to response rate. The manufacturer suggested that the numbers of patients in whom complete response and nodular partial response was seen, drove the overall survival advantage. The manufacturer also suggested that this was 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.

- 3.10 The manufacturer reported on an unpublished abstract that described results from study 02CLLIII after a median observation time of 54 months. The results from this study showed that bendamustine offered significantly greater response rates and progression-free survival and a much longer time to next treatment than chlorambucil. The manufacturer commented that this confirmed 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

- 3.11 During the treatment period, patients' quality of life was assessed using the 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 explained in its submission that the quality-of-life data collected during the trial showed that patients receiving the 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

- 3.12 The manufacturer's submission reported that most adverse events in study 02CLLIII were haematological, that these were generally higher in number 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. 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.
- 3.13 Overall, 54 (34%) of patients in the bendamustine group and 46 (31%) in

the chlorambucil group needed 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 reactions (nine patients treated with bendamustine and two treated with chlorambucil).

Cost effectiveness

- 3.14 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 chronic lymphocytic leukaemia 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 started with the patient entering a course of first-line treatment with either bendamustine or chlorambucil. Patients who remained progression free on chlorambucil for at least 12 months were re-treated with chlorambucil, whereas the base-case analysis assumed that patients could be treated with bendamustine only once. All patients began treatment in the stable disease health state. In the next model cycle they moved to the state representing their best overall response: stable disease, partial response, complete response, progressive disease or death. The patient moved around the model according to transition probabilities, derived from study 02CLLIII, until death. Alternatively if the patient entered the progressive state they could move to a second stage of the model, in which they had an equal chance of being offered treatment with fludarabine plus cyclophosphamide, or best supportive care.
- 3.15 If the patient entered the fludarabine plus cyclophosphamide treatment option, they were modelled as receiving treatment, starting in the stable disease state, then moving around the model in the same way as for first-line treatment. In this part of the model, if the patient moved into the

progressive disease stage they may have moved into supportive care, or entered the death state. At the supportive care stage, the patient received best supportive care until death. In total, 39 health states were modelled.

- 3.16 The costs used were from the perspective of the NHS and Personal Social Services (PSS) and were for drug acquisition, drug administration, disease management (such as visits to the haematologist, blood tests and blood transfusions), and for adverse events. The manufacturer commissioned an advisory board of five UK haematologists to investigate treatment pathways and estimate resource use for other costs of chronic lymphocytic leukaemia 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.
- 3.17 The mean cost of bendamustine per person assumed in the manufacturer's model was £4741.54 assuming a body surface area of 1.72 m², and an average treatment course of 4.9 cycles (including product wastage). Drug costs for chlorambucil and fludarabine plus cyclophosphamide were taken from the 'British national formulary' (edition 59). The mean cost of chlorambucil was £91.76 based on a Broca's weight of 68.73 kg for 4.9 treatment cycles. The mean cost of second-line treatment with fludarabine plus cyclophosphamide was £1250.54. Total costs of treatment (including cost of therapy and other costs – the costs of infusion, haematologist outpatient visits, blood count, biochemistry and antiemetic cost per cycle) were: £7673.00, £1136.60 and £2232.51 for treatment with bendamustine, chlorambucil, and fludarabine plus cyclophosphamide respectively.
- 3.18 Utilities in the manufacturer's model were derived using two different methods. One 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). With the exception of the treatment period (see below), utility values were assigned to health states based on Beusterien et al (2010).

- 3.19 In the second method, utilities in the treatment period were based on the quality-of-life data collected in study 02CLLIII (EORTC-C30) and obtained by using a mapping equation to derive EQ-5D utility estimates from the EORTC-C30. 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. For the bendamustine and chlorambucil treatment period (about 4.9 months), utility was set to 0.70 in both groups.
- 3.20 The results of the manufacturer's model gave a total cost (including cost of therapy and other costs [see 3.17]) per cycle of £49,000 for bendamustine and £33,821 for chlorambucil. Bendamustine was associated with more quality-adjusted life years (QALYs) than chlorambucil: 4.82 QALYs compared with 3.55 QALYs, resulting in a cost per QALY gained of £11,960 for bendustamine. Treatment with bendamustine was predicted to yield a mean of 1.27 extra QALYs compared with chlorambucil, of which 0.98 were gained in progression-free survival and 0.29 in progressive disease. Treatment with bendamustine was expected to cost £15,179 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 (+£4576), first-line drug administration (+£1216), blood transfusion (+£6299), and haematologist visits in progressive disease (+£2379).
- 3.21 The manufacturer presented estimates of cost effectiveness 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 suggested that the treatment effect of bendamustine was maintained across these subgroups, although uncertainty around the treatment effects was high due to the smaller sample sizes. Incremental cost-effectiveness ratios (ICERs) were lower than £15,000 regardless of subgroup.
- 3.22 The manufacturer conducted univariate sensitivity analyses 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, time horizon, patient's body surface

area, time to retreatment, response rates and costs. The one-way sensitivity analyses had little effect on the cost effectiveness of bendamustine relative to chlorambucil, with results of the cost per QALY gained ranging from £4886 to £13,387.

- 3.23 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.

ERG comments

Clinical effectiveness

- 3.24 The ERG commented that the manufacturer conducted appropriate searches, that the submission contained all the relevant studies and the relevant data within those studies, and that the submitted evidence in the manufacturer's submission adequately reflected the decision problem.
- 3.25 The ERG noted that the evidence base for this appraisal comprised only one randomised controlled trial (RCT). Nevertheless, the ERG found that study 02CLLIII was of good quality and reflected 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 chronic lymphocytic leukaemia. The ERG noted that study 02CLLIII was an international study, employing 45 centres across Europe, one of which was in the UK, but that no further details were reported about the other sites involved or the number of patients recruited in the UK, and that no analysis by country was performed. The ERG commented that since any multicentre trial may have inherent variations in disease management, knowing the proportion of trial participants based in the UK may improve confidence about applicability of trial results in this country.

- 3.26 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 O2CLLIII with a WHO performance status of 0, coupled with a relatively young mean age of 63–64 years, were representative of the target population.
- 3.27 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.
- 3.28 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 stopped therapy were not followed up, introducing the possibility of attrition bias.
- 3.29 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 O2CLLIII was broadly consistent with UK clinical practice and so this should be considered a relatively minor issue.

Cost effectiveness

- 3.30 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 haematological malignancies in that the progression-free survival and progressive disease health states were modelled. The ERG considered the model to be more sophisticated than some models for the following two reasons. First, progression-free survival was split according to response: complete response, partial response or stable disease. The depth of response influenced the utilities (better responses having higher utility) and the disease-management costs (better responses carrying lower costs). Second, re-treatment 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.

- 3.31 The ERG commented that the utility data to inform the cost-effectiveness modelling were sparse, however it 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, the ERG stated that this method is supported within the NICE reference case. The ERG noted that the manufacturer based 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 ERG found the cost effectiveness of bendamustine to be relatively insensitive to the source of the utilities.
- 3.32 The ERG was broadly satisfied with the costs used in the model. The ERG found that the modelled dosing schedules of bendamustine and chlorambucil and that the assumption of a mean of 4.9 treatment cycles per patient (as experienced in the RCT), were appropriate. It considered that there was no consensus on the appropriate dosing of chlorambucil, but that any differences between the dosing of chlorambucil in the model and in clinical practice would have a negligible effect on the cost effectiveness of bendamustine, because chlorambucil has a low acquisition cost. The ERG was satisfied with the assumptions about the costs of administration of bendamustine. The ERG considered that the cost for an outpatient visit to a haematologist (per cycle) for a patient taking bendamustine should be £270 not £131. However, the effect of this on the ICER was marginal.
- 3.33 The manufacturer extrapolated survival over many years within the model. The ERG cautioned that although the extrapolation in the model was considered to be reasonable, the extrapolation introduced uncertainty to the modelled overall survival, and hence to the cost effectiveness of bendamustine.

- 3.34 The manufacturer's base-case ICER for bendamustine versus chlorambucil was £12,000 per QALY gained (rounded up in the ERG report from £11,960 in the manufacturer's submission). The ERG disagreed with the assumptions used in the manufacturer's model on three main points (see sections 3.35 to 3.37). However when the ERG used revised figures in the manufacturer's model, the resulting ICERs were lower than the base-case ICER estimated by the manufacturer in all instances.
- 3.35 The ERG disagreed with the assumption in the manufacturer's economic evaluation that patients with progressive disease had a blood transfusion every 3 weeks. Instead, the ERG believed a more appropriate assumption was that patients received 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 £7000 per QALY gained.
- 3.36 The ERG believed that the treatment effect modelled by the manufacturer in terms of the hazard ratio for overall survival was too high, biasing the cost effectiveness in favour of bendamustine. When the ERG applied the hazard ratio for overall survival from the most mature data provided by the manufacturer (1.30 instead of 1.66 as assumed in the manufacturer's model), the manufacturer's base-case ICER decreased from £12,000 to £11,700 per QALY gained. When the ERG applied the hazard ratio of 1.30 for overall survival together with the revised assumptions for blood transfusion costs (see section 3.35), the ICER increased from £7000 to £9700 per QALY. The ERG explained this paradox as follows: when the hazard ratio was reduced, the incremental discounted QALYs fell substantially from 1.27 to 0.70. However, the base-case incremental blood transfusion costs also decreased substantially, from £6300 to £1400. The net effect was 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 fell substantially, the incremental blood transfusion costs remained at zero when the hazard ratio reduced. Therefore, the ICER increased substantially, from £7000 to £9700 per QALY gained.
- 3.37 The ERG disagreed with the manufacturer's assumptions about dose intensities for bendamustine and chlorambucil and frequency of visits to

a haematologist when not treated. Changing 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 decreased from £12,000 to £11,600 per QALY gained. Changing the assumption for the frequency of visits to a haematologist when not treated, the ICER decreased from £12,000 to £11,500 per QALY gained.

- 3.38 When the ERG updated the manufacturer's model with the revised assumptions for blood transfusions, the hazard ratio for overall survival, dose intensities and frequency of visits to a haematologist, as outlined in sections 3.35 to 3.37, the ICER decreased from £12,000 to £9,400 per QALY gained.
- 3.39 The ERG stated that it was not possible to confirm the ICERs in the subgroups (patient's age \geq 65 years; WHO status \geq 1; and patient's age \geq 65 years plus WHO status \geq 1) 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.
- 3.40 The ERG highlighted that a higher proportion of patients in the chlorambucil arm of the RCT were given second-line drugs compared with patients in the bendamustine arm. The ERG was broadly satisfied with the manufacturer's approach to incorporating second-line drug costs, but explored two alternative methods. 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 gained, and the ERG's revised base-case ICER of £9,400 fell to less than £8,700 per QALY gained. In the second method, the ERG did not cost the second-line drugs received in the RCT, but estimated overall survival for each treatment arm assuming no second-line drug treatment. The ICERs fell in the same way.
- 3.41 Although the manufacturer identified no cost-effectiveness studies, the ERG identified a recent poster reporting a cost-effectiveness study of bendamustine versus alemtuzumab and chlorambucil for chronic

lymphocytic leukaemia, 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 gained, or about £33,000 per QALY gained. 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 predicted a far lower life expectancy for people taking bendamustine, compared with those taking bendamustine in study 02CLLIII (predicted median overall survival of 6.1 years for the US study versus 8.3 years for study 02CLLIII) and highlighted the influence of overall survival gains in determining the cost effectiveness of bendamustine.

- 3.42 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bendamustine, having considered evidence on the nature of chronic lymphocytic leukaemia in patients for whom fludarabine combination chemotherapy is not appropriate and the value placed on the benefits of bendamustine by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

- 4.2 The Committee discussed the place of bendamustine in the clinical pathway for chronic lymphocytic leukaemia. The Committee heard from the clinical specialists that bendamustine is used as a first-line treatment in UK clinical practice when fludarabine combination chemotherapy is not considered an appropriate treatment, that a second round of bendamustine may be offered, and that bendamustine is sometimes used as a second-line treatment. The Committee noted that second-line treatment is currently outside of bendamustine's UK marketing authorisation.
- 4.3 The Committee heard from the clinical specialists that bendamustine is less toxic than fludarabine combination therapy and is a useful addition to the available treatments for patients with chronic lymphocytic leukaemia in whom fludarabine combination therapy is unsuitable. The only available treatment for these patients is chlorambucil. The Committee heard that although bendamustine is slightly more toxic than chlorambucil and is associated with more adverse events, the clinical specialists considered bendamustine to be the more effective treatment. The Committee also noted the views of the patient groups in their submissions to NICE that because of its improved efficacy compared with chlorambucil, people with the condition would be willing to accept the side effects associated with bendamustine. The Committee was satisfied from the testimonies of the clinical specialists and patient experts that bendamustine represents an important treatment for

patients with chronic lymphocytic leukaemia for whom fludarabine combination therapy is not appropriate.

- 4.4 The Committee heard from the clinical specialists that there are no definitively agreed criteria for deciding when fludarabine combination therapy is unsuitable as a first-line treatment for patients with chronic lymphocytic leukaemia. They commented that there is a growing consensus that patients should be offered the most effective treatment that they can tolerate first. Therefore fludarabine combination therapy (that is, fludarabine, cyclophosphamide and rituximab) is first choice unless there are important factors related to age, physical fitness and the presence of comorbidities to suggest that fludarabine combination therapy should not be used. The Committee accepted, therefore, that any future NICE-recommended use of bendamustine would be determined by clinical judgement based on the factors listed above.
- 4.5 The Committee discussed the clinical trial data from study 02CLLIII and agreed with the ERG's comments that it was a well-conducted RCT. It noted the higher response rates and longer progression-free survival (21.6 months versus 8.3 months) in patients treated with bendamustine compared with patients treated with chlorambucil. The Committee was concerned, however, about two issues related to the clinical trial evidence. The Committee's first concern was that the trial population may not have been representative of the population that would be treated with bendamustine in clinical practice. The Committee noted the exclusion from trial 02CLLIII of patients with comorbidities including abnormal liver, renal or cardiac function. It was also aware of the high performance status of the majority of participants and the relatively low mean age (63–64 years). However the Committee was reassured by the subgroup analysis conducted by the manufacturer, which demonstrated the clinical effectiveness of bendamustine relative to chlorambucil in the trial participants who had a lower performance status and in patients aged 65 years and over. It also accepted that the exclusion criteria were standard and that there was no reason to suppose that the results would not hold in people with a lower performance status, or people with comorbidities, in particular renal impairment (which is a contraindication of fludarabine). The Committee agreed that inferences could be made about the clinical effectiveness of bendamustine for the population

specified in the marketing authorisation, using the available trial data.

- 4.6 The Committee's second concern about the evidence from study 02CLLIII was that it may have underestimated the clinical effectiveness of chlorambucil. The Committee heard from the clinical specialists how patients treated with chlorambucil in another trial, CLL4 (which compared chlorambucil with fludarabine and fludarabine plus cyclophosphamide), experienced higher response rates and longer progression-free survival compared with the patients treated with chlorambucil in trial 02CLLIII. The Committee discussed the possible reasons for the differences in the results between the two trials. It noted the views of the clinical specialists that the variation in the results may have been because of differences in the patient populations and differences in the doses of chlorambucil used.
- 4.7 The Committee explored the differences in the patient populations between the two trials. It heard from the manufacturer that one way in which the patient populations of the two trials differed was that the 02CLLIII study did not include people with Binet stage A chronic lymphocytic leukaemia. It also heard from the clinical specialists that the patient population in the CLL4 trial may have been healthier than the patient population in trial 02CLLIII. The Committee was satisfied that the differences between the patient populations in the two trials may have contributed to the differences in the results for chlorambucil.
- 4.8 The Committee discussed the different doses of chlorambucil used in the 02CLLIII study compared with the CLL4 trial. The clinical specialists explained that the dose used in trial 02CLLIII was consistent with the dose used for other chronic lymphocytic leukaemia studies, and that the dose used in the CLL4 study was unique at the time the study was set up. The clinical specialists also explained that the cumulative dose for chlorambucil in the 02CLLIII study was approximately 85% of the dose used in the CLL4 trial, which might explain the difference in progression-free survival in the chlorambucil arms of the two trials. The Committee heard from the clinical specialists that many different doses of chlorambucil were used in UK clinical practice, but that there was an increasing shift towards the dose used in the CLL4 study, following on from the results of that trial. Furthermore, new chronic lymphocytic

leukaemia trials with chlorambucil as a comparator were increasingly using the same dose as was used in the CLL4 study. The Committee accepted that the doses of chlorambucil used in the two trials may have contributed to the differences in the results but that the precise impact of this was unknown, and that this represented an important area for future research. The Committee concluded that there was sufficient evidence to demonstrate that bendamustine was more clinically effective than chlorambucil, leading to higher response rates and longer progression-free survival.

Cost effectiveness

- 4.9 The Committee discussed the manufacturer's economic model. It agreed with the ERG that the manufacturer's model was of high quality and was more sophisticated than other models in the disease area. The Committee discussed that because of the added complexity of the model, the data to inform some of the model parameters, such as transition probabilities (particularly for second-line treatment) were sparse. On balance, the Committee considered that the model was appropriate and fit for purpose.
- 4.10 The Committee noted that the cost per QALY gained of treatment with bendamustine compared with chlorambucil was £12,000 in the manufacturer's base-case analysis. The Committee discussed the robustness of the ICER to the subgroup and sensitivity analyses conducted by the manufacturer. The Committee was satisfied with the effect of the subgroup and sensitivity analyses, noting that the ICER remained lower than £15,000 in all of the analyses.
- 4.11 The Committee was aware that the ERG had made some adjustments to the assumptions used in the manufacturer's economic model about the frequency of blood transfusions, the hazard ratio for overall survival, the dose intensity of bendamustine and chlorambucil and the frequency of visits to a haematologist. The Committee heard from the clinical specialists that the ERG's changes to the assumptions reflected clinical practice. The Committee noted that the effect of these adjustments caused the ICER to fall from £12,000 to £9400, thus becoming more favourable to bendamustine than the base-case ICER presented by the

manufacturer. The Committee agreed that the adjustments made by the ERG were reasonable and was satisfied with the resulting effect on the ICER.

- 4.12 The Committee discussed the potential effect on the ICER of comparing bendamustine with the higher dose of chlorambucil given in the CLL4 study. The Committee considered that an increased dose of chlorambucil would push up the cost of chlorambucil as well as increase the number of QALYs gained. The Committee accepted that since the influence of a higher chlorambucil dose on the clinical effectiveness of the treatment had not been determined, any resulting effect on the ICER could not be quantified with any precision. The Committee agreed, however, that the ICER of bendamustine would be unlikely to increase above the level generally considered to be a cost-effective use of NHS resources. It therefore concluded that bendamustine should be recommended as a first-line treatment option for patients with chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is not appropriate.

Summary of Appraisal Committee's key conclusions

TA216	Appraisal title: bendamustine for the first-line treatment of chronic lymphocytic leukaemia	Section
Key conclusion		
Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.		1.1
Current practice		
Clinical need of patients, including the availability of alternative treatments	Bendamustine is less toxic than fludarabine combination therapy and is a useful addition to the available treatments for patients with chronic lymphocytic leukaemia in whom fludarabine combination therapy is unsuitable. The only available treatment for this group of patients is chlorambucil.	4.3
The technology		

Proposed benefits of the technology	Bendamustine is considered to be a more effective treatment than chlorambucil.	4.3, 4.8
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	People treated with bendamustine had, on average, higher response rates and longer progression-free survival than people treated with chlorambucil.	4.5
What is the position of the treatment in the pathway of care for the condition?	Bendamustine is used as a first-line treatment in UK clinical practice when fludarabine combination chemotherapy is not considered an appropriate treatment.	4.2
Adverse effects	Bendamustine is associated with more adverse events compared with chlorambucil. However, because of its improved efficacy in comparison with chlorambucil, the patient groups considered that people with the condition would be willing to accept the side effects associated with bendamustine.	4.3

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee agreed with the ERG's comments that study 02CLLIII was a well conducted randomised controlled trial.	4.5
	The Committee was concerned that the evidence from study 02CLLIII may have underestimated the clinical effectiveness of chlorambucil. The Committee was satisfied that the differences between the patient populations in the 02CLLIII study and the CLL4 study may have contributed to the differences in the results for chlorambucil. The Committee accepted that the doses of chlorambucil used in the two trials may also have contributed to the differences in the results, but that the precise impact of this was unknown. The Committee concluded that there was sufficient evidence to demonstrate that bendamustine is more clinically effective than chlorambucil.	4.6, 4.7, 4.8

Relevance to general clinical practice in the NHS	The Committee was concerned that the trial population in study 02CLLIII may not have been representative of the population that would be treated with bendamustine in clinical practice. The Committee agreed that inferences could be made about the clinical effectiveness of bendamustine for the population specified in the marketing authorisation, using the available trial data.	4.5
Uncertainties generated by the evidence	There are no definitively agreed criteria for deciding when fludarabine combination therapy is unsuitable as a first-line treatment for patients with chronic lymphocytic leukaemia. Fludarabine combination therapy (that is, fludarabine, cyclophosphamide and rituximab) is generally first choice unless there are important factors related to age, physical fitness and the presence of comorbidities to suggest that fludarabine combination therapy should not be used.	4.4
	The influence of a higher chlorambucil dose on the relative clinical effectiveness of bendamustine has not been determined, and this represents an important area for future research.	4.8, 4.12
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The subgroup analyses conducted by the manufacturer demonstrated clinical effectiveness of bendamustine relative to chlorambucil in the trial participants who had a lower performance status and in patients aged 65 years and over.	4.5
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Clinical trial data from study 02CLLIII showed higher response rates and longer progression-free survival (21.6 months versus 8.3 months) in patients treated with bendamustine compared with patients treated with chlorambucil.	4.5
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee agreed with the ERG that the manufacturer's model was of high quality and was more sophisticated than other models in the disease area.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee discussed that because of the added complexity of the model, the data to inform some of the model parameters, such as transition probabilities (particularly for second-line treatment) were sparse. On balance, the Committee considered that the model was appropriate and fit for purpose.	4.9
	The ERG had made some adjustments to the assumptions used in the manufacturer's economic model about the frequency of blood transfusions, the hazard ratio for overall survival, the dose intensity of bendamustine and chlorambucil and the frequency of visits to a haematologist. The Committee agreed that the adjustments made by the ERG were reasonable and was satisfied with the resulting effect on the ICER (a change from £12,000 to £9400).	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?	There were no issues raised about health-related quality-of-life values that were thought to be relevant. No health-related benefits were identified that were not included in the economic model.	n/a

Are there specific groups of people for whom the technology is particularly cost effective?	The base-case ICER was found to be robust to subgroup analysis. The ICER remained lower than £15,000 in all of the analyses.	4.10
What are the key drivers of cost effectiveness?	Higher response rates and longer progression-free survival.	4.5
Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that the adjustments made by the ERG to the manufacturer's model were reasonable and it was satisfied with the resulting change in the ICER from £12,000 to £9400. The Committee accepted that because the influence of a higher chlorambucil dose on the clinical effectiveness of the treatment had not been determined, any resulting effect on the ICER could not be quantified with any precision. The Committee agreed, however, that the ICER of bendamustine would be unlikely to increase above the level generally considered to be a cost-effective use of NHS resources.	4.11, 4.12
Additional factors taken into account		
Patient access schemes (PPRS)	No patient access schemes were submitted.	n/a
End-of-life considerations	The Committee did not discuss end-of-life considerations because bendamustine was considered to be cost-effective.	n/a
Equalities considerations and social value judgements	No equalities issues raised were thought to be relevant.	n/a

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic lymphocytic leukaemia and the doctor responsible for their care thinks that bendamustine is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 To help organisations put this guidance into practice, NICE has developed a costing template and report that can be used to estimate the national and local savings and costs associated with implementation. These are available on our website (<http://guidance.nice.org.uk/TA216>).

6 Recommendations for further research

- 6.1 Research should be carried out to compare the clinical effectiveness of bendamustine with chlorambucil at the higher dose used in the CLL4 trial.

7 Related NICE guidance

- [Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab](#). NICE technology appraisal guidance 202 (2010).
- [Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia](#). NICE technology appraisal guidance 193 (2010).
- [Rituximab for the first-line treatment of chronic lymphocytic leukaemia](#). NICE technology appraisal guidance 174 (2009).
- [Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukemia](#). NICE technology appraisal guidance 119 (2007).
- [Improving outcomes in haematological cancers](#). NICE cancer service guidance (2003).

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review in December 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
February 2011

Appendix A: Appraisal Committee members and NICE project team

A 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 four 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 Daniele Bryden

Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett

Director for Health Improvement and Medical Director, NHS Barnet, London

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Dr Christine Davey

Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York

Richard Devereaux-Phillips

Public Affairs and Reimbursement Manager UK and Ireland, Medtronic, Watford

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Wasim Hanif

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Eugene Milne

Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Dr Neil Myers

General Practitioner, Glasgow

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Ellen Rule

Programme Director, NHS Bristol

Professor Andrew Stevens

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

Professor Paul Trueman

Professor of Health Economics, Brunel University, London

Dr Judith Wardle

Lay Member

B NICE project team

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

Dr Helen Starkie

Technical Lead

Zoe Charles

Technical Adviser

Lori Farrar

Project Manager

Appendix B: Sources of evidence considered by the Committee

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

- Hoyle M, Crathorne L, Jones-Hughes T et al. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia, October 2010.

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 bendamustine for the treatment of chronic lymphocytic leukaemia by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- Napp Pharmaceuticals

II) Professional/specialist and patient/carers groups:

- British Society for Haematology
- Cancer Research UK
- Chronic Lymphocytic Leukaemia Support Association (CLLSA)
- Leukaemia CARE
- Lymphoma Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Chronic Lymphocytic Leukaemia Forum

III) Other consultees:

- Department of Health
- Welsh Assembly Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Leukaemia & Lymphoma Research
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme
- NHS Quality Improvement Scotland
- Peninsula Technology Assessment Group, University of Exeter (PenTAG)

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on bendamustine for the treatment of chronic lymphocytic leukaemia by providing oral evidence to the Committee.

- Dr Chris Fegan, nominated by Royal College of Physicians, NCRI, RCR, ACP, JCCO – clinical specialist
- Professor Andrew Pettitt, nominated by Royal College of Pathologists and United Kingdom Chronic Lymphocytic Leukaemia Forum – clinical specialist
- Jane Barnard, nominated by Chronic Lymphocytic Leukaemia Support Association – patient expert
- Chonette Taylor, nominated by Chronic Lymphocytic Leukaemia Support Association – patient expert

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

- Napp Pharmaceuticals

Changes after publication

February 2014: implementation section updated to clarify that bendamustine is recommended as an option for treating chronic lymphocytic leukaemia. Additional minor maintenance update also carried out.

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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Accreditation

