NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

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

Napp Pharmaceuticals Limited

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Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia amongst adults in industrialised countries.[1] In 2007, the incidence of CLL in the UK was 2.8 per 100,000 and 2,339 new cases were diagnosed.[2] The risk of developing CLL increases with age and it accounts for 40% of all leukaemia cases in those aged over 65 years.[3] The median age at diagnosis is between 65 and 70 years.

For most patients, CLL is incurable, and follows a relapsing and remitting course. It is estimated that around one-third of patients will be asymptomatic and never require treatment. The subset of patients who do need treatment is heterogeneous in terms of age, co-morbidities and performance status, and clinicians have to decide whether to adopt a 'palliative' approach (treat symptomatic disease with regimens causing minimal treatment-related toxicity) or to aim for deep remission (complete response; CR), and hence prolonged progression-free survival (PFS) and, hopefully, longer overall survival.

CLL is typically responsive to several courses of chemotherapy before the gradual onset of extensive bone marrow infiltration, bulky disease and recurrent infection. Eventually, the disease may transform into a localised high-grade lymphoma (Richter's transformation) or into prolymphocytic leukaemia.

Bendamustine

Bendamustine hydrochloride (***Levact*** i.v.) is an alkylating anti-tumour agent with unique activity. Its anti-tumour effect is based essentially on cross-linking of DNA strands, which causes impairment of DNA matrix functions and inhibition of DNA synthesis. In human tumour cell lines, bendamustine's activity profile has been shown to be markedly different from that of other alkylating agents. There was little or no cross-resistance in human tumour cell lines with different resistance mechanisms; this is at least partly owing to a comparatively persistent DNA interaction. Clinical trials have shown that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab (however, the number of patients assessed was small).[4]

Bendamustine was granted a UK marketing authorisation in August 2010 (see Sections 1.3 and 1.4). It is licensed for:

- first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate;

- indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during, or within 6 months following, treatment with rituximab or a rituximab-containing regimen;
- front-line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment.

This submission focuses on the use of bendamustine hydrochloride in the first-line treatment of CLL.

Bendamustine is available as a white, crystalline powder for reconstitution as a concentrate for solution for infusion. It is available in vials containing 25 mg or 100 mg bendamustine. The 25 mg vials are available in packs of 5 (costing £347.26) and 20 (costing £1379.04). The 100 mg vials are available in packs of 5 (costing £1379.04).

As monotherapy for first-line treatment of CLL, bendamustine should be given at a dose of 100 mg/m^2 body surface area on Days 1 and 2 every four weeks. It is expected that maximal response is seen within six cycles. The mean number of cycles in the pivotal trial presented here was 4.9 (±1.7).

Clinical evidence

The clinical evidence presented in this submission is drawn from a single Phase III, randomised, controlled trial against the alkylating agent, chlorambucil, which is the most commonly used agent in the patient population concerned (i.e. patients who are unsuitable for fludarabine-containing regimens). These patients generally tend to be the more elderly with co-morbidities and lower performance status, and whilst chlorambucil is generally well tolerated by these patients, it has relatively poor efficacy in terms of CR and depth of remission.

A deep remission is an important treatment goal in CLL because it has been shown to be linked to longer PFS.[5-8] In the case of FCR (fludarabine/cyclophosphamide plus rituximab; the 'gold standard' fludarabine-containing first-line regimen), this has been shown to translate into an overall survival benefit for some patients.

Recent data presented at the 2009 American Society for Hematology meeting comparing FCR with FC (fludarabine/cyclophosphamide) in first-line treatment of CLL suggest that higher CR rates (and hence longer PFS) with this regimen correlate with higher overall survival rates in patients with Binet stage A or B disease.[9] The CR rate was 44.1% with FCR and 21.8% with FC (P<0.001). The overall survival rate at 37.7 months was 84.1% with FCR and 79% with FC (P = 0.01).

To date, treatments for patients unsuitable for fludarabine-based regimens have not shown an overall survival benefit. There is, therefore, a clear need for new, effective

options to treat such patients, especially if they can confer an advantage in terms of PFS and overall survival.

The results from the study described in this submission (Study 02CLLIII)[10-13] show that bendamustine offers substantial benefits over chlorambucil for patients with previously untreated CLL (see Section 5.5 for full details). Compared with chlorambucil, bendamustine demonstrated:

- a >15-fold increase in CR rate (31% *vs.* 2%; *P*<0.0001);
- significantly longer median progression-free survival (21.6 months *vs.* 8.3 months; *P*<0.0001);
- a >2-fold longer median duration of response (21.8 months *vs.* 8.0 months; *P*<0.0001);
- a numerical overall survival benefit [31 deaths in the bendamustine group compared with 41 in the chlorambucil group; hazard ratio (95% CI) = 1.45 (0.91 – 2.31); *P* = 0.1623]. Moreover, a more recent analysis of these data to be published at the end of the year confirms a statistically significant survival advantage for responders (see Section 6.10.5).

The high CR rate achieved with bendamustine is important, as there is evidence that the CR is associated with longer PFS.[5-8] Longer PFS equates to longer time without symptoms and treatment, and hence to longer time in an improved health state.[14] This correlates with improved quality of life for patients.

Economic model

A cost-utility analysis was performed whereby health effects were expressed as quality-adjusted life years (QALYs) and the perspective for costing was that of the NHS and PSS. The model had a lifetime time horizon and a Markov approach was used to enable estimation of health outcomes and costs associated with the anticipated (established) treatment pathway following first-line bendamustine or chlorambucil treatment. Study 02CLLIII was used to populate major model inputs.

Utility values were assigned to health states according to Beuerstein *et al*,[14] with the exception of the treatment period, which was based on the quality of life data collected in Study 02CLLIII. The utility values from Beuerstein *et al* were adjusted to closely reflect the patients in the study; with the stable disease health state utility values set equal to the utility values calculated from Study 02CLLIII during the treatment period.

All patients start treatment with stable disease (SD) and transition to their best response state within the first cycle. The model incorporated different response categories [SD, partial response (PR), CR and progressive disease (PD)]. This was important as the patient's quality of life and duration of response varies depending on the category of response.

Health states representing subsequent lines of therapy were included and were important in order to capture changes in quality of life as a patient received subsequent lines of therapy. This meant it was possible for a patient to exit PD after first-line therapy.

Extrapolation was required in order to estimate costs and health outcomes over a patient's lifetime. The model extrapolates time to progression and overall survival using parametric survival curves as not all patients had experienced these events during trial follow-up. The model also extrapolates transitions through health states [FC and best supportive care (BSC)] outside the period of trial follow-up based on data from Study 02CLLIII and the literature, as again these transitions were not observed during the trial period. Based on Robak *et al*,[15] chlorambucil is assumed to confer a positive but reduced benefit in the re-treatment setting. Bendamustine patients could not receive retreatment in the model.

The model assumes that bendamustine offers an overall survival benefit over chlorambucil. This assumption is made given the difference between arms observed with respect to this endpoint in Study 02CLLIII. In addition, a more recent analysis of these data confirms a statistically significant overall survival advantage in responders.

A summary of the base-case results is shown in Table 0.1. The ICER of £11,960 indicates that although bendamustine is associated with higher acquisition and administration costs compared to chlorambucil, the health benefits (increased quality of life and overall survival) generated by better and more durable response rates would be considered to be good value at conventional decision thresholds (£20 - 30,000/QALY). Extensive sensitivity analysis was undertaken and the ICER remained under £14,000 in all cases.

Table 0.1 Base-case cost-effectiveness results

	Bendamustine	Chlorambucil
Technology acquisition cost	£4,726	£150
Other costs	£44,274	£33,671
Total costs	£49,000	£33,821
Difference in total costs	N/A	£15,179
LYG	7.81	5.83
LYG difference	N/A	1.99
QALYs	4.82	3.55
QALY difference	N/A	1.27
ICER	N/A	£11,960

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: ***Levact***® i.v.

Approved name: Bendamustine hydrochloride

Therapeutic class: Alkylating agent (ATC code L01AA09)

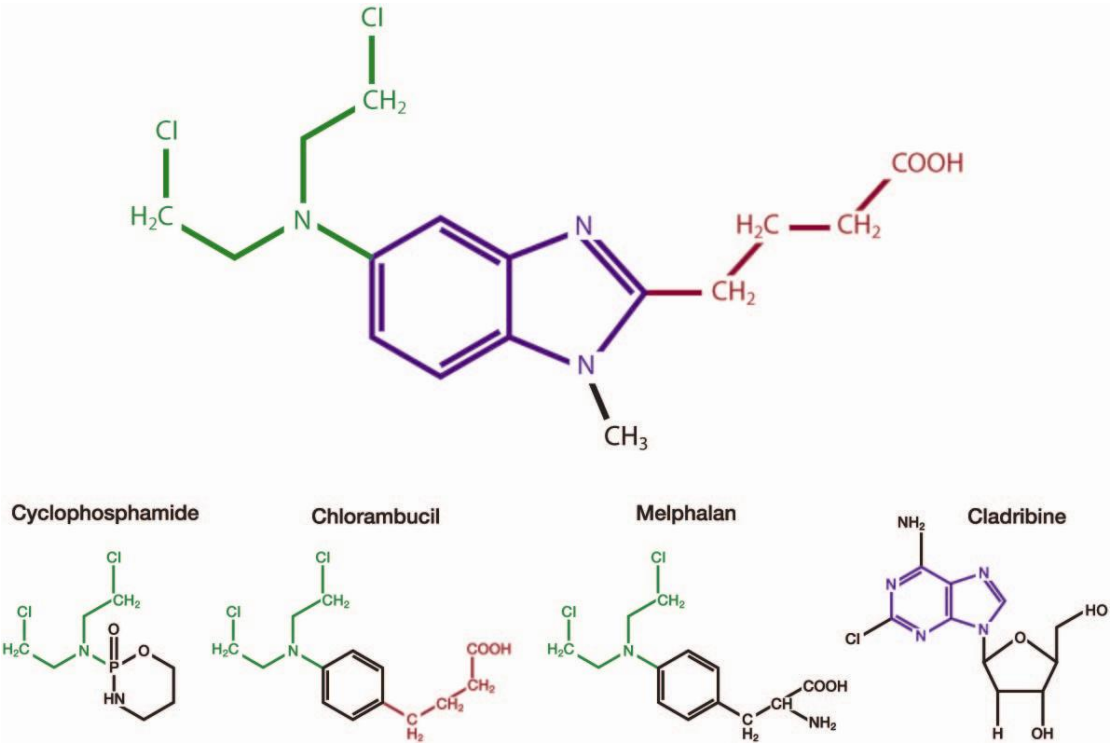
1.2 What is the principal mechanism of action of the technology?

Bendamustine has a unique mechanism of action that may be related in part to its distinct chemical structure. The bendamustine molecule is comprised of three structural elements:

- A 2-chloroethylamine group that bendamustine shares with other nitrogen mustard derivatives, including cyclophosphamide, chlorambucil and melphalan. The chloroethylamine group is largely responsible for bendamustine's alkylating action.
- A butyric acid side chain, which bendamustine shares with chlorambucil.
- A benzimidazole central ring system, which is shared with purine analogues such as fludarabine and cladribine.

Figure 1.1 shows the structure of bendamustine compared with cladribine and alkylators.

Figure 1.1 Structure of bendamustine



Several *in vitro* experiments have demonstrated bendamustine's unique mechanism of action, which appears to have several different cellular consequences.[16] In addition, bendamustine shows little or no cross-resistance in human tumour cell lines with different resistance mechanisms; this is at least partly owing to a comparatively persistent DNA interaction.

Clinical trials have shown that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab (however, the number of patients assessed was small).[4] The potential lack of cross resistance with these other agents makes bendamustine an important addition to the haematologist's armamentarium, especially in treating conditions such as CLL where the use of multiple lines of therapy is inevitable.

Unique mechanistic profile

Computer programs that identify similarities between the structure and function of thousands of clinically used and experimental anti-cancer drugs can predict whether two compounds are likely to share a mechanism of action. Function in these terms is based on growth inhibitory activity in 60 cell lines. Using this approach, melphalan, chlorambucil and cyclophosphamide's active metabolites have shown similar patterns to numerous other compounds (25, 25 and 23, respectively), most of which are DNA-alkylating agents.[16] In contrast, bendamustine did not strongly correlate with any other anti-cancer compounds, including other alkylating agents.

DNA strand breaks

In common with other alkylating agents, bendamustine cross-links DNA. This impairs DNA replication by the enzyme DNA polymerase, which leads to breaks in the double helix across one or two strands. However, bendamustine produces more extensive and more durable single and double strand breaks in human ovarian and breast carcinoma cell lines than the alkylators cyclophosphamide, cisplatinum (cisplatin), or carmustine.

Induction of apoptosis

Bendamustine induces apoptosis ('programmed cell death') in several *in vitro* tumour models through three complementary mechanisms:

- It seems to increase the expression of numerous genes that trigger apoptosis, including those linked to p53.
- It seems to regulate genes controlling expression of receptors that are members of the tumour necrosis factor (TNF) super-family.
- It has been shown to lead to an 8-fold up-regulation of Ser15-phosphorylated p53 in non-Hodgkin's lymphoma cells. Phosphorylation of p53 at Ser15 is a key event in triggering apoptosis. Chlorambucil produces only minor increases in phosphorylation, whereas phosphoramide mustard (an active metabolite of cyclophosphamide) has no effect.

Effect on DNA repair pathways

Damage to DNA by chemotherapeutics leads to up-regulation of various DNA repair pathways, depending on the mechanism of the DNA damage. Bendamustine induces a unique 'fingerprint' of DNA repair pathways compared with other alkylating agents. For example:

- it induces a 2.5-fold increase in expression of exonuclease-1 in non-Hodgkin's lymphoma (NHL) cells. In contrast, phosphoramide mustard and chlorambucil increased exonuclease-1 expression only 1.5- and 1.8-fold, respectively;
- it induces a repair pathway that uses base excision;
- conventional alkylating agents induce a repair mechanism in a Burkitt's lymphoma cell line that uses an enzyme called alkyltransferase. In two lymphoma cell lines, bendamustine did not seem to influence the alkyltransferase repair mechanism.

Variations in DNA repair pathways may contribute to the different activity and resistance profiles between bendamustine and conventional alkylating agents.

Inhibition of mitotic checkpoints and mitotic catastrophe

The cell cycle includes several checkpoints that send abnormal cells either for repair, or along an apoptotic pathway. Mitotic catastrophe is a necrotic form of cell death that occurs during metaphase and is morphologically distinct from apoptosis.

Hallmarks of this process are chromatin condensation and micronucleation. It has been shown to occur *in vitro* in the absence of p53 or in cells where caspase-dependent apoptosis is inhibited. Mitotic catastrophe may destroy cancer cells that are resistant to apoptosis following exposure to previous chemotherapeutics.

In addition to damaging DNA, bendamustine seems to inhibit certain cell cycle checkpoints in a number of cell lines. Therefore, it may allow cells with heavy DNA damage (such as that produced by alkylation) to enter the next stage in the cell cycle. This may trigger mitotic catastrophe. Two key strands of evidence support this suggestion:

- Flow cytometric analysis of the effect of several chemotherapeutic agents (used in equitoxic doses) on cell cycle progression in an NHL cell line showed that bendamustine increased the proportion of cells in S phase (DNA replication). Compared with a control rate of 37%, 60% of bendamustine-treated cells entered S phase. Figures for chlorambucil and phosphoramide were 45% and 37%, respectively.
- Chromatin condensation and micronucleation are hallmarks of mitotic catastrophe. One study treated multi-drug resistant breast and colon cancer cell lines with pan-caspase (apoptotic) inhibitors. In these cells, bendamustine induced such morphological changes in 26% of cells, compared with 6% of untreated (DMSO) controls.

The apparent ability of bendamustine to cause mitotic catastrophe in certain cell lines, as well as apoptosis, may help account for bendamustine's effectiveness in drug resistant cells.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The CHMP issued a positive opinion on bendamustine on 18th March 2010. The EC formally accepted the decision on 7th July 2010 and the UK licence was granted by the MHRA on 3rd August 2010.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

There is currently no EPAR available for bendamustine.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

- First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
- Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during, or within 6 months following, treatment with rituximab or a rituximab-containing regimen.
- Front-line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There is one completed study in the first-line treatment of CLL (Study 02CLLIII).[10-13] There are currently no ongoing studies of bendamustine monotherapy in this indication.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Not applicable.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

The UK licence was granted under the DCP process. Recently, a number of other countries have been granted marketing authorisation under this process – these include France, Denmark and Austria.

Bendamustine is currently licensed in Germany under the trade name ***Ribomustin***® for:

- first-line therapy of advanced indolent non-Hodgkin lymphomas in a combination protocol;
- advanced multiple myeloma stage II with progress or stage III (acc. to Salmon and Durie) in combination with prednisone;
- chronic lymphocytic leukaemia.

It is also licensed under the same trade name in Switzerland for chronic lymphocytic leukaemia.

Bendamustine is licensed in the United States under the trade name ***Treanda*** for:

- treatment of patients with chronic lymphocytic leukaemia;
- treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

We expect that the SMC will assess bendamustine in this indication. Timelines for this assessment have not yet been set.

1.10 For pharmaceuticals, please complete the table below.

Table 1.1 Unit costs of technology being appraised

Pharmaceutical formulation	White crystalline powder for reconstitution as a concentrate for solution for infusion
Acquisition cost (excluding VAT)	25 mg x 5 = £347.26 25 mg x 20 = £1379.04 100 mg x 5 = £1379.04
Method of administration	Intravenous infusion over 30 – 60 minutes
Doses	As monotherapy for CLL: 100 mg/m^2 body surface area on Days 1 and 2, every 4 weeks
Dosing frequency	As above
Average length of a course of treatment	Approximately five months
Average cost of a course of treatment	Assuming a body surface area of 1.72 m^2 and an average treatment course of 4.9 cycles, the average cost of treatment is £4741.54. This estimate includes product wastage.
Anticipated average interval between courses of treatments	Bendamustine is licensed for first-line use only.
Anticipated number of repeat courses of treatments	n/a
Dose adjustments	<u>Non-haematological toxicity</u> A 50% dose reduction is recommended if a patient experiences CTC grade 3 toxicity. Interruption of treatment is recommended in cases of CTC grade 4 toxicity. <u>Hepatic impairment</u> No dose adjustment is needed in patients with mild hepatic impairment (serum bilirubin <1.2 mg/dl). A 30% dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2 - 3.0 mg/dl). There are no data available in patients with severe hepatic impairment (serum bilirubin >3.0 mg/dl). <u>Renal impairment</u> No dose adjustment is needed in patients with a creatinine clearance >10 ml/min. Experience is limited in patients with severe renal impairment. <u>Elderly patients</u> There is no evidence that dose adjustments are needed in elderly patients.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests or investigations are needed for selection of patients. Bendamustine is administered by intravenous infusion on two consecutive days; this will require provision of adequate resource in haematology chemotherapy clinics.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

There is no need for monitoring of patients receiving bendamustine over and above usual clinical practice.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No therapies are specifically recommended to be given as routine at the same time as bendamustine. Some therapies may be needed to treat or prevent adverse events experienced during treatment; details of these are given in Section 2.7.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Epidemiology

CLL is a B-cell lymphoproliferative disorder. Affected cells have a prolonged lifespan with impaired apoptosis, and accumulate in the blood, bone marrow, liver, spleen and lymph nodes.

CLL is the most common leukaemia among adults in industrialised countries.[1] In 2007, the incidence of CLL in the UK was 2.8 per 100,000 and 2,339 new cases were diagnosed.[2]

The risk of developing CLL increases with age and it accounts for 40% of all leukaemia cases in those aged over 65 years.[3] The median age at diagnosis is between 65 and 70 years.

Diagnosis

Patients may present with swollen lymph glands, anaemia, bruising or bleeding caused by thrombocytopenia, bacterial infections, and splenomegaly and/or hepatomegaly. However, most cases are diagnosed following a routine blood test.

For a definitive diagnosis, clinicians look for an absolute B-lymphocyte count of $>5 \times 10^9$/L. At least 70% of the white cells on a blood film are small lymphocytes. Immunophenotyping reveals cells that weakly express surface immunoglobulin that is monoclonal owing to the expression of only one form of light chain. CLL cells are also $CD5^+$ and $CD23^+$, but $CD79b^-$ and $FMC7^-$.

Prognostic markers

Prognostic markers can be tested for at diagnosis, as it is becoming increasingly clear from trial data that these may predict a number of variables, such as initial response to treatment, potential aggressiveness of the disease and prognosis.

Fluorescence in situ hybridisation (FISH) can be used to identify chromosomal abnormalities. The four most common abnormalities are deletion of 13q14, trisomy 12, deletions at 11q23, and structural abnormalities of 17p that involve the p53 gene. These abnormalities are significant in terms of prognosis (see Table 2.1).

In CLL, approximately 50% of patients have hypermutation in their immunoglobulin heavy chain (IgV_H) gene; the remaining 50% have no mutations in this gene. CLL with unmutated IgV_H genes has an unfavourable prognosis.

ZAP-70 is a protein tyrosine kinase that is involved in cell signalling following binding of an antigen by receptors on the lymphocyte. Normally, ZAP-70 is only expressed on T-cells, but in CLL, it can be expressed on B-cells. Its expression is associated with an unfavourable outcome.

Table 2.1 Prognostic factors in CLL

	Favourable	Unfavourable
Stage	Binet A	Binet B, C
Sex	Female	Male
Lymphocyte doubling time	Slow	Rapid
Bone marrow biopsy appearance	Nodular	Diffuse
Chromosomes	Deletion 13q14	Trisomy 12 Deletion 17p Deletion 11q23
IgV_H gene	Hypermutated	Unmutated
ZAP-70 expression	Low	High
CD38 expression	Negative	Positive
Lactate dehydrogenase levels	Normal	Raised

Staging

Staging a patient at diagnosis helps determine prognosis and decide on therapy. There are two staging systems: the Binet system is most commonly used in Europe and the Rai system is used in the United States. The Binet staging system is shown below.

Binet staging system[17]

Stage	Organ enlargement*	Haemoglobin (g/dL)	Platelets (x 10^9/L)
A	<3 areas	-	-
B	3 – 5 areas	≥10	≥100
C	Not considered	<10	and/or <100

*One area = lymph nodes >1 cm in neck, axillae, groin or spleen, or liver enlargement

Patients with stage A disease generally survive for at least 10 years. For patients with stage B disease, the median survival time is 5 to 8 years, and for those with stage C disease, it is 1 to 3 years.[18]

Course of the disease

For most patients, CLL is incurable (some may be cured by allogeneic bone marrow transplant), and follows a relapsing and remitting course. It is estimated that around one-third of patients (usually Binet stage A) will be asymptomatic and never need treatment. For those who do need treatment, depth and length of remission are important treatment goals.

The subset of patients requiring treatment is heterogeneous in terms of age, co-morbidities and performance status, and clinicians have to decide whether to adopt a 'palliative' approach (treat symptomatic disease with regimens causing minimal treatment-related toxicity) or to aim for deep remission (CR), and hence prolonged PFS and, hopefully, longer overall survival.

CLL is typically responsive to several courses of chemotherapy before the gradual onset of extensive bone marrow infiltration, bulky disease and recurrent infection. Eventually, the disease may transform into a localised high-grade lymphoma (Richter's transformation) or into pro-lymphocytic leukaemia.

Burden of the disease and quality of life

Although CLL is an incurable disease, patients can live for a number of years. However, CLL impacts on patients' quality of life in a number of ways. Compared with healthy controls, patients with untreated CLL report:

- impaired physical, role, cognitive and social functioning;[19,20]
- more sleep disturbance;[20]
- more fatigue, nausea and vomiting, appetite loss and constipation.[19,20] In addition, CLL patients are more prone to recurrent infections, some of which can be serious.[21]

A study by Else *et al* suggests that the impact on quality of life is greatest in Binet stage A-progressive disease with B-symptoms (night sweats, fever and weight loss).[20]

In most patients, the treatment goal is a deep remission (CR) leading to PFS for as long as possible. There is an increasing body of evidence demonstrating the relationship between improved PFS and improved quality of life. A study by Hancock (which has been used in two previous NICE submissions) showed a difference in utility of 0.2 between progressed and progression-free health states.[22] Ferguson *et al* established utilities using the time trade-off from members of the general public and showed a utility difference of 0.237 between progressed and progression free health states following first line treatment.[23] A more recent study by Beusterien *et al* showed that a greater response rate will lead to a greater quality of life.[14] The difference in utility between CR and progressed was 0.23; assuming that patients with a CR are

progression-free, this difference is very similar to those shown by Hancock and Ferguson *et al*. The Beusterien study was applied in the health economic analysis; the justification for using this study can be found in Section 6.4.

Rationale for bendamustine

Fludarabine plus cyclophosphamide [FC; often combined with rituximab (FCR)] is considered the 'gold standard' first-line treatment for CLL. This regimen has recently been shown to confer an overall survival benefit in patients with Binet stage A and B disease.[9] However, the toxicity profile of fludarabine (particularly immunosuppression due to long-term T-cell toxicity) makes it unsuitable for around 50% of patients (generally the more elderly and those with co-morbidities and poor performance status). The alternative is chlorambucil, which is generally well tolerated, but has relatively poor efficacy in terms of CR and depth of remission. No treatment for the group of patients who are unsuitable for fludarabine has demonstrated an overall survival benefit until now (although recent evidence from the bendamustine study 02CLLIII shows a significant overall survival advantage for responders; see Section 6.10.5). There is clearly a need for new, effective options to treat these patients, especially if they can confer an advantage in terms of longer PFS and overall survival.

2.2 How many patients are assumed to be eligible? How is this figure derived?

Bendamustine has a clear position in the treatment pathway, i.e. as an alternative to chlorambucil. Therefore, the most accurate way to estimate the number of patients eligible for bendamustine was to first determine the number currently being treated with chlorambucil. Data from the IMS Oncology Analyzer provided estimates of the number of patients receiving first-line treatment for CLL and the number of these patients receiving chlorambucil in the UK.[24] In 2009, approximately 2,552 patients were receiving first-line treatment for CLL and 1,323 of these were receiving chlorambucil.[24]

Based on 2008 population predictions from the Office of National Statistics,[25] it can therefore be estimated that in 2010, 1,182 patients will receive chlorambucil in England and Wales.

Assuming that 90% of chlorambucil-treated patients will be eligible for bendamustine,[26] we estimate that in 2010, **1,064** patients in England and Wales will be eligible for bendamustine. See Section C for a more detailed explanation of how we estimated the number of eligible patients.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

In February 2007, NICE did not recommend fludarabine monotherapy for first-line treatment of CLL. They did not assess the combination of fludarabine plus cyclophosphamide, as this is outside of the product's licence.[27]

In July 2009, NICE recommended rituximab in combination with fludarabine and cyclophosphamide as an option for the first-line treatment of CLL for people in whom the combination of fludarabine and cyclophosphamide is appropriate.[28]

In July 2010, NICE recommended rituximab in combination with fludarabine and cyclophosphamide as an option for treatment of relapsed or refractory CLL, except when patients are refractory to fludarabine or have previously been treated with rituximab. NICE recommended rituximab in combination with fludarabine and cyclophosphamide only in the context of research in patients previously treated with rituximab. Rituximab in combination with other chemotherapies was also recommended only in the context of research.[29]

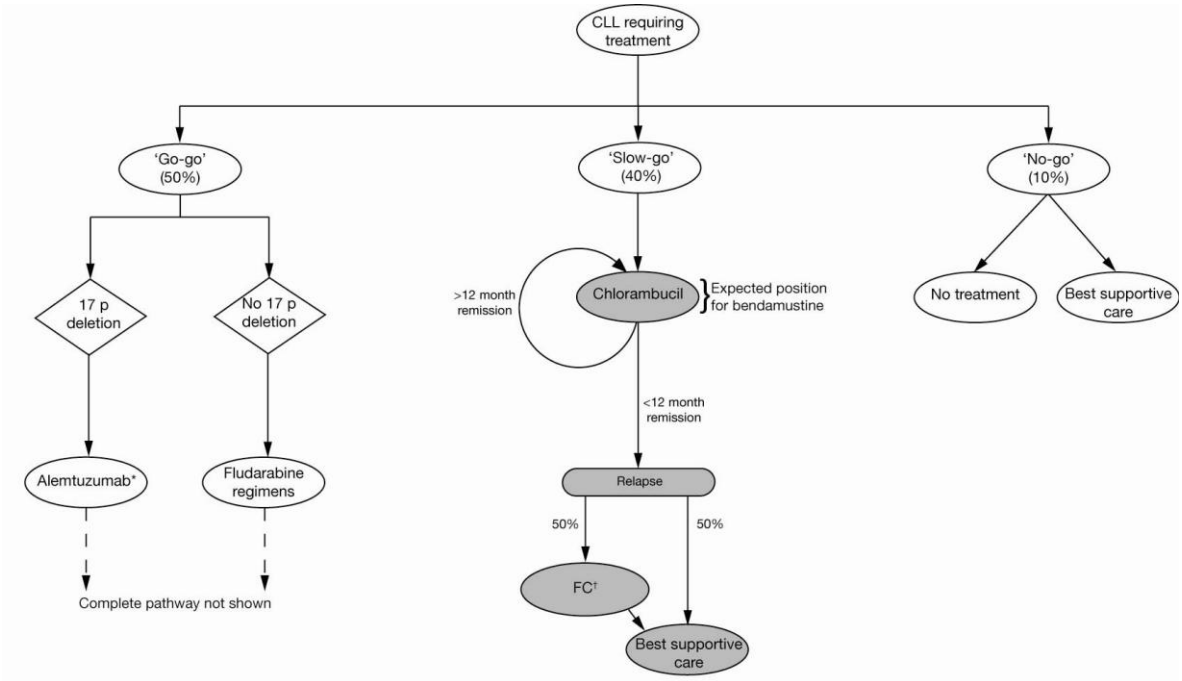
2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

There is no definitive treatment pathway for CLL. The most recent British Committee for Standards in Haematology guideline on the diagnosis and management of CLL, published in 2004,[3] states that CLL presents significant management problems owing to its heterogeneity. Although this guideline offers information on the various treatment options, it is not particularly prescriptive in terms of the types of patients who are suitable for each treatment. Several regional guidelines exist;[30-37] these vary in the level of detail they contain, but again, are not prescriptive.

Using these regional and national guidelines, we have defined the UK treatment pathway for CLL shown in Figure 2.1. This has been verified by UK CLL experts through an advisory board.[26] The part of the model used in the economic analysis is shown in grey. Note that in the base-case of the economic model, re-treatment with bendamustine is not included as it is outside the decision problem. However, this was investigated in the sensitivity analysis and is discussed further in the economic section.

The inclusion of fludarabine in the treatment pathway may seem counterintuitive given that the licensed indication for bendamustine is for patients who are not suitable for fludarabine-based combination therapy. However, there was clear feedback from the clinical experts that this is a very realistic scenario, as patients' health status can improve after first-line therapy, rendering them 'fit' enough for fludarabine as second-line therapy. In addition, fludarabine may be used at a reduced dose or as monotherapy in some instances.

Figure 2.1 UK treatment pathway for CLL



*Entry to a clinical trial is another option at this step
†By this stage, patients may be considered strong enough to try treatment with a fludarabine regimen. FC = fludarabine plus cyclophosphamide

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There are currently no definitive criteria for determining which patients are 'unfit' for treatment with fludarabine combination therapy. The current national guidelines give only severe renal impairment and autoimmune cytopenia as reasons not to treat with fludarabine.[3] A review of local treatment guidelines[30-37] also found that the only specific criterion given is related to renal impairment (fludarabine is contra-indicated in patients with a creatinine clearance <30 ml/min). However, ineligibility for fludarabine owing to such severe renal impairment is unlikely to be the defining reason for treatment choice for most patients in the first-line setting.

The German CLL Study Group has developed the CIRS (cumulative illness rating scale) score to provide an objective means of quantifying co-morbidities. It has also sometimes been used to group patients into 'go-go', 'slow-go' and 'no-go' with respect to first-line treatment. Although UK clinicians are familiar with this scoring system, it has not yet been validated as a tool to determine suitability for fludarabine

combination therapy and is not routinely used in the UK for this purpose, either in clinical trials or in clinical practice. Indeed, NICE guidance for first-line FCR in CLL relies on the clinician's clinical judgement in determining suitability for this regimen.

In the UK, the next national trial being planned in first-line CLL (CLL9: bendamustine-ofatumumab *vs*. chlorambucil-ofatumumab for treatment-naïve patients with CLL who are not suitable for fludarabine)[38] has recently been submitted to the Clinical Trials Advisory and Awards Committee for approval. This study has been designed so that the criteria used by clinicians when entering patients into this trial can be used to construct an objective 'real life' definition of 'slow-go' or unsuitability for fludarabine combination therapy. The exact criteria for inclusion are still the subject of debate at the time of this submission.

In the absence of any formal criteria, the decision about first-line treatment in the 'real-world' setting is currently a matter of physician (and patient) judgement. Factors that influence the decision include performance status, age and co-morbidities. The latter two are often interlinked as, in general, older patients have more co-morbidities than younger patients: in the US, the National Institute on Aging/National Cancer Institute Surveillance, Epidemiology and End Results (SEER) study on co-morbidity and cancer in the elderly showed that the mean number of co-morbidities for patients aged 55 – 64 years was 2.9.[39] This increased to 3.6 for those aged 65 – 74, and to 4.2 for those aged ≥75 years. The number of co-morbidities in any single patient ranged from none to 12 - 14. The NICE FAD on rituximab in relapsed/refractory CLL states that "The Committee heard from clinical specialists that the most frequently used first-line treatments are: fludarabine plus cyclophosphamide with or without rituximab; and chlorambucil for people unable to have fludarabine because of poor performance status".[29]

Given the lack of specific criteria, the group of patients currently treated with chlorambucil in the UK is heterogeneous with respect to these three parameters. In Study 02CLLIII, 51% of patients were aged <65 years and 49% were aged ≥65 years, and there was a range in patients' WHO performance status (67% with WHO 0, 28% with WHO 1 and 3% with WHO 2). Of the 45 centres across Europe that took part in the study, one was in the UK. However, there is nothing to suggest that there would be any differences between patients recruited in the UK and those recruited elsewhere. In addition, it would be anticipated that those investigators outside the UK who were recruiting patients into the study were making similar decisions about treatment choices to UK physicians. These physicians would naturally have been making a decision about whether patients were suitable for fludarabine-based therapy or not, as there was a study of fludarabine combination therapy recruiting at the same time (CLL8). Therefore, the population in this study is representative of the group of patients in the UK who would usually be treated with chlorambucil.

To demonstrate that the clinical and cost-effectiveness of bendamustine is maintained across this heterogeneous group, sensitivity analyses were carried out on different age groups (as a proxy for co-morbidities) and on performance status (see Section 6.9).

2.6 Please identify the main comparator(s) and justify their selection.

In the UK, chlorambucil is currently used as standard first-line therapy in patients not considered suitable for a fludarabine-containing regimen (see Figure 2.1). Therefore, using chlorambucil as the comparator is representative of UK clinical practice.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The table below shows the therapies that may be prescribed to manage the adverse events associated with bendamustine.

Table 2.2 Management of adverse events associated with bendamustine

Adverse event	Suggested treatment
Cytopenia	Granulocyte colony-stimulating factor and erythropoietin (i.v. infusion)
Nausea ± vomiting (grade 1 or 2)	Anti-emetics, e.g. metoclopramide and domperidone
Anaemia (grade 3 or 4)	Red blood cell transfusion
Pyrexia (grade 3 or 4)	Antibiotics/hospital care
Pneumonia (grade 3 or 4)	Antibiotics/hospital care
Diarrhoea (grade 1 or 2)	Loperamide, codeine

Patients who experience grade 1 or 2 infusion reactions should be prescribed antihistamines, antipyretics, corticosteroids and other prophylactic treatments in subsequent treatment cycles.

Tumour lysis syndrome associated with bendamustine can be treated with urate oxidase. Allopurinol could be prescribed to high-risk patients during the first one or two weeks of treatment, but not necessarily as standard. In the trial described in this submission, two patients experienced tumour lysis syndrome; both patients had received their first cycle of bendamustine. However, these events were not fatal and the patients continued treatment.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Intravenous administration means that out-patients need to remain in hospital for longer than those receiving oral medication, which utilises a small amount of nurse time, and incurs the costs of normal saline and intravenous giving sets. The infusion time is 30 - 60 minutes, and provided there are no adverse events, patients can usually be discharged immediately after their infusion.

Patients will require two infusions of bendamustine per cycle. Based on HRG coding, the cost of administering the first infusion is £272.10 (HRG code SB12Z); the second infusion costs £226.88 (HRG code SB15Z).[40]

2.9 Does the technology require additional infrastructure to be put in place?

It is not expected that the use of bendamustine will require any additional infrastructure to be put in place. Bendamustine has been available on a compassionate use basis for several months with over 450 patients treated, and Napp has received no reports of major issues or concerns from clinicians or centres regarding the administration schedule.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

No issues relating to equity or equality have been identified.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No issues relating to equity or equality have been identified.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable as none have been identified.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with previously untreated CLL for whom fludarabine combination chemotherapy is not appropriate	Of those people who require therapy for CLL, approximately 50% will not be suitable for the 'gold standard' of fludarabine-containing regimens (usually because of their age or co-morbidities). In this submission, the population is limited to those untreated patients who are unsuitable for fludarabine combination therapy. It is anticipated that this equates to 1,064 patients in England and Wales in 2010.
Intervention	Bendamustine	This submission examines the clinical and cost-effectiveness of bendamustine for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
Comparator(s)	Chlorambucil	Chlorambucil is the current standard first-line therapy for patients not suitable for a fludarabine-containing regimen. The pivotal, Phase III randomised study (02CLLIII) provides a direct comparison of bendamustine with chlorambucil.
Outcomes	Progression-free survival Response rates Overall survival Adverse effects of treatment Health-related quality of life	These outcomes are covered in the submission.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost-effectiveness of bendamustine is expressed as a cost per QALY. A lifetime time horizon was used as the delayed progression associated with bendamustine impacts upon both costs and health outcomes for the duration of a patient's lifetime. Costs are considered from a NHS and PSS perspective.

Subgroups to be considered	If evidence allows, the appraisal will consider subgroups of people defined by their: • performance status; • stage of disease (Binet B and C); • co-morbidities.	A sensitivity analysis is presented based on patients' WHO performance status. Response rates and progression-free survival are presented for patients according to disease stage. An analysis is presented based on patients' age, which is a proxy for co-morbidities.
Special considerations, including issues related to equity or equality	None noted	n/a

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor.

A search was carried out in the following databases: Embase, Medline, Medline in-Process and The Cochrane Central Register of Controlled Trials (CENTRAL). The search was performed on 22nd April 2010.

The RCT search terms used in the searches were taken from the Scottish Intercollegiate Guidelines Network website (http://www.sign.ac.uk/methodology/filters.html), and were used in combination with CLL disease terms, and the generic and brand names for bendamustine. The CLL disease terms used in the search were based on the terms used in a Cochrane review of CLL.[41]

The full search syntax used in each search is provided in Section 9.2.

The searches retrieved the following numbers of results: 115 from Embase, 23 from Medline, one from Medline in-Process and five results from CENTRAL. These results were combined into Reference Manager (144 results) and after removal of duplicates, the combined search results totalled 121 papers.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent.

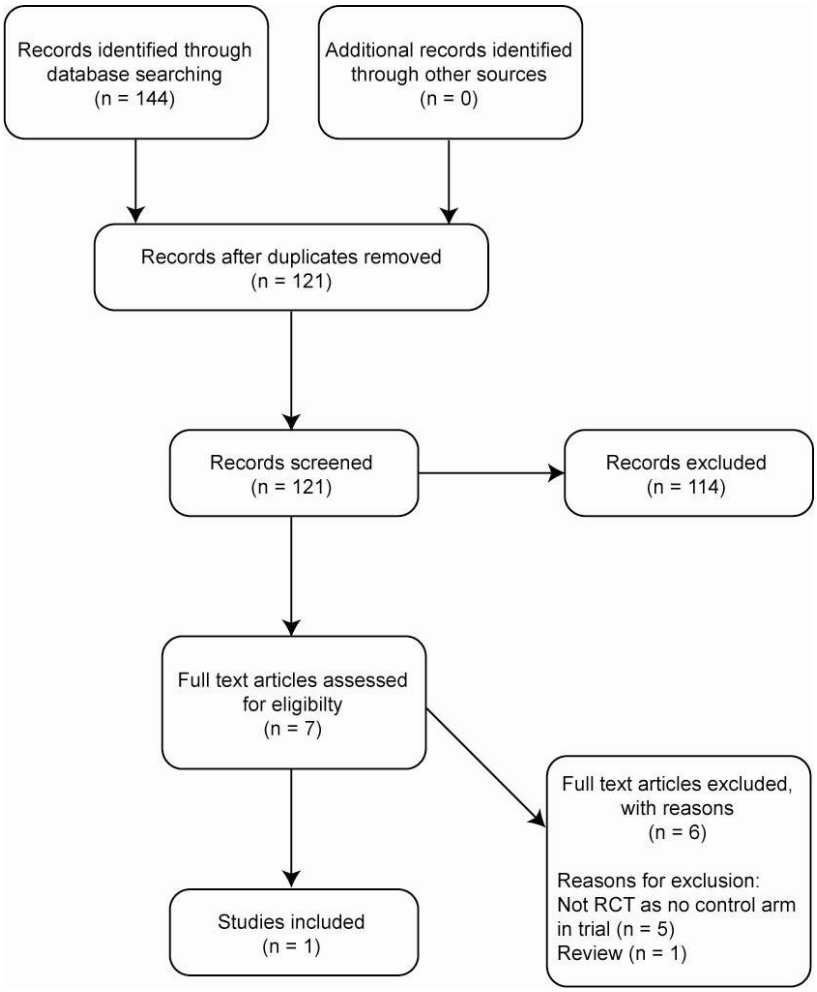
Table 5.1 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population: CLL
	Interventions: bendamustine compared with any other treatment
	Outcomes: any
	Study design: RCTs
	Language restrictions: English only
Exclusion criteria	Population: non-CLL patients
	Interventions: don't include bendamustine-based treatment as a comparator
	Outcomes: no exclusions
	Study design: non RCTs
	Language restrictions: non-English

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Figure 5.1 uses the QUOROM statement flow diagram to show the number of studies included and excluded at each stage.

Figure 5.1 Flow diagram of number of studies included and excluded



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

As shown above, there is only one RCT that is relevant for inclusion in this submission. The data presented in this submission have been drawn from several sources:

- The published paper.[10]
- The clinical study report[11] and other data on file[12]
- A poster presented at the 2009 American Society for Hematology annual meeting.[13]

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group.

Table 5.2 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
02CLLIII	Bendamustine	Chlorambucil	Previously untreated CLL	Knauf WU, et al. J Clin Oncol 2009;27:4378-84

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

Study 02CLLIII is the only RCT that compares bendamustine directly with chlorambucil in patients with previously untreated CLL who are not suitable for fludarabine-based therapy.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Not applicable: one relevant RCT was identified and forms the basis for the current submission.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion.

A systematic search of non-RCTs identified two studies (Table 5.3). Full details of the search can be found in Sections 5.8 and 9.6.

Table 5.3 List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.
CLL2M	Bendamustine plus rituximab	Previously untreated CLL	To assess the efficacy and toxicity of bendamustine in combination with rituximab in previously untreated CLL patients	Fischer K, *et al* Blood (ASH Annual Meeting Abstracts) 2009;114:205[42]
n/a	Bendamustine	Previously untreated and treated CLL		Kath R, *et al*. J Cancer Res Clin Oncol 2001;127:48-54[43]

The study by Fischer *et al* has been excluded from further discussion because follow-up is still ongoing; only interim results are available.

The study by Kath *et al* has been excluded from further discussion because:

- the dose schedule of bendamustine used in the trial does not reflect current clinical practice and does not reflect the licensed dosing of bendamustine;
- only 13 patients in the study had previously untreated CLL.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org).

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.

Location

This study was carried out at 45 sites across Europe, including one centre in the UK.

Design

It was a Phase III, open-label, multicentre parallel group international study comparing initial treatment of patients with CLL in Binet stage B or C requiring

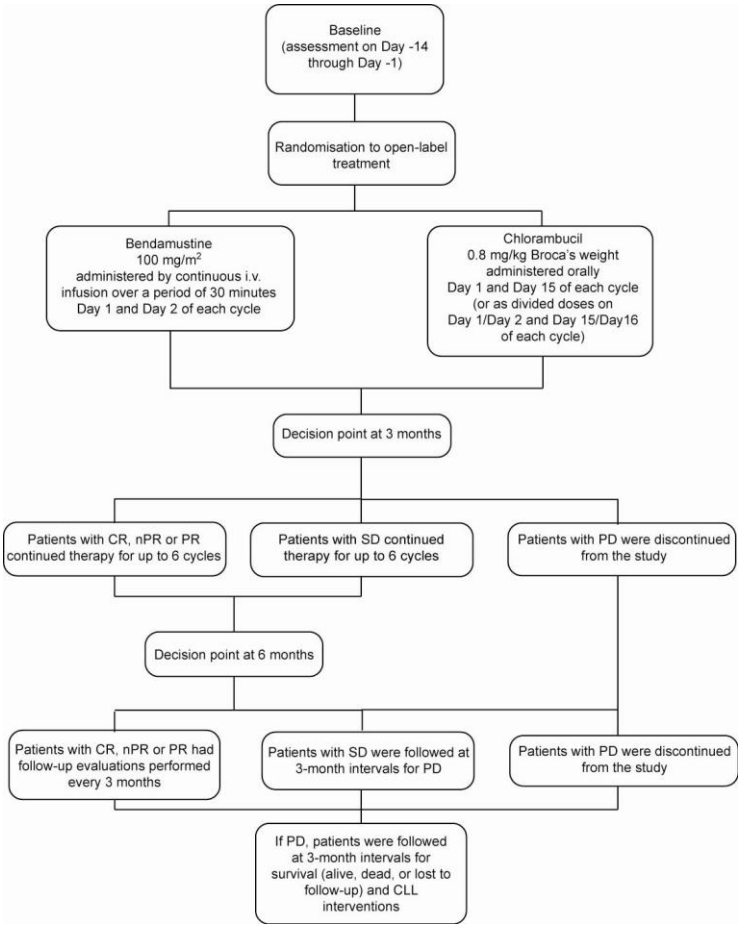
treatment. Patients were randomised 1:1 to receive either intravenous bendamustine or oral chlorambucil (stratified by centre and Binet stage).

An interim tumour assessment was performed after three treatment cycles. Further treatment was dependent on each patient's status, as follows:

- Patients showing progressive disease (PD) were discontinued from the trial.
- Patients showing stable disease (SD) received a maximum of three additional treatment cycles.
- Patients showing partial response (PR), nodular partial response (nPR) or complete response (CR) received at least two (maximum three) further treatment cycles for consolidation.

A final assessment was performed at the end of treatment. Patients with CR, nPR, or PR then had follow-up evaluations at 3-month intervals. Patients with SD were monitored every 3 months for PD only. After PD, patients were monitored at 3-month intervals to document their final outcome as alive, dead, or lost to follow-up. Figure 5.2 shows the study design.

Figure 5.2 02CLLIII study design



Duration of study

Recruitment started in November 2002 and the last patient completed follow-up in June 2008.

Method of randomisation

Patients were randomised 1:1 to receive either bendamustine or chlorambucil according to a computer-generated randomisation list. They were randomised consecutively in the order of study entry. Randomisation was in blocks of four (investigators were unaware of this) and was prospectively stratified by study centre and Binet stage. Stratification by Binet stage was carried out because of the differing prognoses between patients with Stage B and C disease.

Method of blinding

Owing to the difficulties that blinding different formulations (i.e. intravenous and oral) presents, this was an open-label study. However, the investigators' assessments of patients' responses were checked by an independent committee for response assessment (ICRA); members of the ICRA were blinded to treatment.

Results quoted in this submission are those as assessed by the ICRA.

Intervention and comparator

Bendamustine (n = 162): 100 mg/m^2/day intravenously over 30 minutes on Days 1 and 2 of a 28-day treatment cycle. The next cycle started on Day 29.

Chlorambucil (n = 157): 0.8 mg/kg (Broca's normalised weight*) orally on Days 1 and 15 or, if necessary, given as divided doses on Day 1/2 and Day 15/16 of a 28-day treatment cycle. The next cycle started on Day 29.

*Broca's weight in kg = height in cm minus 100

Timings of assessments

Patients' response to treatment was assessed after three treatment cycles and at the end of treatment.

Duration of follow-up

Patients were followed up every three months. The follow-up period ended one year after the last enrolled patient completed treatment.

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Inclusion criteria

To enter the study, patients had to:

- be treatment-naïve, legally competent adults <75 years of age and be capable of following study instructions;
- give written informed consent;
- have a WHO Performance Status of 0 – 2;
- have a life expectancy >3 months;
- use contraception for at least 6 months after therapy;
- have confirmed chronic B-cell lymphocytic leukaemia (co-expression of CD5, CD23 and either CD19 or CD20 or both);
- have symptomatic Binet stage B (i.e. more than three groups of enlarged lymph nodes and a high white blood cell count) or Binet stage C (i.e. enlarged lymph nodes or spleen, low white blood cell count, and low red blood cell and platelet counts) disease.

All of these criteria had to be met.

In addition, patients had to meet *at least one* of the following need-to-treat criteria:

- Haematopoietic insufficiency with non-haemolysis-induced haemoglobin <10 g/dL.
- Thrombocytopenia <100 x 10^9/L (equivalent to Binet stage C).
- B symptoms defined as:
    - unexplained >20% weight loss in the last 6 months;
    - persistent or recurrent pyrexia of unknown origin >38°C;
    - night sweats.
- Rapidly progressive disease (such as rapid lymphoma growth, rapid increase in lymphocyte count, rapid fall in haemoglobin or platelet count not due to autoimmune phenomena).
- Risk of organ complications from bulky lymphomas (e.g. vascular compression).

Exclusion criteria

- Previous treatment with other cytotoxic drugs.
- Participation in another clinical trial in the four weeks before, or during, this study.
- Mental disorders, drug or alcohol dependence, or any other disorder suggesting compliance problems or limited ability to co-operate in the study.
- History of a second malignancy (except cured basal cell carcinoma or cured cervical cancer).
- Manifest immune haemolysis that could be treated with glucocorticoids alone.
- Manifest immune thrombocytopenia that could be treated with glucocorticoids alone.
- Richter's syndrome or transformation to pro-lymphocytic leukaemia
- Hepatic dysfunction: bilirubin >2.0 mg/dL and/or transaminases >3 x upper limit of normal.
- Renal dysfunction (creatinine clearance <30 mL/min, calculated).
- Any of the following concomitant diseases:
    - Overt heart failure.
    - Cardiomyopathy.
    - Myocardial infarction within the last six months.
    - Severe, uncontrollable diabetes mellitus.
    - Severe, uncontrollable hypertension.
    - Active infection that required systemic antibiotic therapy.
    - Uncontrollable infection.
    - Clinically manifest cerebral dysfunction.
- Known HIV infection.
- Major surgery in the 30 days before the start of the trial.
- Pregnancy, lactation.
- Hypersensitivity to any of the study drugs.
- Women of childbearing potential without adequate contraception.

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Table 5.4 shows patients' baseline characteristics. Overall, these were well balanced between the groups. The mean (SD) time from initial diagnosis to registration in the

study was 18.8 (32.3) months in the bendamustine group and 24.6 (33.9) months in the chlorambucil group (*P* = 0.12).

Table 5.4: Baseline demographics

	Bendamustine (n = 162)		Chlorambucil (n = 157)	
Gender, n (%)				
Female	60	(37)	62	(39)
Male	102	(63)	95	(61)
WHO performance status, n (%)				
Missing	3	(2)	5	(3)
WHO0	113	(70)	102	(65)
WHO1	43	(26)	45	(29)
WHO2	3	(2)	5	(3)
Age (years)				
Mean (SD)	63.0	(7.5)	63.6	(8.8)
Min-max	45.0 – 77.0		35.0 – 78.0	
Median	63.0		66.0	
Q1-Q3	58.0 – 70.0		59.0 – 70.0	
Binet stage, n (%)				
B	116	(72)	111	(71)
C	46	(28)	46	(29)
B-symptoms, n (%)				
Yes	80	(49)	79	(50)
No	81	(50)	74	(47)
Unknown	1	(<1)	4	(3)
LDH, n (%)				
Normal	84	(52)	80	(51)
Out of normal range	73	(45)	66	(42)
Not done	5	(3)	6	(4)

The median number of treatment cycles per patient was six in both groups. The mean (SD) number of treatment cycles per patient was 4.9 (1.7) in both groups. 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.

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes.

Primary outcomes

There were two primary outcomes:

- Overall response rate (ORR; included CR, nPR and PR).
- PFS, i.e. the time from randomisation to first PD or relapse after intercurrent remission or death owing to any cause (whichever occurred first).

The response evaluation was based on the following criteria defined by the National Cancer Institute Sponsored Working Group on CLL.[44,45]

Complete response (CR)

Patients were considered to have a CR if all of the following criteria were met for at least 8 weeks after first response was observed:

- Enlarged lymph nodes no longer detectable by palpation (X-ray or ultrasound were optional).
- Absence of hepatomegaly or splenomegaly, confirmed by palpation (CT and ultrasound were optional).
- No disease symptoms (i.e. B-symptoms).
- Blood counts:
    - lymphocytes ≤4.0 x 10^9/L;
    - neutrophils ≥1.5 x 10^9/L;
    - Platelets >100 x 10^9/L;
    - Haemoglobin >11 g/dL (without blood transfusion).

A bone marrow biopsy (histology and cytology) was to be performed 8 weeks after meeting the above criteria. The bone marrow had to be at least normocellular for age, with less than 30% lymphocytes.

Nodular partial response (nPR)

Patients who met all of the criteria for a CR, including <30% lymphocytes in the bone marrow sample, but who still showed focal infiltration were considered to have a nPR.

Partial response (PR)

Patients were considered to have a PR if all of the following criteria were met for at least 8 weeks:

- ≥50% decrease in peripheral blood lymphocyte count from the pre-treatment baseline value.
- ≥50% reduction of enlarged lymph nodes (total of affected lymph nodes).

and/or:

- 50% reduction of hepatomegaly and/or splenomegaly

plus at least one of the following criteria:

- Neutrophils ≥1.5 x 10^9/L or 50% improvement *vs.* baseline.
- Platelets >100 x 10^9/L or 50% improvement *vs.* baseline.
- Haemoglobin >11 g/dL or 50% improvement *vs.* baseline (without blood transfusion).

Progressive disease (PD)

Patients were considered to have PD if at least one of the following criteria was met on two consecutive occasions at least 2 weeks apart:

- ≥50% enlargement in lymph nodes (from the nadir; total of enlargement from at least two lymph nodes, one of which was to have a diameter of at least 2 cm) on two consecutive occasions at two weeks apart and/or new palpable lymph nodes.
- ≥50% increase (from baseline) in liver or spleen size (as determined by measurements under the respective costal arch); definable hepatomegaly or splenomegaly that had not been previously detectable.
- ≥50% increase in absolute lymphocyte count (ALC; from the nadir) to at least 5 x 10^9/L.
- Transformation to a more aggressive histology (Richter or prolymphocytic leukaemia with more than 55% prolymphocytes).

Stable disease (SD)

Patients were considered to have stable disease if they met none of the criteria for CR, nPR, PR or PD.

The investigator could decide the tumour measures and methods (e.g. CT, X-ray, ultrasound, palpation) used to evaluate response. The method was documented before patient enrolment, and the same method was used at baseline and in all subsequent evaluations. For the ICRA response assessment, the evaluation by

palpation was decisive. If no palpation was performed, assessment was carried out based on imaging data.

The response criteria had to be met for at least eight weeks in order for patients to be classified as complete or partial responders. Patients were classified as 'non-responders', if neither PR nor CR were confirmed or their tumour response was not evaluable. A patient had stable disease if CR, PR, and PD criteria were not met. Response was assessed after three treatment cycles and at the end of treatment.

Secondary outcomes

- Time to progression (TTP), i.e. the time from randomisation to PD or relapse after intercurrent remission or CLL related death.
- Duration of response/remission, i.e. the time from the ICRA date of the first observation of response (CR, nPR or PR) to PD or death due to any cause.
- Overall survival, i.e. the time interval between randomisation and death.
- Quality of life [assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ) EORTC QLQ-C30 and EORTC QLQ-CLL25].
- Adverse events (toxicities)

All these outcomes are relevant to the decision problem, are valid outcomes in oncology clinical trials, and are used in clinical practice.

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

Primary hypothesis

The primary hypothesis was that bendamustine would show superior efficacy (in terms of response rates and PFS) over chlorambucil in the initial treatment of CLL patients with Binet stage B or C disease requiring treatment.

Statistical analysis

Primary endpoints

Statistical analysis of the two primary endpoints was by a combination of a priori sequenced hypothesis testing and an adaptive group sequential test procedure. All tests were two-tailed, using a multiple significance level of α = 5%. ORR was analysed by Fisher's exact test, and PFS by a log-rank test. Analysis of both endpoints was stratified to adjust for the influence of patients' status according to Binet stage (Binet B or Binet C).

Relative risk and rate differences (and their associated 95% CIs) were calculated post-hoc.[12]

Interim analyses

A five-stage adaptive group sequential procedure with Pocock cut-offs of αi = 0.016 was used. A maximum of four interim analyses was planned, of which three were performed (the first after 85 patients treated with a follow-up of at least 5 months, the second after 158 patients and the third after 264 patients). In each interim analysis, ORR was tested first; PFS was only tested if ORR was significant, thus controlling for multiple testing.

The *P* values of the individual sequences were combined using the Φ^{-1} method; as the patients were still under observation, these were used only to determine whether to terminate the study or continue using the new sample size. At the third interim analysis the Independent Data Monitoring Committee recommended termination of recruitment and the final analysis be performed using the data available.

Secondary endpoints

The secondary efficacy endpoints (TTP, duration of remission, duration of CR and duration of PR) were analysed using the log-rank test, stratified for Binet stage.

The safety analysis was descriptive and comprised all documented adverse events, serious adverse events, laboratory variables, and vital signs (blood pressure, pulse, temperature).

Hazard ratios (and their associated 95% CIs) were calculated post-hoc.[12]

Sample size and power calculation

Sample size calculations were based on results from a study comparing fludarabine and chlorambucil in previously untreated patients[46] that suggested a 30% difference in ORR between treatments and a 6-month difference in PFS. From this, it was calculated that approximately 42 patients would be needed in each group to achieve 80% power to show a significant difference in ORR at the 0.05 significance level.

The sample size required for PFS was calculated as 326 patients in total (if no interim analyses were to be performed).

As it was uncertain whether the assumptions used in the previous study would hold also for this study, the five-stage adaptive group sequential procedure described above was used. Using this approach, the final sample size was estimated to be approximately 350 patients.

Populations analysed

The efficacy analyses were carried out on the intent-to-treat (ITT) population, i.e. all patients randomised (regardless of whether they received study drug or not).

The primary and secondary endpoints were additionally analysed for the per-protocol (PP) population, which included all patients with no violations of the inclusion and exclusion criteria or protocol deviations that might interfere with outcome evaluation.

A patient was excluded from the PP population if:

- s/he discontinued the study prematurely;
- s/he had a WHO Performance Status greater then 2;
- s/he had no confirmed chronic B-cell lymphocytic leukemia;
- s/he had no symptomatic Binet stage B or Binet stage C disease;
- s/he had previous treatment with other cytotoxic drugs;
- s/he had a history of a second malignancy (except cured basal cell carcinoma or cured cervical cancer);
- s/he showed Richter's syndrome or transformation to prolymphocytic leukaemia at baseline;
- s/he had major surgery within 30 days before the start of the trial;
- s/he showed hypersensitivity to any of the study drugs;
- s/he did not fulfil the “need to treat criteria” according to the NCI-Working Group Criteria.[44]

The violation of other inclusion/exclusion criteria had no impact on endpoint evaluation including age, liver and kidney function tests. The decision to exclude particular patients from the PP population was based on a complete list of all protocol violations prepared from the patient data.

The safety population included all patients who received at least one dose of study medication.

Handling of missing data

Patients with CLL-related death and non-CLL-related deaths that occurred during remission were censored at the time of death. Patients who were alive without progression at the time of the final analysis were right censored and entered into the analysis with time from start of treatment to the last date at which occurrence of PD or relapse could be excluded by tumour evaluation.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

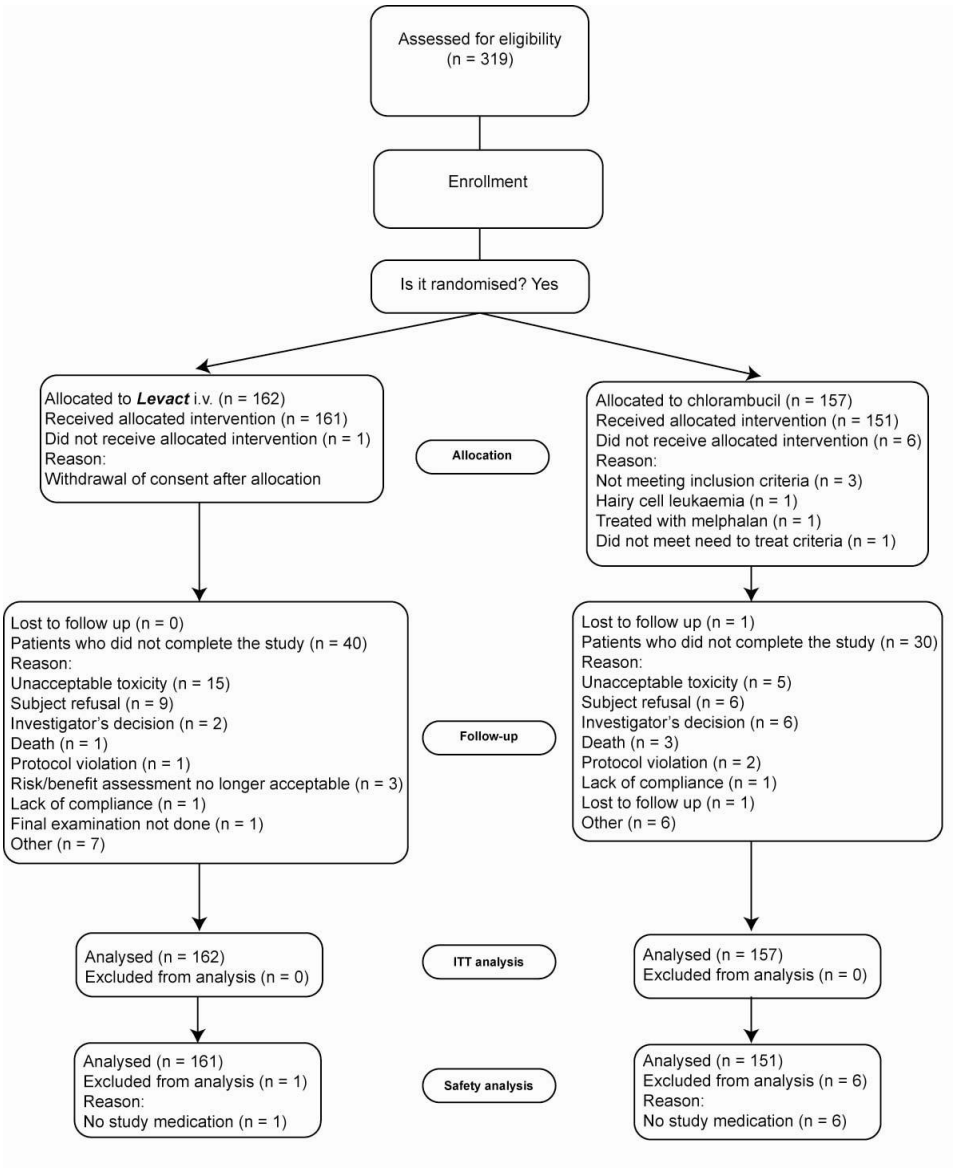
A post-hoc analysis was carried out to compare the efficacy and tolerability of bendamustine and chlorambucil in subgroups of patients defined by age (<65 years *vs.* ≥65 years) and specific indicators of disease activity (presence of B-symptoms, Binet stage and lactate dehydrogenase levels). These factors are of interest because each can influence prognosis.

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 5.3 shows the flow of patients through the study.

Figure 5.3 Patient disposition



5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

See Section 9.3 for the quality assessment of Study 02CLLIII.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.

Not applicable as there is only one RCT. See Section 9.3 for the quality assessment of Study 02CLLIII.

5.5 Results of the relevant RCTs

Unless otherwise stated, results are presented for a median (range) observation time of 35 (1 – 68) months.

Primary outcomes

Overall response rate

Figure 5.4 shows the response rates. The ORR was significantly higher in the bendamustine group than in the chlorambucil group (68% *vs*. 31%; *P*<0.0001). More patients reported a CR with bendamustine than with chlorambucil (31% *vs.* 2%; *P*<0.0001). The proportion of patients with nPR was also higher in the bendamustine group than in the chlorambucil group (11% *vs.* 3%). The high CR rate achieved with bendamustine is important, as there is evidence that the CR is associated with longer PFS.[5-8] Longer PFS equates to longer time without symptoms and treatment, and hence to longer time in an improved health state.[14] This correlates with improved quality of life for patients.

Figure 5.4 Response rates

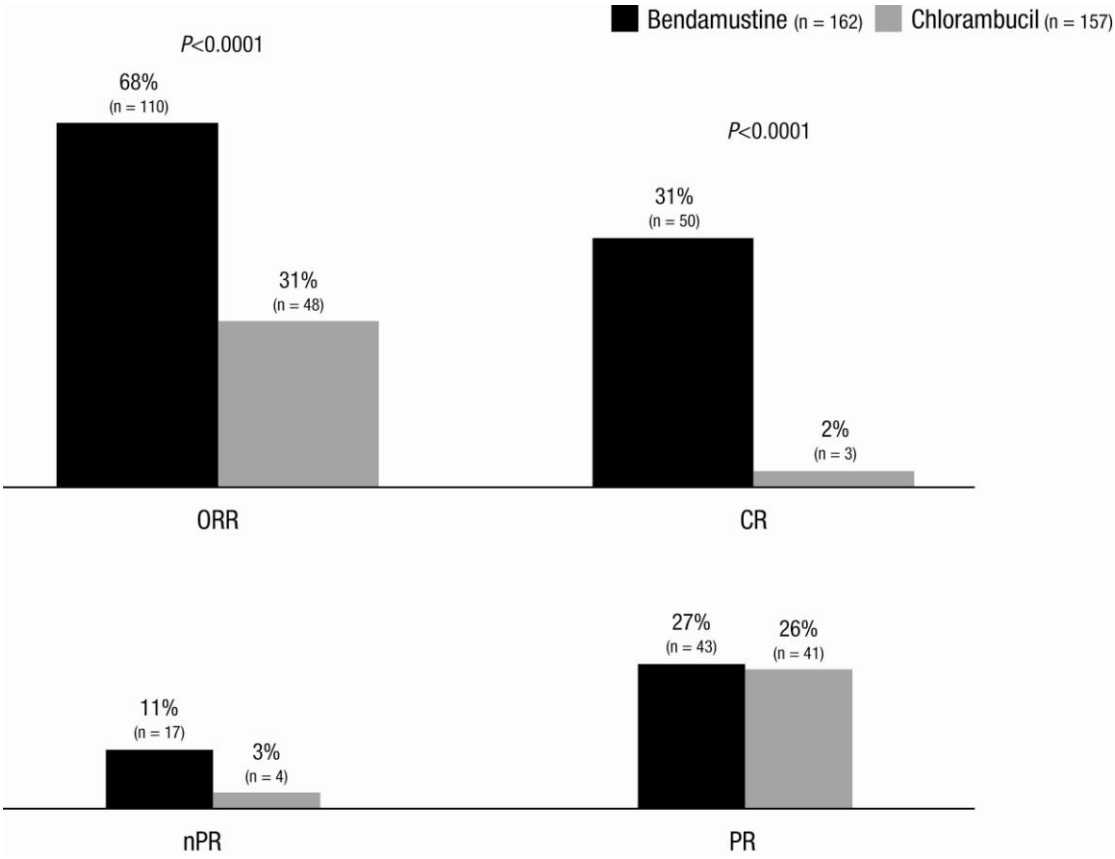


Table 5.5 shows the response rates according to Binet stage. Regardless of Binet stage, patients showed a higher likelihood of CR with bendamustine than with chlorambucil.

Table 5.5 Response rates according to Binet stage (ITT population)

	Number (%) of patients				Relative risk (95% CI)		Rate difference (95% CI)		*P* value
	Bendamustine		Chlorambucil						
Binet B	**n = 116**		**n = 111**						
CR	41	(35.3)	3	(2.7)	13.08	(5.81 – 29.46)	0.326	(0.23 – 0.42)	0.0000
nPR	14	(12.1)	4	(3.6)	3.35	(1.22 – 9.16)	0.085	(0.02 – 0.15)	0.0186
PR	27	(23.3)	31	(27.9)	0.83	(1.30 – 0.53)	-0.047	(-0.16 – 0.07)	0.4228
ORR	82	(70.7)	38	(34.2)	2.06	(1.59 – 2.68)	0.365	(0.24 – 0.48)	0.0000
Binet C	**n = 46**		**n = 46**						
CR	9	(19.6)	0	0			0.196	(0.08 – 0.31)	0.0017
nPR	3	(6.5)	0	0			0.065	(-0.01 – 0.14)	0.0799
PR	16	(34.8)	10	(21.7)	1.60	(0.82 – 3.12)	0.130	(-0.05 – 0.31)	0.1671
ORR	28	(60.9)	10	(21.7)	2.80	(1.64 – 4.77)	0.391	(0.21 – 0.58)	0.0002
Binet B+C	**n = 162**		**n = 157**						
CR	50	(30.9)	3	(1.9)	16.15	(7.36 – 35.46)	0.290	(0.22 – 0.36)	0.0000
nPR	17	(10.5)	4	(2.5)	4.12	(1.56 – 10.88)	0.079	(0.03 – 0.13)	0.0043
PR	43	(26.5)	41	(26.1)	1.02	(0.70 – 1.47)	0.004	(-0.09 – 0.10)	0.9309
ORR	110	(67.9)	48	(30.6)	2.22	(1.76 – 2.81)	0.373	(0.27 – 0.48)	0.0000

Table 5.6 shows the response rates according to patients' age. In the bendamustine group, there was a suggestion that response rates vary with age: patients aged <65 years had an ORR of 72%, compared with 64% in patients aged >65 years (*P*>0.3). This trend was tested in the economic model (see Section 6). In the chlorambucil group, the corresponding figures were 28% and 33%, respectively (*P*>0.6).

The difference in response rates between the treatment groups was maintained regardless of age. This is important since age, (when linked to co-morbidity or poor performance status) is one of the factors clinicians consider when determining unsuitability for fludarabine-based treatment. These superior response rates for bendamustine are therefore applicable to the licensed patient population.

Table 5.6 Response rates according to age (ITT population).

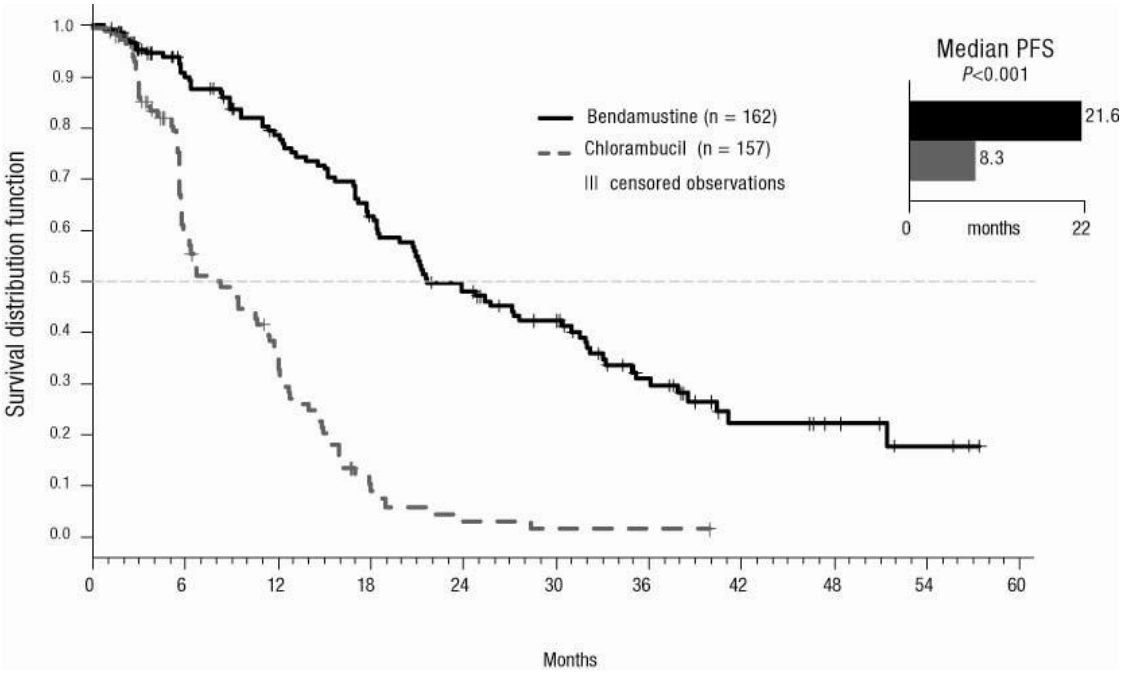
	Number (%) of patients			
	<65 years		≥65 years	
	Bendamustine	Chlorambucil	Bendamustine	Chlorambucil
n	88	74	74	83
CR	31 (35)	2 (3)	19 (26)	1 (1)
nPR	12 (14)	1 (1)	5 (7)	3 (4)
PR	20 (23)	18 (24)	23 (31)	23 (28)
Unconfirmed response	2 (2)	3 (4)	2 (3)	2 (2)
SD	11 (13)	11 (15)	8 (11)	21 (25)
PD	7 (8)	28 (38)	8 (11)	25 (30)
Not examined	5 (6)	11 (15)	9 (12)	8 (10)
ORR	63 (72)	21 (28)	47 (64)	27 (33)

Progression-free survival

Figure 5.5 shows PFS. Median PFS was significantly longer with bendamustine than with chlorambucil [21.6 months *vs*. 8.3 months; hazard ratio (95% CI) = 4.37 (3.14 – 6.07); *P*<0.0001]. This difference was evident in patients with Binet stage B disease (21.4 months *vs.* 9.0 months) as well as in stage C disease (25.4 months *vs.* 6.3 months). It is interesting to note that patients in the bendamustine group with stage C disease had a longer PFS than those with stage B disease, whereas this was not the case in the chlorambucil group. Owing to the small number of patients with stage C disease, it is difficult to say whether this is purely down to chance, although it is of note that nine patients in the bendamustine group with stage C disease achieved a CR, compared with none in the chlorambucil group. This

suggests that bendamustine offers an effective treatment option even for those patients with advanced disease.

Figure 5.5 PFS (ITT population)



Benefits in terms of PFS were still apparent when comparing patients aged above and below 65 years, patients with normal or elevated lactate dehydrogenase levels, and patients with Binet stage B or C disease. Hazard ratios (95% CIs) were 4.13 (2.81 – 6.06) for patients with stage B disease (*P*<0.0001) and 5.18 (2.66 – 10.07) for patients with stage C disease (*P*<0.0001). However, patients in the bendamustine group who had B symptoms (i.e. unexplained >20% weight loss in the last 6 months, persistent or recurrent pyrexia of unknown origin >38°C and night sweats) had a significantly longer median PFS than those without (30.4 months *vs*. 17.7 months; *P*<0.0001). Median PFS was not affected by the presence of B symptoms in the chlorambucil group.

Secondary analyses

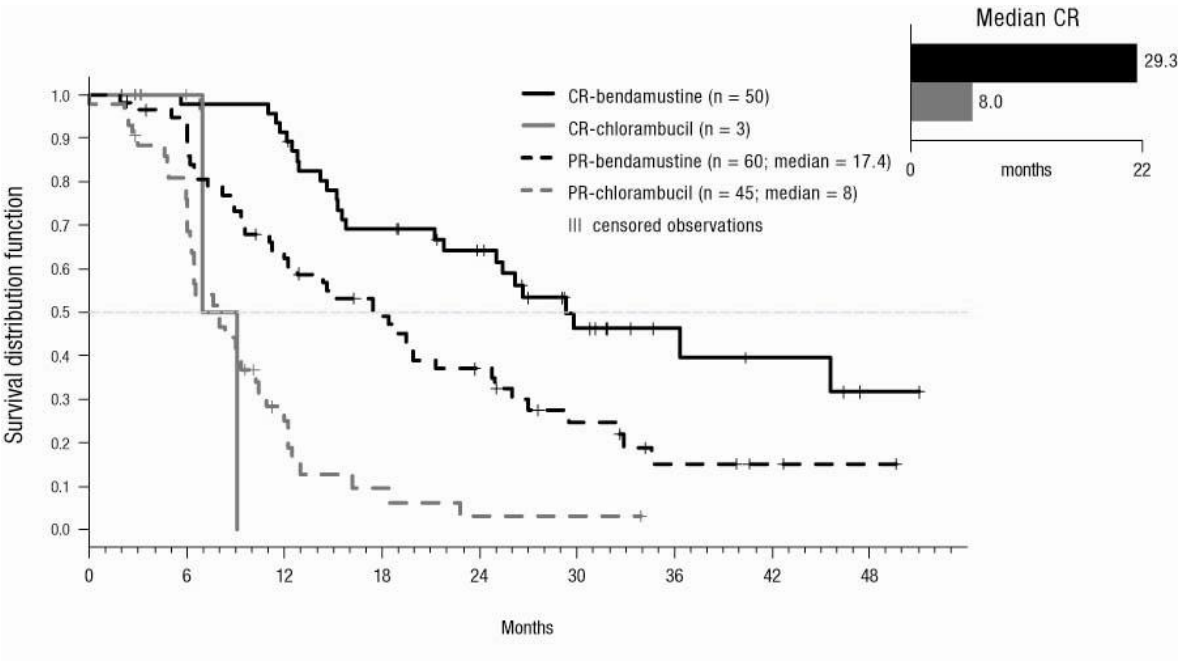
Duration of response

Figure 5.6 shows duration of response.

According to the ICRA, there were 158 responders. The median duration of response was 21.8 months in the bendamustine group and 8.0 months in the chlorambucil group [hazard ratio (95% CI) = 4.46 (2.89 – 6.88); *P*<0.0001].

The median duration of CR was 29.3 months for patients treated with bendamustine and 8.0 months for those treated with chlorambucil [hazard ratio (95% CI) = 45.11 (3.87 – 525.3); *P*<0.0001]. The median duration of PR was 17.4 months with bendamustine and 8.0 months with chlorambucil [hazard ratio (95% CI) = 2.84 (1.77 – 4.56); *P*<0.0001].

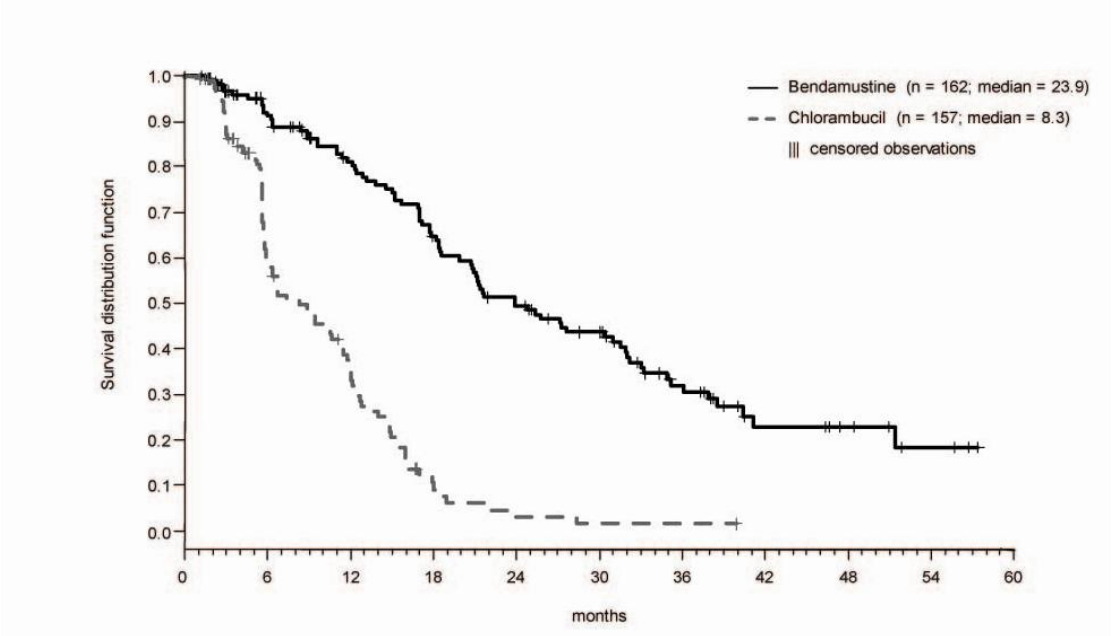
Figure 5.6 Duration of complete and partial response (ITT population)



Time to progression

Figure 5.7 shows time to progression (TTP; i.e. the time from the start of therapy to PD or relapse after intercurrent remission or death due to CLL). Median TTP was significantly longer for bendamustine than for chlorambucil [23.9 months *vs*. 8.3 months; hazard ratio (95% CI) = 4.70 (3.36 – 6.58); *P*<0.0001].

Figure 5.7 TTP (ITT population)



Overall survival

Results of the 35-month analysis strongly suggested an overall survival advantage for bendamustine, although this had not yet reached statistical significance (*P* = 0.1623). Overall, 72 patients (31 in the bendamustine group and 41 in the chlorambucil group) died during follow-up. Death due to CLL was reported for 13 patients in the bendamustine group and 21 patients in the chlorambucil group. An estimation of median overall survival was only possible for patients in the chlorambucil group (65.4 months). The hazard ratio (95% CI) was 1.45 (0.91 – 2.31).

A breakdown of overall survival according to response rate shows that it is the numbers of patients achieving CR and nPR that are driving the overall survival advantage (see Figure 5.8). This is in line with the published literature, which contains increasing evidence that a meaningful remission is required, particularly a complete remission, to gain an improvement in overall survival from therapy. This is discussed further in Section 5.10.4.

Figure 5.8 Overall survival according to response (ITT population)

Recently available data (median observation time = 54 months) showed a statistically significant advantage in overall survival for responders (see Section 6.10.5).

Quality of life

Patients' quality of life was assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires during the treatment period. Patients' overall quality of life (measured by global health status) was modestly improved in both groups during treatment with no significant differences between the groups. Significant differences (*P*<0.05) in favour of chlorambucil were seen in the following individual parameters:

- Physical functioning (Cycles 1, 2 and 3).
- Role functioning (Cycles 1 and 2).
- Emotional functioning (Cycle 5).

- Fatigue (Cycle 2).
- Appetite loss (Cycle 1).

The greatest relative differences were seen for fatigue, nausea and vomiting, dyspnoea, and appetite loss; these were consistent with the higher incidence of these adverse events in the bendamustine group (which is to be expected when receiving a more effective therapy) and did not negatively affect the global health status of the patients in this group.

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.The quality of life data collected in the trial were not appropriate to capture the long-term benefit of bendamustine after therapy was stopped, because they were only collected during the treatment period (i.e. for a maximum of six cycles) and patients who were discontinued from the study were not followed up with respect to quality of life. The EORTC-C30 data were mapped to obtain utility scores (which were applied in the economic model during the treatment period) and to inform a baseline utility score when applying the utility values from Beusterien *et al* after the treatment period.[14] This is described in more detail in Section 6.4.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

Not applicable, as there is only one study available.

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

Not applicable, as Study 02CLLIII is a head-to head RCT.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results.

Identification of studies

A search was carried out in the following databases: Embase, Medline, Medline in-Process, BIOSYS and The Cochrane Central Register of Controlled Trials (CENTRAL). The search was performed on 2nd July 2010.

The RCT search terms used in the searches were taken from the Scottish Intercollegiate Guidelines Network website (http://www.sign.ac.uk/methodology/filters.html), and were used in combination with CLL disease terms, and the generic and brand names for bendamustine. The CLL disease terms used in the search were based on the terms used in a Cochrane review of CLL.[41]

The full search syntax used in each search is provided in Section 9.6.

The searches retrieved the following numbers of results: 155 from Embase, 33 from Medline, one from Medline in-Process, 33 from BIOSYS and seven from CENTRAL. These results were combined into Reference Manager (228 results) and after removal of duplicates, the combined search results totalled 190 papers.

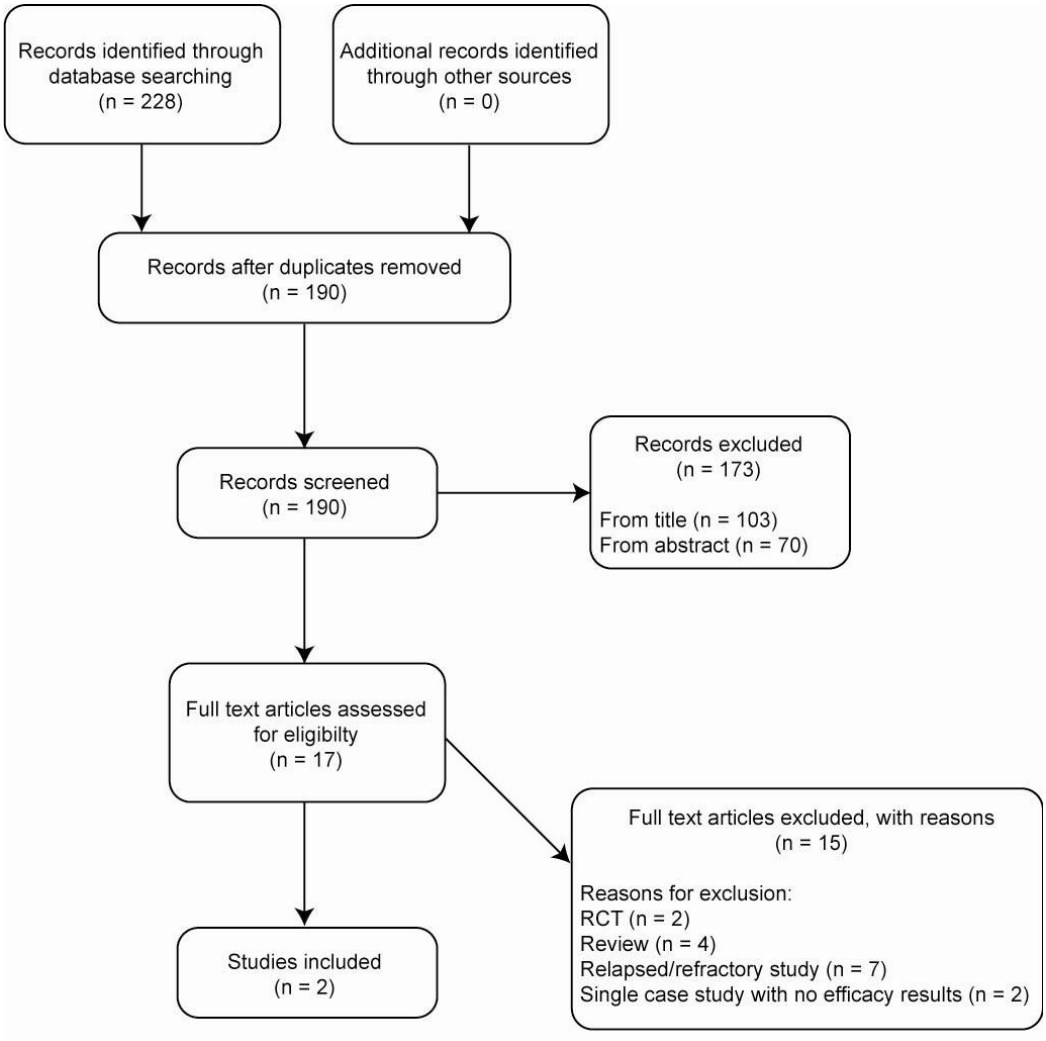
Study selection

Table 5.7 shows the inclusion and exclusion criteria used in the non-RCT searches. Figure 5.9 shows the number of studies included and excluded.

Table 5.7 Eligibility criteria used in search strategy (non-RCTs)

	Clinical effectiveness
Inclusion criteria	Population: patients aged ≥18 years with CLL; no restriction on race or gender
	Interventions: bendamustine compared with or combined with: rituximab alemtuzumab chlorambucil cyclophosphamide methylprednisolone ofatumumab placebo no treatment All combinations of regimens of the above. No restrictions in dose, formulation or mode of delivery
	Outcomes: overall survival, event-free survival, PFS, response rates, duration of response, time to response
	Study design: prospective and retrospective studies. Non-RCTs, including single arm, observational, and cohort and case series.
	Language restrictions: English only
Exclusion criteria	Population: non-CLL patients
	Interventions: fludarabine. Bendamustine-based treatment as a comparator
	Outcomes: no exclusions
	Study design: RCTs
	Language restrictions: non-English

Figure 5.9 Flow diagram of number of non-RCT studies included and excluded



The searches found two non-RCTs. However, as described in Section 5.2.7, both were subsequently discounted.

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results.

Through a systematic review of the clinical literature, four Phase III RCTs investigating bendamustine were identified (see Section 9.8). None of the four studies are relevant for the decision problem, since none included chlorambucil as a comparator and none were in CLL.

Out of the 83 non-comparative clinical studies identified through the literature review, six abstracts were judged to be relevant. These were all related to the study described in this submission (Study 02CLLIII). Details of the adverse events in this study are given in Section 5.9.2.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Most adverse events in Study 02CLLIII were haematological. As expected, the number of haematological events was generally higher in the bendamustine group than in the chlorambucil group. These events were generally manageable and of short duration.

The safety population (i.e. those patients who received at least one dose of study medication) included 312 patients (161 in the bendamustine group and 151 in the chlorambucil group). Overall, adverse events were reported in 143 patients (89%) in the bendamustine group and 122 (81%) in the chlorambucil group. Table 5.8 shows adverse events occurring in ≥5% of patients.

Table 5.8 Summary of adverse events occurring in ≥5% of patients: all grades

	Number (%) of patients				Relative risk (95%CI)		Rate difference (95% CI)		*P* value
	Bendamustine (n = 161)		Chlorambucil (n = 151)						
Blood and lymphatic system disorders									
Neutropenia/granulocytopenia	44	(27)	21	(14)	1.97	(1.25 – 3.10)	0.134	(0.05 – 0.22)	0.0036
Thrombocytopenia	40	(25)	31	(21)	1.21	(0.80 – 1.83)	0.043	(-0.05 – 0.14)	0.3644
Anaemia	35	(22)	21	(14)	1.56	(0.96 – 2.54)	0.078	(-0.01 – 0.16)	0.0721
Leukopenia	28	(17)	4	(3)	5.25	(2.35 – 11.76)	0.141	(0.08 – 0.21)	0.0001
Lymphopenia	10	(6)	1	(1)	9.38	(1.79 – 49.06)	0.055	(0.02 – 0.09)	0.0080
Gastrointestinal disorders									
Nausea	31	(19)	21	(14)	1.38	(0.84 – 2.29)	0.053	(-0.03 – 0.14)	0.2060
Vomiting	25	(16)	10	(7)	2.34	(1.20 – 4.59)	0.089	(0.02 – 0.16)	0.0129
Diarrhoea	16	(10)	6	(4)	2.50	(1.04 – 6.00)	0.060	(-0.00 – 0.12)	0.0401
General disorders and administration site conditions									
Pyrexia	40	(25)	8	(5)	4.69	(2.49 – 8.84)	0.195	(0.12 – 0.27)	0.0000
Asthenia	14	(9)	7	(5)	1.88	(0.79 – 4.45)	0.041	(-0.01 – 0.10)	0.1533
Fatigue	14	(9)	7	(5)	1.88	(0.79 – 4.45)	0.041	(-0.01 – 0.10)	0.1533
Chills	9	(6)	2	(1)	4.22	(1.06 – 16.85)	0.043	(0.00 – 0.08)	0.0415
Immune system disorders									
Hypersensitivity	8	(5)	3	(2)	2.50	(0.71 – 8.82)	0.030	(-0.01 – 0.07)	0.1541

Infections and infestations									
Nasopharyngitis	11	(7)	11	(7)	0.94	(2.10 – 0.42)	-0.005	(-0.06 – 0.05)	0.8762
Infection	10	(6)	2	(1)	4.69	(1.21 – 18.13)	0.049	(0.01 – 0.09)	0.0251
Investigations									
Weight decreased	9	(6)	5	(3)	1.69	(0.59 – 4.86)	0.023	(-0.02 – 0.07)	0.3320
Metabolism and nutrition disorders									
Hyperuricaemia	12	(7)	2	(1)	5.63	(1.54 – 20.60)	0.061	(0.02 – 0.11)	0.0091
Respiratory, thoracic and mediastinal disorders									
Cough	10	(6)	7	(5)	1.34	(0.52 – 3.42)	0.016	(-0.03 – 0.07)	0.5407
Skin and subcutaneous tissue disorders									
Rash	15	(9)	7	(5)	2.01	(0.86 – 4.70)	0.047	(-0.01 – 0.10)	0.1071
Pruritus	8	(5)	4	(3)	1.88	(0.59 – 5.98)	0.023	(-0.02 – 0.07)	0.2877

Grade 3 or 4 neutropenia occurred in 37 patients (23%) treated with bendamustine and 16 (11%) treated with chlorambucil. Granulocyte colony stimulating factors were used at the discretion of the investigators in 23 of 783 cycles (3%) in the bendamustine group and in two of 733 cycles (0.3%) in the chlorambucil group. Erythropoietin was used in 0.5% and 0.3% of all cycles in the bendamustine and chlorambucil groups, respectively.

A total of 23 patients (18 in the bendamustine group and five in the chlorambucil group) were withdrawn from the study due to unacceptable toxicity or because the risk/benefit assessment was no longer considered acceptable by the investigator. 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).

Two patients in the bendamustine group and none in the chlorambucil group experienced grade 3 hypersensitivity reactions. There were no grade 4 hypersensitivity reactions. A full description of grade 3/4 adverse events can be found in the published paper.[13]

One hundred and thirty-four patients (83%) in the bendamustine group and 99 (66%) in the chlorambucil group had adverse events that were considered to be related to treatment.

There were 72 deaths during the study: 31 in the bendamustine group and 41 in the chlorambucil group. Most occurred at least 100 days after the last dose of study drug; disease progression was the most common cause of death.

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.

One patient in the bendamustine group was diagnosed with a lung neoplasm during treatment and was withdrawn from the study. There was one report of a new malignancy during follow-up: a bronchial carcinoma in a patient who had received bendamustine was detected 12 months after the patient had finished the study.

Two patients experienced tumour lysis syndrome; both patients had received their first cycle of bendamustine. However, these events were not fatal and the patients continued treatment.

Adherence to the dosing schedule was high in both groups. In total, 90% of the planned bendamustine dose and 95% of the planned chlorambucil dose were administered.

Fifty-eight patients (36%) in the bendamustine group and six (4%) in the chlorambucil group received anti-emetics. These were given as preventive therapy in 46 of the 58 patients in the bendamustine group and in two of the six patients in the chlorambucil group.

Severe infections are of particular interest, as they are a major cause of morbidity and mortality in CLL patients.[48] Grade 3/4 infections were reported by 8% of patients treated with bendamustine and 3% treated with chlorambucil in Study 02CLLIII. These infections were generally manageable and of short duration.

During the study there were nine documented, treatment-related hospitalisations in the bendamustine group and three in the chlorambucil group. One patient (<1%) in the bendamustine group died during the treatment period (owing to COPD and acute cardiac and pulmonary failure), compared with three patients (2%) in the chlorambucil group (owing to CLL, haemorrhagia and heart failure). These death rates are comparable with that in a recent study of FCR *vs*. FC,[9] in which treatment-related death was reported for 2% of patients treated with FCR and 1.5% treated with FC.

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Bendamustine was generally well tolerated for an agent in this class in patients with previously untreated CLL (the rates of AEs, haematological toxicities and infections were not unexpected). This is in line with its long-established safety and tolerability profile. As expected for a more effective agent, its toxicity was slightly greater than that of chlorambucil.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The results of Study 02CLLIII show that bendamustine offers substantial benefits over chlorambucil for patients with previously untreated CLL. Patients receiving bendamustine had a significantly higher ORR than those in the chlorambucil group (68% *vs.* 31%; *P*<0.0001). More patients reported a CR with bendamustine than with chlorambucil (31% *vs*. 2%; *P*<0.0001). The high CR rate achieved with bendamustine is important, as there is evidence that CR is associated with longer PFS[5-8] and that deeper response leads to an improved overall survival advantage (see Section 5.10.4).

Median PFS was significantly longer with bendamustine than with chlorambucil (21.6 months *vs.* 8.3 months; *P*<0.0001). Longer PFS equates to longer time without symptoms and treatment, and hence to longer time in an improved health state. This correlates with improved quality of life for patients. A more recent analysis (54 months) has reconfirmed the PFS advantage and demonstrated an overall survival advantage for responders (see Section 6.10.5).

For chemotherapy agents, there is often a trade-off between efficacy and toxicity. In Study 02CLLIII, bendamustine was associated with a higher incidence of haematological adverse events than chlorambucil, but these were as expected and were generally manageable.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

The study presented in this submission (Study 02CLLIII) is a randomised clinical trial against the current standard of care for the patient population under consideration. The results of this study (in terms of the benefits offered by bendamustine) are impressive. The considerable improvement in patient's response (PR and CR) and PFS should lead to quality of life improvements for patients after the treatment period. Study results also demonstrate an overall survival advantage with bendamustine – with the greatest overall survival advantage found with patients who achieved a CR, a pattern that is consistent with other studies. These results are strengthened by a more recent analysis showing a statistically significant overall survival advantage in responders (see Section 6.10.5).The evidence also shows that bendamustine has a manageable tolerability profile for an agent in this class.

The results of the study were assessed by an independent, blinded committee to mitigate against physician bias (see Section 5.10.4).

Limitations

Minimal residual disease was not measured during the study, nor were cytogenetic tests carried out. However, these procedures were not routine at the time the study was started.

The open-label nature of the study may have introduced some bias. For example, patients receiving bendamustine may have been more inclined to report lower quality of life or more adverse events, as they may have associated a treatment given intravenously as 'harsher' than a treatment taken orally.

Quality of life data (EORTC-C30) were only collected during the treatment period in Study 02CLLIII, and patients who discontinued the study were not followed up long-term, meaning that it was not possible to use these data for the entire duration of the economic analysis. As discussed in Sections 6.4.3 and 6.4.4, baseline utility values were mapped from the EORTC-C30 to EQ-5D utilities and applied for the treatment period in the economic model (approximately 4.9 months), and were also used to inform the stable disease health state when applying the utility values from Beusterien *et al*[14] after the treatment period.

There were some errors in dosing of chlorambucil during the study; these are described in Section 5.10.4.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Overall, the evidence base is relevant to the decision problem as it includes the appropriate patient population, comparator and outcomes. The outcomes assessed in Study 02CLLIII were of direct relevance to benefits that would be experienced by patients in practice. As CLL is incurable, the quality of patients' response to treatment is particularly relevant, as a CR is associated with longer PFS. PFS is a relevant outcome, as a longer time without symptoms and treatment would be expected to be related to improved quality of life. Measurement of response rates is also important when assessing the impact on overall survival.

The only outcome which was not captured optimally was quality of life (as measured using the EORTC-C30). Quality of life data were only collected during the treatment period, and patients who discontinued the study were not followed up long-term with respect to quality of life. For example, the number of global health status questions completed at baseline was 132 in the bendamustine group and 113 in the chlorambucil group. By Visit 6, this had decreased to 84 and 68 in the bendamustine and chlorambucil groups, respectively. This has the potential to create considerable bias as patients who left the study before completion of six treatment cycles were more likely to be in a more severe health state. Importantly, there were no long-term data from Study 02CLLIII capturing the improvement in health status *after* the treatment period. For these reasons, it was not possible to apply the quality of life data collected during the clinical trial in the economic analysis.

As described in Section 5.5, the EORTC-C30 quality of life data collected during the treatment period showed modest improvements in global health status from baseline to

end of treatment for both bendamustine and chlorambucil, but did not show any significant differences between the treatment arms. This is to be anticipated, as the improvement in quality of life that bendamustine patients would be expected to experience due to being in a better health state is likely to be outweighed by the adverse events during the treatment period. This pattern has been observed in other therapies for CLL. In the CLL4 study,[49] patients treated with fludarabine plus cyclophosphamide reported lower EORTC quality of life scores during treatment and higher scores after treatment than patients receiving either fludarabine alone or chlorambucil – the authors concluded that this reflected the more frequent adverse events and better response rate with fludarabine plus cyclophosphamide. The FACT-G questionnaire was used to assess the quality of life of patients in the REACH trial for rituximab-refractory/relapsed CLL.[50] Assessments were made at the end of Cycles 3 and 6, and after 1 year. The study reports that FACT-G scores did not change substantially over the study period and showed very little difference between treatment groups. As with Study 02CLLIII, quality of life in the REACH trial was not assessed for those with progressed disease and was only captured in patients who started a new CLL treatment before progression; therefore the results need to be interpreted with caution.

Five of the NICE submissions for CLL therapies have not used the quality of life measures in the clinical data package to determine utilities for the economic model.[50-54] All five submissions have used utility measures from outside the clinical trial data. A similar approach was taken for the current appraisal, with utility values from Beusterien *et al*[14] being included in the health economic analysis for bendamustine - the rationale for selection of this study is described further in Section 6.4.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Chlorambucil efficacy

Table 5.9 shows the response rates for chlorambucil in published studies.

Table 5.9 Chlorambucil response rates

Study	ORR	CR	PR	nPR
02CLLIII[10]	31%	2%	26%	3%
Rai[46]	37%	4%	33%	-
Eichhorst[50]	51%	0%	51%	-
Hillmen[56]	55%	2%	53%	-
Catovsky (CLL4)[49]	72%	7%	46%	19%

These studies were identified from a systematic review on comparative efficacy of first-line therapies for chronic lymphocytic leukaemia undertaken by Janssens *et al*.[57]

Of particular note is the large difference in the ORRs reported in Study 02CLLIII (31%) and the CLL4 trial (72%). A breakdown of the ORRs shows that the CR rates are similar between the studies; the variation is in the proportion of patients considered to have had partial responses. One explanation for this is that there tends to be more scope for subjective judgement in the assessment of a PR than in the assessment of a CR. In addition, CLL4 (in which 65% of patients had a PR or nPR) used a modified version of the NCI-WG criteria when assessing PR. The other studies appear to have used unmodified versions of these criteria.

Other factors that may have contributed to the wide variation in response rate are:

- Independent assessment of response: the CLL4 trial was investigator-led, whereas Study 02CLLIII was a regulatory trial and would therefore have been subject to different controls, assessment and monitoring. For example, the responses recorded in Study 02CLLIII and in the Hillmen study (which was also a regulatory study) were assessed by an independent data monitoring committee. The other studies make no mention of any independent blinded review of responses.

  In Study 02CLLIII, the investigators' assessments gave an ORR of 40%; following the independent assessment, this was adjusted to 31%. A recent analysis of studies in solid tumours showed that investigators do tend to overestimate response rate compared with independent blinded review committees by a mean of 4.57% (95% CI 2.95% to 6.19%).[58] The authors give several possible explanations for this. For example, some variability is expected in assessment of response due to chance alone, and investigators may be influenced by knowledge of the clinical status of the patient. In addition, there may have been a behavioural element – investigators in Study 02CLLIII may have been more conservative with their assessments if they knew they were going to be monitored independently.

- Stage of disease: Study 02CLLIII was the only study that did not include patients with stage A progressive disease (or the Rai staging equivalent). It might be

expected that patients with stage A progressive disease would respond better to treatment, hence the higher response rates in the other studies.

The table below summarises the differences between the methodology in these studies.

Table 5.10 Comparison of methodology in published chlorambucil studies

	02CLLIII	Rai	Eichhorst	Hillmen	Catovsky
Was this a regulatory study?	✓	×	×	✓	×
Were the responses independently assessed?	✓	Not stated	Not stated	✓	Not stated
Did the study include patients with stage A disease (or Rai equivalent)?	×	✓	✓	✓	✓
Were the NCI-WG criteria used to define response?	✓	✓	✓	✓	Modified version

Chlorambucil dosing

The current treatment guidelines for CLL give no specific regimen for chlorambucil dosing.[3] Discussions with haematologists during advisory boards have confirmed that there is currently no real consensus on chlorambucil dosing, and that the chlorambucil dose used in this study was not at odds with current clinical practice. Table 5.11 shows the chlorambucil doses used in published studies, including Study 02CLLIII: cumulative doses (where reported) were broadly similar between studies.

Table 5.11 Comparison of chlorambucil doses in published studies

		Dose (mg)		
Study	Regimen	Total per cycle	Per m^2 per cycle	Median cumulative
02CLLIII[10]	0.8 mg/kg Days 1 + 15	112	60	522
Rai[46]	40 mg/m^2 every Day 28	74	40	N/A
Eichhorst[50]	0.4-0.8 mg/kg Days 1 + 15	56 - 112	30 - 60	455
Hillmen[56]	40 mg/m^2 every Day 28	74	40	515
Catovsky[49]	10 mg/m^2 Days 1 - 7	130	70	N/A

Errors in calculation of chlorambucil dose

Whereas the intravenous administration of bendamustine guaranteed a good compliance with the dosing instruction in the protocol for Study 02CLLIII, it appeared that oral administration of chlorambucil led to some deviations from the dosage prescribed by the protocol. In some of these cases, the basis for the dose calculation was not Broca's normal weight (height of the patient in cm minus 100 cm), but the real weight of the patient. This approach followed a dosing method as described by Knospe *et al* who introduced the bi-weekly oral administration of chlorambucil in the treatment of CLL.[59]

The average weight of the population in the chlorambucil group according to Broca's normal weight was 68.5 kg (height 168.5 cm – 100 cm). This corresponds to a planned average dose according to the protocol of 110 mg. The average real weight of the population in the chlorambucil group was 73.9 kg, which corresponds to an average dose of 118 mg and is therefore higher than the dose according to Broca's formula.

It therefore appears that some patients received higher doses of chlorambucil than planned during the first cycle of treatment. In most cases, the dosing was corrected in subsequent cycles when the investigators became aware of this error (usually after visits by monitors).

The comparison of average doses showed that patients in the chlorambucil group were not undertreated due to errors in the dose calculation and the interpretation of the efficacy data resulting from this trial was not compromised.

The average dose applied in the chlorambucil group reached 95% of the planned dose whereas 90% was achieved in the bendamustine group.

It is also worth noting that in clinical practice doses are always tailored to the individual disease conditions of the patient. It can be assumed that small differences of doses in oral administration of chlorambucil in this trial are clinically without relevance and certainly do not compromise the assessment of the endpoints of this study.

Overall survival

At the time of the main analysis, the results for overall survival showed an improvement in the number of events between the two treatments with 31 deaths reported in the bendamustine group and 41 in the chlorambucil group [hazard ratio (95% CI) = 1.45 (0.91 – 2.31)]. Despite the strong overall survival trend in favour of bendamustine, no statistically significant treatment difference in overall survival was evident in Study 02CLLIII to date. This is probably because the data are not sufficiently mature. An estimation of median overall survival was only possible for patients in the chlorambucil group as more than half the patients receiving bendamustine were still alive. However, a more recent analysis showed a significant overall survival advantage in responders (see Section 6.10.5).

A recent analysis showed a significant overall survival advantage in responders, which at present has not translated into a significant difference in overall survival between the two treatments. The fact that a statistically significant overall survival advantage between the two treatments has not emerged to date is not surprising given the indolent nature of the disease (patients have a relatively long life expectancy). A survival benefit would not be expected until after an extended follow-up period, particularly in the first-line setting. The lack of a statistically significant overall survival advantage in the initial analysis was also the case for the two most recent innovations in CLL: the purine analogue, fludarabine, and the immunomodulator, rituximab. The efficacy of fludarabine in front-line treatment

was shown to be superior to chlorambucil in terms of response rates and duration of remission,[46] but a frequent criticism of these studies is that overall survival was not improved by fludarabine in any of the initial reports. However, extended follow-up of the CALGB9011 study, presented at the 2009 American Society of Hematology meeting, showed that patients treated with fludarabine experienced superior overall survival compared with those treated with chlorambucil: 8-year overall survival was 31% *vs*. 19% for FC and chlorambucil, respectively [P = 0.04 (0.07 adjusted for covariates)].[60] Likewise, in CLL8 the initial results showed no overall survival benefit,[5] but a 3 year follow-up analysis reported by Hallek *et al* found that there was a statistically significant difference for Binet B stage patients in favour of FCR compared with FC (HR 0.45; P<0.001).[9] An overall survival benefit in this patient group is relevant for bendamustine, as over 70% of the patients in Study 02CLLIII had Binet stage B disease.

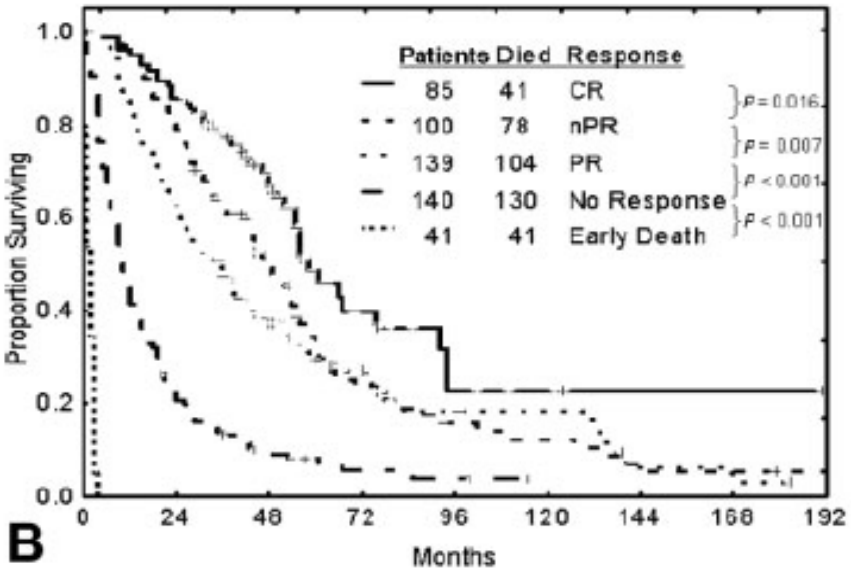
Although it is not common for a therapy to reach a statistically significant overall survival benefit during the initial analysis of a first-line trial, the depth of response is a good indicator of whether an overall survival benefit is likely to be achieved. Prior to Hallek's report, Tam *et al* had already investigated the impact of the intensity of response on overall survival, following initial therapy with FCR. In this study, it was established that patients experiencing a CR or nPR had a significantly longer survival period compared with partial responders (P =0.01) and non-responders.[6]

Similarly, in a recent prospective investigation on the efficacy of fludarabine/cyclophosphamide/mitoxantrone (FCM) as initial therapy for CLL, Bosch *et al* reported on the probability of survival according to the degree of response to therapy.[8] If the overall survival was 70% at 4 years, survival times differed greatly according to depth of initial response:

- Patients with CR or nPR had a survival probability at 3 years of 100%.
- Patients with a PR had a survival probability at 3 years of 51% (P<0.05).
- Patients not responding (SD, PD) had a median survival of 11 months.

This link between depth of response and overall survival had previously been established in a retrospective study comparing three sequential groups of patients with relapsed or refractory CLL treated with fludarabine-based regimens.[61] For all groups combined (fludarabine, FC and FCR), the median survival was significantly longer (P<0.05) for responders, particularly for CR compared with PR. In addition, the comparison established that the treatment resulting in the highest CR rate, FCR (with a CR rate of 25% compared with 5 – 10% for fludarabine and 10 – 15% for FC) was the treatment associated with the longest estimated median overall survival: 49 months (compared with 20 months for fludarabine and 31 months for FC; Figure 5.10).

Figure 5.10 Estimated overall survival function by response type



In light of these observations, combined with the high proportion of CR and nPR achieved by patients in the bendamustine group compared with the chlorambucil group (42% *vs.* 5%), it is likely that as further results from Study 02CLLIII become available, a statistically significant overall survival benefit will become apparent in favour of bendamustine over chlorambucil. The relationship of greater overall survival for patients with CR and nPR is already present in Study 02CLLIII (see Section 5.5) and is now statistically significant at 54 months for responders (see Section 6.10.5).

It should also be noted that patients receiving a less effective treatment will relapse earlier and will often be given the treatment that patients in the other group received. This is exemplified by the number of subsequent antineoplastic therapies received by patients in the two groups of Study 02CLLIII (Table 5.12). Notably, almost 30% of patients in the chlorambucil group were given a bendamustine-based therapy as subsequent treatment.

Table 5.12 Summary of antineoplastic therapy after progression in Study 02CLLIII

	Number (%) of patients	
	Bendamustine (n = 162)	Chlorambucil (n = 157)
All antineoplastic therapies	79 (48.8)	99 (63.1)
Bendamustine-based therapies	21 (13)	46 (29.2)
Rituximab-based therapies	8 (5)	20 (12.7)

In addition, patients in the chlorambucil group were more than twice as likely to be given a rituximab-based chemotherapy following progression than patients in the

bendamustine group, which in light of recent data on the long-term impact of immunochemotherapies on overall survival for front-line and relapsed CLL patients,[9,60,62] is likely to contribute to an underestimation of an overall survival benefit provided by bendamustine over chlorambucil. To date, Napp has not undertaken any formal statistical analysis to estimate the impact of subsequent lines of therapy on the overall survival benefit, but this is a potential area of research given the bias it introduces against bendamustine.

In summary, the significantly greater response rate in the bendamustine group suggests that the overall survival advantage currently present is likely to be reinforced over time as has occurred in other recent CLL trials. This overall survival advantage is even more impressive given the bias against bendamustine caused by patients being crossed-over between the two arms of the study to receive second-line bendamustine, and the substantially fewer follow-up therapies received by bendamustine patients.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem.

A review of cost-effectiveness literature was conducted and aimed to identify studies reporting both costs and effects associated with bendamustine compared with any other treatment in CLL. The searches were carried out in June 2010 in Medline, Medline in Process, Embase and EconLIT using OVID SP as the search provider. A search was also carried out in NHS EED. The Medline, Medline in Process and Embase search strategies combined CLL disease terms with cost-effectiveness search terms and specific drug terms for bendamustine. The EconLIT and NHS EED databases were searched using disease terms only. All search syntax is shown in Section 9.10.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology.

The cost-effectiveness search retrieved one entry in Medline and Medline in Process that was not relevant, and two entries in Embase that were also not relevant. NHS EED and EconLIT retrieved 69 and 14 hits, respectively, but none of these were relevant.

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

Not applicable.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The model evaluated the cost-effectiveness of first-line bendamustine in CLL patients considered unfit for fludarabine-based therapies. This is in line with the licensed indication, which specifically states that bendamustine should only be used for CLL patients when fludarabine is not appropriate. As discussed in Section 2.5, there are no objective criteria applied in the UK to classify those patients. However, the study population is reflective of the type of patient expected to receive bendamustine in the UK. The group of patients currently treated with chlorambucil in the UK is heterogeneous with respect to age, co-morbidities and performance status. In Study 02CLLIII, 51% of patients were aged <65 years and 49% were aged ≥65 years, and there was a range in patients' WHO performance status (67% with WHO 0, 28% with WHO 1 and 3% with WHO 2). In addition, it would be anticipated that those investigators

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

outside the UK who were recruiting patients into the study were making similar decisions about treatment choices to UK physicians. They would naturally have been making a decision about whether patients were suitable for fludarabine-based therapy or not, as there was a study of fludarabine combination therapy recruiting at the same time (CLL8).

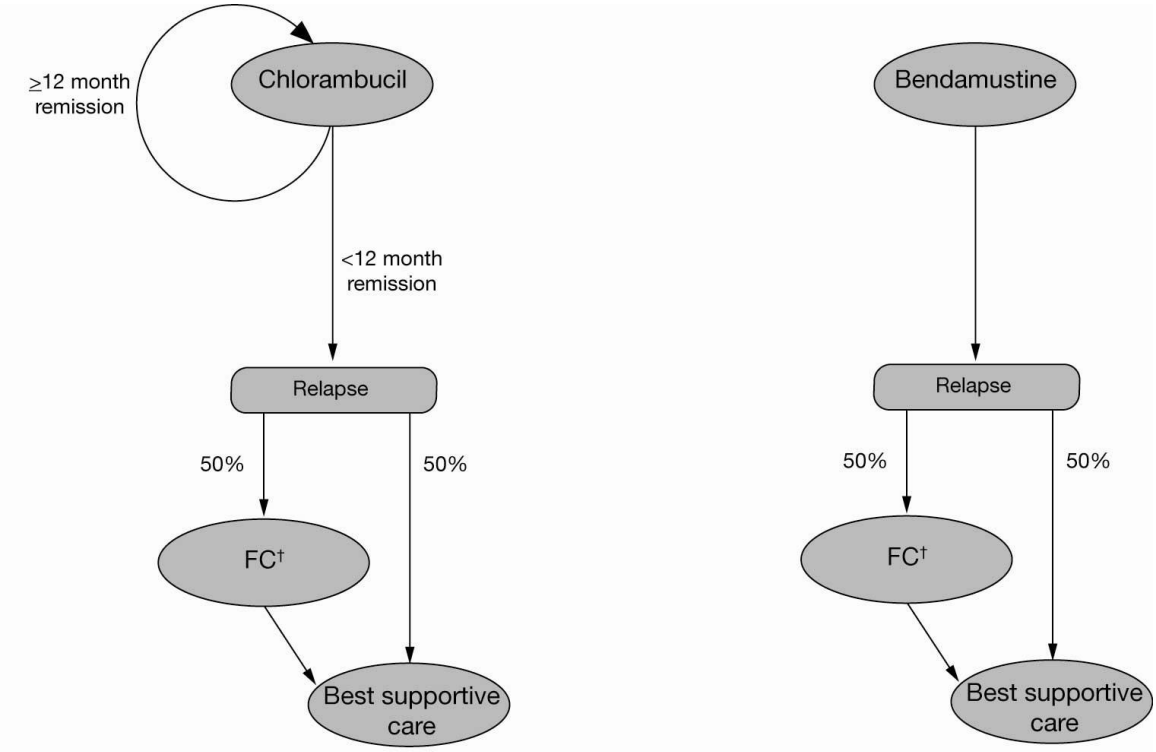
Since no information about the chromosomal markers linked with CLL prognosis was collected during Study 02CLLIII, the model structure and parameters chosen were not reflective of any specific subgroups of CLL patients with respect to those chromosomal abnormalities.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

A Markov process was used to predict long-term health outcomes and costs associated with bendamustine and chlorambucil as based on the current treatment pathway for UK first-line CLL patients. Figure 6.1 shows the treatment pathways assumed in the model. Patients begin treatment on bendamustine or chlorambucil. Following first-line treatment, patients who remain progression-free for at least 12 months on chlorambucil are re-treated. It is assumed that patients can only be treated once with bendamustine, which is in line with the decision problem described in Section 4. Patients who progress within 12 months having received chlorambucil (or all patients treated with bendamustine who progress regardless of duration of response) have a 50% probability of receiving either a FC-based regimen or best supportive care. All patients in the best supportive care health state are assumed to receive no active therapy. Patients who receive FC will automatically move to best supportive care (BSC) once they fail.

Figure 6.1 Treatment pathways assumed in the model



†By this stage, patients may be considered strong enough to try treatment with a fludarabine regimen. FC = fludarabine plus cyclophosphamide

Figure 6.2 shows the health states used to simulate the costs and health outcomes associated with each treatment line. All patients began treatment (with either chlorambucil or bendamustine) in the SD health state. In the next model cycle (3 months), they are allocated to their best overall response state: SD, progressive disease (PD) partial response (PR), or complete response (CR). The CR health state includes patients with a characterised CR and patients with characterised nodular PR (previously named nodular complete responders[63]). This is in accordance with the definition from the NCI-WG criteria on CLL that define patients with complete remission and persistent bone marrow nodules as nPR.[44] Patients who enter the SD state and those who enter the CR and PR disease states then faced a probability of progressing. Patients with PD faced a probability of initiating the next line of treatment (where they then faced the same possible transitions), with the exception of patients who were in the BSC health state, and remained in this health state until transition to death.

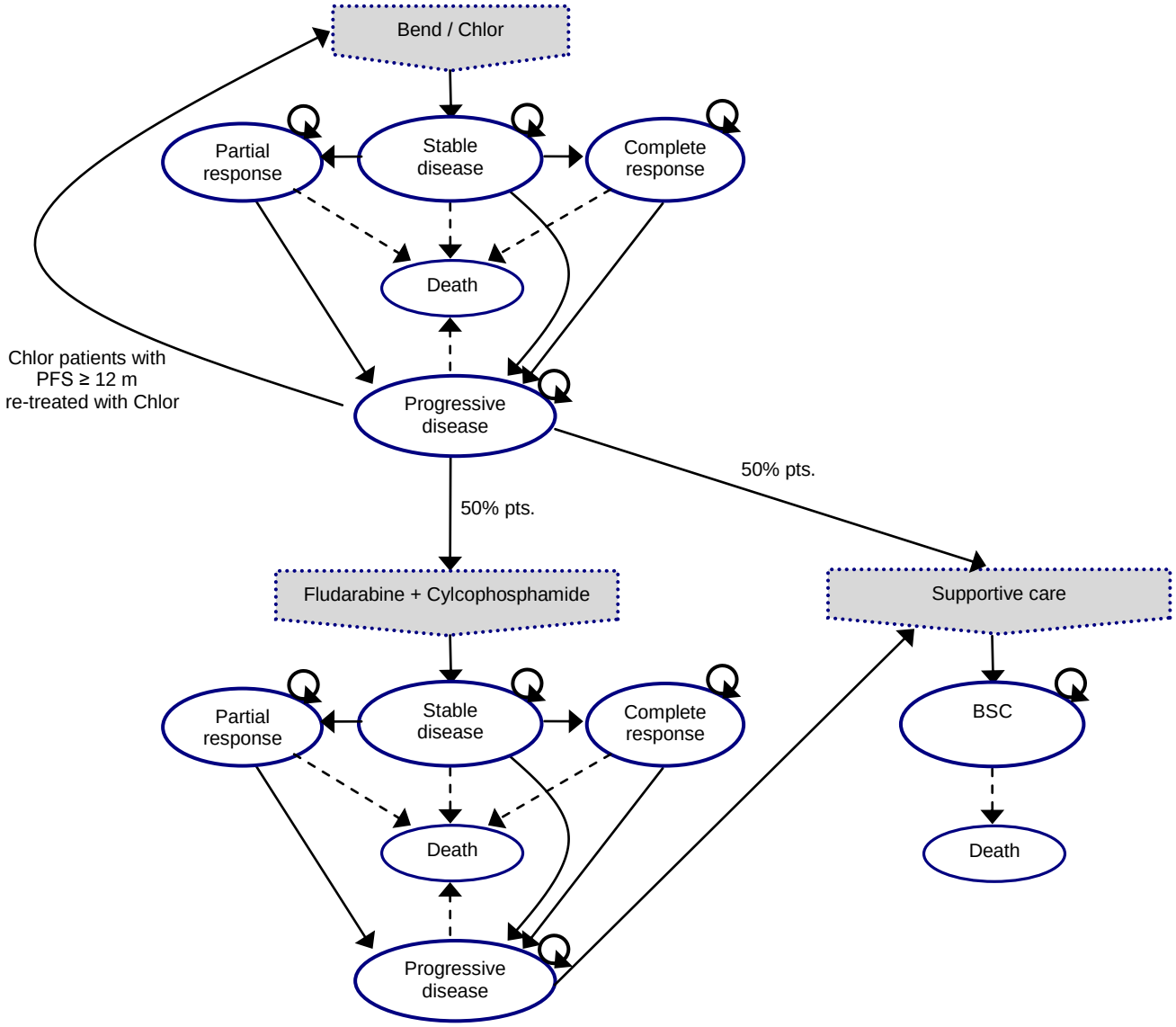
During the treatment period both therapies (bendamustine and chlorambucil) were assigned the baseline utility value recorded from Study 02CLLIII (generated by mapping from the EORTC-C30 quality of life instrument to utility values) plus the disutility from adverse events. Following the treatment period, differences in the quality of life

experienced by patients in different health states were assigned using values from a recent cross-sectional study of 89 members of the general population.[14] This is explained in further detail in Section 6.4.

Overall survival was estimated directly using a 'partitioned survival model' (Area Under Curve) type approach where parametric survival curves were fitted to overall survival data independently of the health states.

The differential adverse event profiles associated with bendamustine and chlorambucil and with subsequent line treatment were also captured in the model.

Figure 6.2 Schematic of model structure



Note: adverse events were modelled separately.

6.2.3 Please justify the chosen structure in line with the clinical pathway of *care* identified in section 2.4.

The economic model was designed primarily to reflect the treatment pathway of CLL patients in the UK, and to take into account the health benefits and costs expected for those patients. The treatment pathway was developed based on national[3] and local[30-37] treatment guidelines and consultation with five haematologists involved in the treatment of CLL patients in England and Wales.[26]

The comparator in the economic model was chlorambucil, which is the standard therapy used in the UK for patients who cannot receive fludarabine. Chlorambucil is well tolerated, but offers lower response rates and reduced PFS compared with FC. Bendamustine presents a manageable toxicity profile, and offers superior response rates and extended PFS compared with chlorambucil.[10] It is therefore evaluated as an alternative to chlorambucil in this patient group.

Alemtuzumab is not considered as a comparator in the present submission as this evaluation is not focused on patients harbouring the 17p chromosomal deletion, for whom it is assumed that alemtuzumab will be the relevant treatment.

Rituximab is also not considered to be a relevant comparator in the current evaluation since it has only been recommended for use in previously untreated CLL patients if the patient is judged fit for fludarabine-based therapies.[28]

After potential retreatment progressed patients could receive fludarabine or best supportive care, in line with UK treatment practice. Having fludarabine as a second-line therapy might seem counter intuitive, given the bendamustine licence is specifically for patients where fludarabine in not appropriate. However, consultation with UK clinical experts confirmed that some patients would be expected to receive fludarabine at second line, even if not judged fit at first-line, because their health status would have improved sufficiently following first-line therapy. In addition, there may be few other therapy options available at this stage.[26]

The chosen design captures the differential gains in quality of life patients experience according to the depth of their clinical remission, as recently evidenced by Beusterien *et al*.[14] This design was also chosen to take into account the differences in time to progression for the different health states; which will again be influenced by the depth of the clinical remission following treatment (see Section 6.3.6 for further details and published evidence).[8,64]

Including overall survival in the model was important given the early, but clear, overall survival benefit seen for the bendamustine group in Study 02CLLIII, and the recent

reports on the positive link between improved overall survival and the intensity of clinical remission following therapy.[6,8,61] See Section 5.10.4 for further discussion.

6.2.4 Please define what the health states in the model are meant to capture.

The model consists of a total of 39 health states. These are described below.

Health states describing first-line treatment outcomes:

1. Stable disease
2. Partial response
3. Complete response
4. Progressive disease (either as a patient's best overall response or following a period of stable disease, partial response or complete response)

Health states describing re-treatment:

5. Re-treatment state (tunnel state describing first 3 months of active treatment phase of re-treatment)
6. Stable disease re-treatment state (tunnel state describing second 3 months of active treatment phase of re-treatment for those who achieve a best overall response of stable disease)
7. Stable disease dwell 6-9 months (tunnel states required to track time of progression – this determines whether chlorambucil patients will be re-treated or moved on to second line therapy)
8. Stable disease dwell 9-12 months (as above)
9. Stable disease dwell 12-15 months (as above)
10. Stable disease dwell 15-18 months*
11. Stable disease dwell 18-21 months*
12. Stable disease dwell 21-24 months*
13. Stable disease dwell >24 months*

States 14 - 29 repeat states 6 - 13 for partial and complete responders to re-treatment.

30. Progressive disease re-treatment state (tunnel state describing second 3 months of active treatment phase of re-treatment)

31. Progressive disease to be considered for re-treatment (progressive disease post-treatment state for patients eligible for re-treatment)
32. Progressive disease to be allocated to second-line (progressive disease post-treatment state for patients not eligible for re-treatment)

Health states describing second-line treatment:

33. FC state (tunnel state describing active treatment phase of second line treatment)
34. Stable disease
35. Partial response
36. Complete response
37. Progressive disease (either as a patient's best overall response to FC or following a period of stable disease, partial response or complete response)
38. BSC state (assumed equivalent in cost and quality of life terms to progressive disease following second line treatment)
39. Death state

The possible transitions between these health states are described in Figure 6.2 above.

*Note that these greyed-out states are not required for the base case analysis, but are required for a sensitivity analysis where bendamustine re-treatment is administered to patients who progress after 24 months or more following first-line bendamustine.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model incorporates different response categories (SD, PR, CR and PD). Having a detailed model input according to the depth of remission is important as the patient's quality of life and time to progression are linked to response.

Underlying disease progression was captured as patients moved into a progressive PD health state. Patients could subsequently exit the PD health state when receiving retreatment or subsequent lines of therapy. The health states representing subsequent lines of therapy are important to capture changes in quality of life as a patient responds to future therapies. Other models submitted to NICE have not allowed retreatment (and

the subsequent remission) and arguably did not sufficiently represent current UK practice.[50,52]

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported.

Table 6.1 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	35 years	NICE guidelines specify a life-time analysis. By year 35 0.54% of the bendamustine group and 0.02% of the chlorambucil group are no longer predicted to be alive by the model	NICE. Guide to the methods of technology appraisal June 2008[65]
Cycle length	3 months	3 months which enabled sufficient accuracy for modelling purposes but also kept the number cycles in the model manageable for computation	NICE. Guide to the methods of technology appraisal June 2008[65]
Half-cycle correction	Half cycle correction applied	Per reference case	NICE. Guide to the methods of technology appraisal June 2008[65]
Were health effects measured in QALYs; if not, what was used?	Quality adjusted life years	Per reference case	NICE. Guide to the methods of technology appraisal June 2008[65]
Discount of 3.5% for utilities and costs	Discount rate 3.5% applied	Per reference case	NICE. Guide to the methods of technology appraisal June 2008[65]
Perspective (NHS/PSS)	Perspective (NHS/PSS)	Per reference case	NICE. Guide to the methods of technology appraisal June 2008[65]

NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The bendamustine dose is as per the licence and reflects what patients received during Study 02CLLIII.

Chlorambucil is available in the UK under the brand name Leukeran. According to the SPC for Leukeran, "Treatment with Leukeran is usually started after the patient has developed symptoms or when there is evidence of impaired bone marrow function (but not bone marrow failure) as indicated by the peripheral blood count. Initially Leukeran is given at a dosage of 0.15 mg/kg/day until the total leucocyte count has fallen to 10,000 per µL. Treatment may be resumed 4 weeks after the end of the first course and continued at a dosage of 0.1 mg/kg/day."

This differs from the regimen used in Study 02CLLIII, in which patients received a dose of 0.8 mg/kg (Broca's normal weight) orally on Days 1 and 15. Use of Broca's normal weight is designed to prevent overweight patients being overdosed with toxic chemotherapy agents and is therefore a safer measure of weight for dosing calculations in this context. Using this calculation, a 70 kg patient would receive a very similar total dose of chlorambucil in each cycle to the licensed UK dose given over seven days per cycle (as in the CLL4 trial and as per common practice in the UK). The only difference is the splitting of the total dose and the days of each cycle the dose is administered, i.e. for a 70 kg patient:

- Licensed chlorambucil dose of 0.15 mg/kg/day for 7 days = a total dose of 73.5 mg for the first cycle and 49 mg for subsequent cycles. Over 12 months, the cumulative dose would be 612.5 mg.
- Study 02CLLIII dose of 0,8 mg/kg (assuming 70 kg Broca's normal weight) on Days 1 and 15 = a total dose of 112 mg per cycle. Over approximately five cycles (as in the study), the total cumulative dose would be approximately 560 mg.

In the UK, chlorambucil has been extensively used for the treatment of CLL, however, there is no UK or international consensus on the appropriate dosing schedule. Cumulative dosing is broadly similar with the different schedules used both in clinical practice across the UK and in international CLL trials (see Section 5.10.4). However, one key difference is that in the UK, treatment can last for approximately 12 months if well tolerated. Therefore, the economic model is based on a dose per cycle that reflects the UK licence, and a cumulative dose that reflects UK common practice. However, the

scheduling of the dosing differs from that described in the SPC for chlorambucil. The dosing used in Study 02CLLIII is therefore appropriate for the decision problem.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed?

No additional treatment discontinuation rules were evaluated in the submission. The number of cycles of therapy that bendamustine and chlorambucil patients received was according to Study 02CLLIII.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Initial response: first-line bendamustine/chlorambucil

During the first cycle of treatment, the model categorises patients according to their best overall response. Four response categories were used: complete response (including CR and nPR), PR, SD, and PD.

As discussed in Section 6.2, patients recorded as experiencing nodular partial response (nPR) were classified as CRs. The potential differences in PFS durations for nPR and CR patients were captured in the model as both subsets of patients were pooled for the time to progression analysis as well as the initial response classification.

Patients recorded as having an unconfirmed response were classified as having stable disease. For the economic analysis, patients for whom no examination data were available (14 in the bendamustine arm and 19 in the chlorambucil arm) were not included in the initial response or time to progression analyses. The response rates applied in the economic analysis are summarised in Table 6.2.

Note that although the absolute number of patients with a response is the same between the clinical (Section 5.5) and economic sections (Table 6.2), the percentage of patients in each response category is slightly different between the two sections. This is because those patients for whom there were no examination data were included in the clinical analyses reported in Section 5.5, but not in the economic analysis.

Table 6.2 Best overall response to first-line treatment

Treatment type		Stable disease (SD + unconfirmed response)	Partial response (PR)	Complete response (CR + nPR)	Progressive disease (PD)
Bendamustine (n = 148)	n	23 (19 + 4)	43	67 (50 + 17)	15
	%	**16**	**29**	**45**	**10**
Chlorambucil (n = 138)	n	37 (32 + 5)	41	7 (3 + 4)	53
	%	**27**	**30**	**5**	**38**

Source: 02CLLIII

Time to progression following initial response: first-line bendamustine/chlorambucil

Parametric survival analyses were fitted to the 02CLLIII data in order to estimate the differential time to progression of patients with CR, PR and SD. In all analyses, death was considered as a censoring event, as death is accounted for separately in the model. Other censoring events were as per the main clinical analysis.

Four parametric distributions were trialled for each survival analysis (exponential, Weibull, log-normal, log-logistic) and models were run with a treatment covariate. The treatment covariate was retained regardless of significance, in order to accurately capture the differences between treatments observed in the trial. Uncertainty around the magnitude of these treatment effects is reflected in the probabilistic sensitivity analysis. Sensitivity analyses are also presented where the survival analyses are run without treatment covariates.

Selection of the preferred parametric form for the hazard function was based on visual comparison of empirical and fitted survival curves and comparison of Akaike's Information Criteria (AIC) across models with $\alpha=3$. For partial and complete response, conclusions drawn from visual comparison of the fitted and empirical survival curves and the AIC concurred. For stable disease the model with the lowest AIC (the Weibull) predicted a larger difference between treatments and seemed to be heavily influenced by the end part of the bendamustine curve. To be conservative the log-logistic, which appears to provide the best fit by visual inspection, is therefore used. Sensitivity analyses are presented using different parametric models.

Time to progression for patients with SD

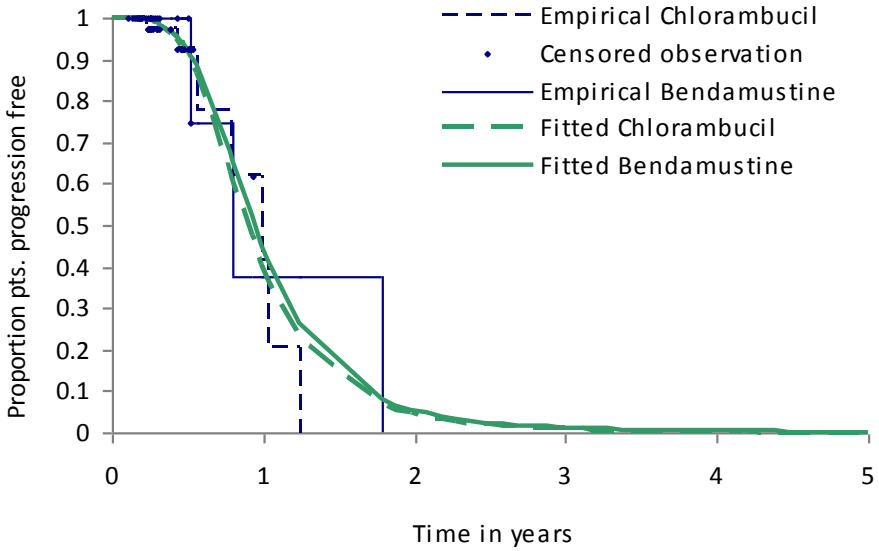
For patients with SD the log-logistic model was used. The results of the analysis are presented in Table 6.3 and a comparison of the empirical and fitted survival curves in Figure 6.3. The fitted curves provide a reasonable approximation to the empirical data. Both the empirical curves and fitted model provide little evidence of different time to progression across treatment arms, for patients with stable disease.

Table 6.3 Results of fitting parametric survival curve to time to progression: SD

Coefficient	Mean	s.e.
Intercept	-0.1052	0.1467
Scale	0.2600	0.0546
Bendamustine	0.0513	0.2895

Source: 02CLLIII
Distribution = Log-Logistic; Events = 10; Censored observations = 50; Covariates = treatment

Figure 6.3 Comparison of empirical and fitted survival curves for time to progression: SD



Time to progression for patients with PR

For patients with a PR, the log-normal model provided the best fit. The results of the analysis are presented in Table 6.4 and a comparison of the empirical and fitted survival curves in

Coefficient	Mean	s.e.
Intercept	0.1259	0.0753
Scale	0.4578	0.0422
Bendamustine	0.5247	0.1084

Source: 02CLLIII
Distribution = Log-normal; Events = 61; Censored observations = 23; Covariates = treatment

6.4. The fitted curves appear to provide a good approximation to the empirical data.

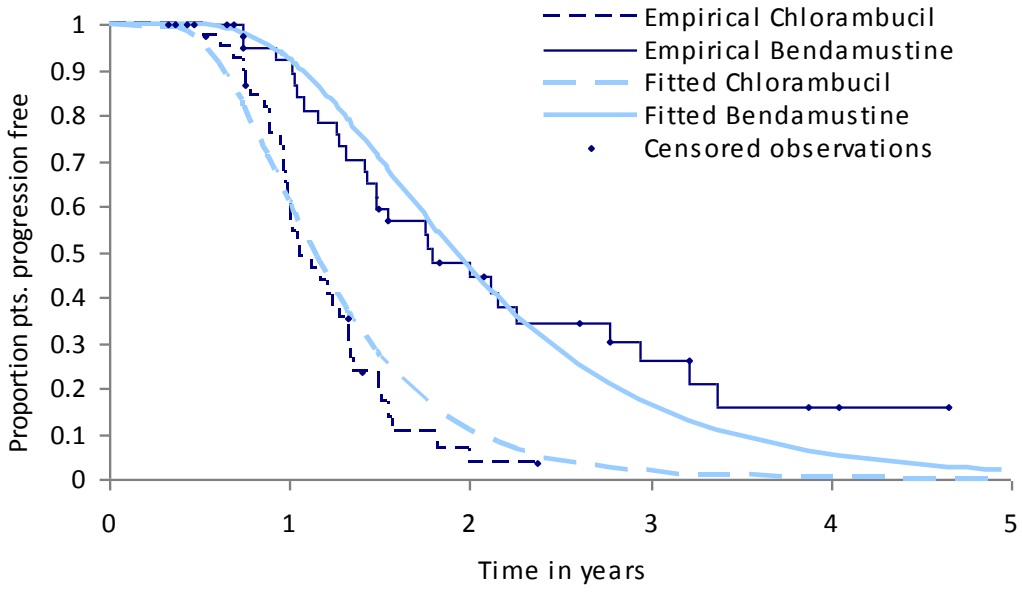
The exponential of the coefficient on the treatment covariate has an accelerated failure time interpretation, thus the analysis tells us that bendamustine is estimated to increase median (or any other percentile) time to progression for partial responders by 69%. This indicates that in addition to bendamustine exerting a treatment effect on time to progression by increasing the proportion of patients in the response categories associated with longer progression-free periods, it also increases progression-free time conditional upon (partial) response status.

Table 6.4 Results of fitting parametric survival curve to time to progression – partial responders

Coefficient	Mean	s.e.
Intercept	0.1259	0.0753
Scale	0.4578	0.0422
Bendamustine	0.5247	0.1084

Source: 02CLLIII
Distribution = Log-normal; Events = 61; Censored observations = 23; Covariates = treatment

Figure 6.4 Comparison of empirical and fitted survival curves for time to progression: partial responders



Time to progression for patients with CR

For patients with a CR the log-normal model provided the best fit. The results of the analysis are presented in Table 6.5 and a comparison of the empirical and fitted survival

curves in **Error! Reference source not found.**6.5. This fitted curve appears to provide a good approximation to the empirical data.

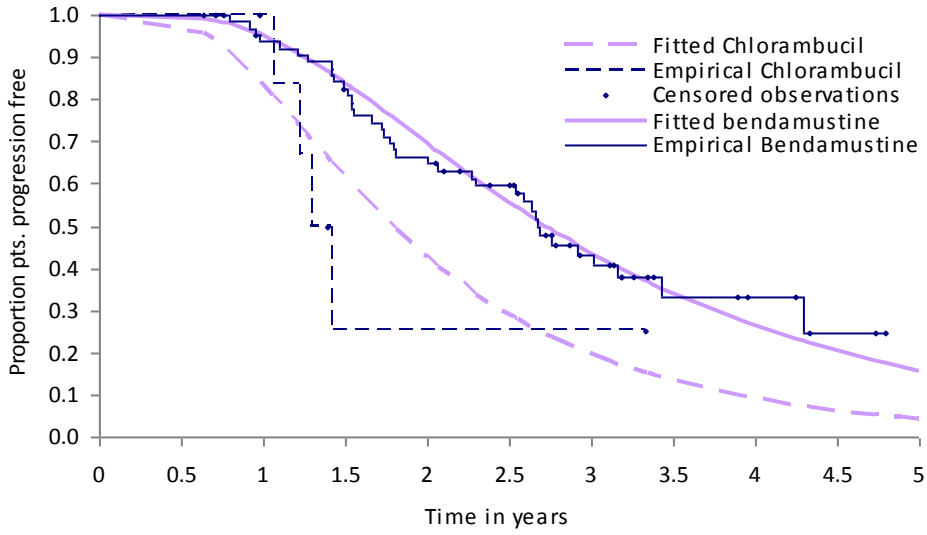
The analysis suggests that median (or any other percentile) time to progression for complete responders is 52% longer for bendamustine patients than for those allocated to chlorambucil.

Table 6.5 Results of fitting parametric survival curve to time to progression: complete responders

Coefficient	Mean	s.e.
Intercept	0.5795	0.2545
Scale	0.6047	0.0712
Bendamustine	0.4217	0.2660

Source: 02CLLIII
Distribution = Log-normal; Events = 41; Censored observations = 33; Covariates = treatment

Figure 6.5 Comparison of empirical and fitted survival curves for time to progression: complete responders

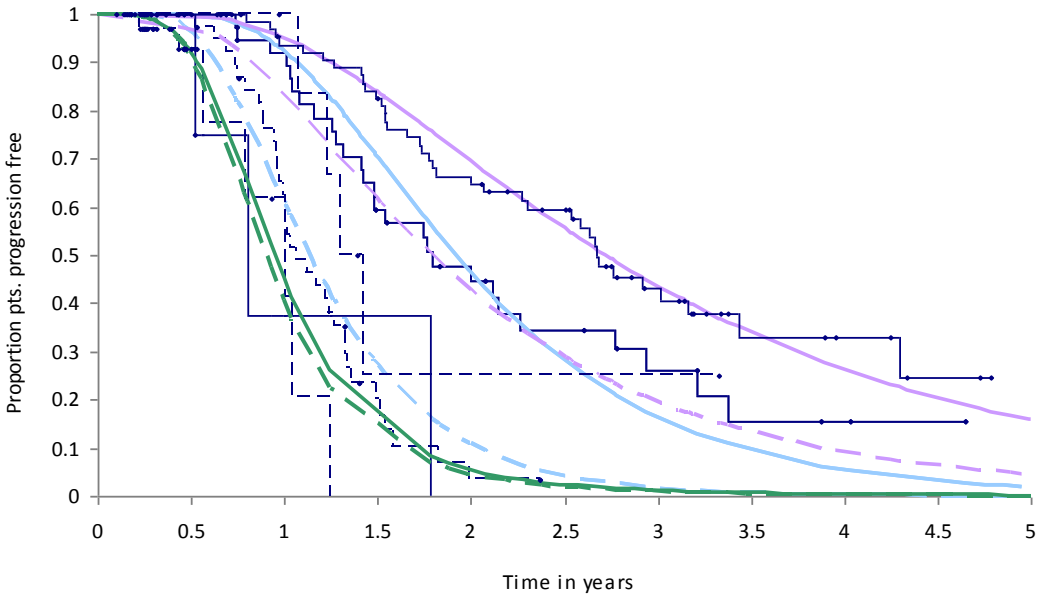


Summary of time to progression data

A summary of time to progression data by best overall response category is shown in Figure 6.6. This shows that the treatment benefit in the model is driven by:

- better response profile in the bendamustine group;
- longer time to progression associated with better response states;
- for partial and complete response states a longer time to progression for bendamustine patients, even when response state is conditioned upon.

Figure 6.6 Summary of time to progression data



Standard formulae were used to convert the parametric survival function parameters to discrete transition probabilities. These formulae are provided in Section 6.3.2.

Time to treatment re-initiation following progression: all treatment lines

Time to treatment re-initiation data is required to inform the probability of entering re-treatment following progression on first-line treatment; the probability of receiving second-line FC following progression on re-treatment/first-line treatment and the probability of entering BSC following progression on second-line FC.

An exponential survival curve was fitted to the 02CLLIII data on time from progression to treatment re-initiation. Although it would be desirable to explore the fit of a range of parametric survival curves to time to re-treatment, this was not pursued as inclusion of a parametric survival curve with a non-constant hazard (e.g. Weibull, log-normal or log-logistic) would have necessitated a more complex modelling approach such as a patient level simulation.

Two individuals who had begun further antineoplastic therapy before progressing were removed from the analysis. Again, death was considered as a censoring event and original treatment allocation is included as a covariate. The results of fitting this curve are presented in Table 6.6.

Table 6.6 Results of fitting parametric survival curve to time to re-treatment

Coefficient	Mean	s.e.
Intercept	0.4097	0.1270
Scale	1.000	-
Bendamustine	-0.0445	0.1861

Source: 02CLLIII
Distribution = exponential; Events = 116; Censored observations = 57; Covariates = treatment

The treatment-specific estimates are applied to estimate the probability of treatment re-initiation following progression on first line treatment and re-treatment. The probability of entering BSC following progression on FC is estimated using the slightly lower probability of treatment re-initiation associated with chlorambucil, reflecting the assumption that patients will be treated less aggressively at this point.

Efficacy of subsequent line therapies

For treatment administered following the first progression event, no efficacy data (response or time to progression) are available from Study 02CLLIII. Data regarding the efficacy of re-treatment and second line fludarabine + cyclophosphamide were therefore sourced from the literature.

A systematic review was conducted to identify papers reporting response, progression free survival or safety data for CLL patients receiving:

- bendamustine or chlorambucil (+/- prednisone) as re-treatment; or
- fludarabine plus cyclophosphamide (+/- rituximab) after an alkylating agent.

Full details of the systematic review are available on request from the sponsor.

Re-treatment with first-line agents

Two studies discussing repeat treatment were identified; both looked at chlorambucil + prednisone administered in a trial setting.[15,66] No data describing repeat bendamustine treatment were identified. Robak *et al* documents outcomes for 19 patients receiving chlorambucil plus prednisone as re-treatment following remission of 12 months or more after receiving this treatment first-line.[15] Montserrat *et al* documents second line chlorambucil plus prednisone outcomes in 17 patients.[66] However, this study does not specify the type or number of prior therapies received, or patient performance on these prior therapies. Robak *et al* was therefore used in the base-case analysis; Montserrat *et al* was used in a sensitivity analysis.

Using these data, re-treatment response rates were calculated by applying the odds ratio comparing overall response in previously treated and treatment-naïve patients with the overall response rates used in the model for first-line treatment (taken from Study 02CLLIII). The response data used are presented in Table 6.7.

Table 6.7 Overall response rates in treatment-naïve and treatment-experienced patients receiving chlorambucil plus prednisone

	Base case[15]		Sensitivity analysis[66]	
	Re-treatment	First-line	Previously treated	First-line
Responders	9	58	6	24
n	19	103	17	34
Odds ratio (re-treatment *vs*. first-line)	0.70		0.23	

In the base-case analysis this approach was used only in the chlorambucil arm, as no bendamustine re-treatment was assumed to occur. In a sensitivity analysis where bendamustine re-treatment is incorporated, the odds ratio comparing previously treated to treatment naïve chlorambucil patients was assumed to be generalisable to the bendamustine arm. This assumption was made in the absence of data regarding bendamustine re-treatment.

Data regarding complete and partial response rates are available from Robak *et al*.[15] These data suggest that the proportion of responders who achieve a CR is higher at re-treatment than at first-line treatment. This is not considered likely and is based on very small numbers of patients (three complete responders of nine overall responders). We therefore assume that the ratio of complete to partial responders following re-treatment is the same as that following first-line treatment in Study 02CLLIII. The ratio of patients with SD to those with PD was not available from Robak *et al* and is therefore also taken from Study 02CLLIII.

Time to progression conditional upon response is not available from Robak *et al* or Montserrat *et al*. This is therefore modelled by using median overall time to progression estimates from Robak *et al* for first-line and re-treatment with chlorambucil plus prednisone. The median time to progression estimates for first line and re-treatment are 17 months and 12 months, respectively (Robak *et al*). These estimates were used to infer response-specific time to progression estimates as follows:

i. A hazard ratio for re-treatment *vs.* first line treatment time to progression was derived from the median estimates presented by Robak *et al*. This was applied to the treatment-specific first-line median time to progression estimates from Study 02CLLIII. This provided estimates of the median time to progression at re-treatment for chlorambucil and bendamustine.

ii. Response-specific time to progression estimates were then generated using hazard ratios describing differences in time to progression across response categories and by constraining median progression free survival for all response

categories to the values generated in step (i). The hazard ratios were estimated from Study 02CLLIII by analysing both arms pooled together using a proportional hazards model. The results of this analysis are presented in Table 6.8. The median time to progression was constrained to the predicted values generated in step (i) by assuming that time to progression follows an exponential distribution and that the proportional hazards assumption applies to the differences in progression rates between partial responders, complete responders and patients with SD. In order to estimate responder specific progression probabilities in this way the 'Solver' application was used in Excel. Solver was used to identify the underlying hazard for a given (arbitrary) response state that predicts the desired median survival whilst preserving the hazard ratios between response states for a given distribution of initial best response. Solver was used to solve the relevant equations numerically, as they were not solvable analytically.

Table 6.8 Hazard ratios for PFS (derived from proportional hazards regression)

	log HR	se (log HR)	HR
PR *vs.* SD	-1.2467	0.3559	0.287
CR *vs.* SD	-2.1913	0.3753	0.112
CR *vs.* PR	-0.9447	0.2053	0.389

Source: 02CLLIII

The resulting probabilities of response and progression following re-treatment are presented in Table 6.9.

Table 6.9 Re-treatment efficacy

	Chlorambucil		Bendamustine *(used in sensitivity analysis only)*	
	% initial response	3 monthly probability of progression	% initial response	3 monthly probability of progression
CR	4%	7%	41%	6%
PR	23%	17%	26%	14%
SD	30%	47%	20%	41%
PD	43%	-	13%	-

Both re-treatment practice for bendamustine and re-treatment efficacy for bendamustine and chlorambucil are associated with uncertainty, therefore extensive sensitivity analysis was undertaken.

Second-line treatment with fludarabine-cyclophosphamide

The literature review identified 10 studies reporting efficacy data for FC administered without rituximab. A large number of these include a significant proportion of patients receiving a FC as a third or subsequent line treatment and do not report separate outcomes for second-line use;[61,67-71] and/or report results in the relevant population for small numbers of patients.[67-73] Conversely, the RCT described by Robak *et al* in 2010 includes patients who have received only one previous treatment and reports response and PFS for 276 patients receiving FC.[74] Although this study is not solely restricted to patients who have received an alkylator as their first-line treatment, the majority (82%) of patients have (with the remainder having received previous fludarabine). This study was therefore used in the model. O'Brien *et al*[69] was used in a sensitivity analysis as this study was used in a previous NICE appraisal.[51]

The response data for fludarabine plus cyclophosphamide used in the model are presented in Table 6.10.

Table 6.10 Response rates for FC administered as second-line treatment

	Base case[74]	Sensitivity analysis[69]
PR	124	9
CR	36	8
SD	61	3
PD	15	
n	236	20

Time to progression estimates are available for responders and for all patients from Robak *et al*.[74] These estimates are 27.7 and 20.6 months, respectively.

A similar approach was used to estimate response-level specific time to progression estimates as described above for re-treatment. Response-specific time to progression estimates were generated using the hazard ratios describing differences in time to progression across response categories from Study 02CLLIII presented in Table 6.8 and by constraining median PFS for all response categories to the values generated from Robak *et al*. This was achieved in two steps:

i. Firstly, the hazard of progression for the partial response state that predicts median PFS for responders whilst preserving the hazard ratio between complete and partial responders was estimated for the specified distribution of initial best response. This was achieved assuming that time to progression follows an exponential distribution and that the proportional hazards assumption applies to the differences in progression rates between partial and complete responders.

ii. Secondly, the hazard for progression for stable disease patients was estimated as the hazard that would predict the median time to progression for all patients given the initial best response distribution, the hazards of progression for partial

and complete responders derived in step (i) and the assumption of proportional and constant hazards.

The resulting probabilities of response and progression following second-line FC are presented in Table 6.11.

Table 6.11 FC second-line efficacy

	% Initial response	3 monthly probability of progression
CR	15%	3%
PR	53%	9%
SD	26%	18%
PD	6%	-

Source: Robak et al 2010

Best supportive care

Patients in the best supportive care state are assumed to achieve no further active treatment and are therefore given no further opportunity to respond or progress.

Overall survival

For overall survival, fitting a Weibull model to the 02CLLIII data provided the best fit.

The results of the analysis are presented in Table 6.12 and a comparison of the empirical and fitted survival curves as Figure 6.7. The fitted survival curve appears to provide a good fit to the empirical data. Importantly, extrapolation of the fitted survival curve beyond the trial duration appears to provide realistic survival estimates with a predicted median survival of 5.8 years in the chlorambucil arm and 8.3 years in the bendamustine arm, and 0.54% and 0.02% of patients predicted to be alive at 35 years, respectively.

The analysis suggests that median (or any other percentile) overall survival for patients receiving bendamustine exceeds that for patients receiving chlorambucil by 43%.

Table 6.12 Results of fitting parametric survival curve to overall survival

Coefficient	Mean	s.e.
Intercept	2.0203	0.1407
Scale	0.7106	0.0782
Bendamustine	0.3611	0.1842

Source: 02CLLIII
Distribution = Weibull; Events = 65; Censored observations = 221; Covariates = treatment

Figure 6.7 Comparison of empirical and fitted overall survival curves

A concern regarding the use of empirical overall survival data from the trial is that any differences between chlorambucil and bendamustine overall survival could be driven by differences between arms with respect to chemotherapy administered post progression (or “cross-over”). However inspection of subsequent therapy data from Study 02CLLIII indicated that patients randomised to chlorambucil were more likely to receive subsequent lines of therapy during the trial follow-up (with 63.1% receiving treatment compared with 48.8% of ben damustine patients) and that the composition of therapies administered (most frequently bendamustine, chlorambucil, cyclophosphamide, fludarabine and vincristine) was similar across arms. This suggests that any bias arising from subsequent line therapy administration would be expected to reduce the impact of bendamustine on overall survival.

Adverse events

The following criteria were used to guide selection of adverse events for inclusion in the model. These criteria were intended to capture events likely to impact substantively on incremental costs or QALYs:

- Grade 1 – 2 and trial arms differed by ≥5 % in % of patients experiencing event.
- Grade 3 – 4 and trial arms differed by ≥2% in % of patients experiencing event.

Following review of the adverse events that met these criteria the following were considered to be suitable for inclusion:

- Neutropenia/thrombocytopenia/leukopenia/lymphopenia any grade. Note: no direct quality of life implications of these adverse events were included. These adverse events were only included in the model to the extent that they results in the use of blood products/growth factors and to the extent that they cause severe infections (pyrexia or pneumonia, which were modelled as separate events).
- Grade 3 – 4 anaemia.
- Grade 1 – 2 nausea.
- Grade 1 – 2 vomiting.
- Grade 1 – 2 diarrhoea.
- Grade 3 – 4 pyrexia.
- Grade 3 – 4 pneumonia.

Grade 3 – 4 pyrexia and pneumonia did not meet the criteria but were included in the model as treatment-related infections are known to be a major cause of morbidity and mortality in CLL patients. Grade 1 – 2 diarrhoea also did not meet the criteria, however again it was thought to be important to capture this side-effect that is likely to occur alongside nausea/vomiting. Grade 1 – 2 anaemia and grade 1 – 2 pyrexia met the criteria but were not included as they are unlikely to have significant QoL or cost implications, particularly as in many cases they would be indistinguishable from the symptoms of CLL. The adverse event rates used in the model are presented in Table 6.13.

Table 6.13 Adverse event data: first-line treatment/re-treatment

	Bendamustine	Chlorambucil
Number of patients in safety analysis	161	151
Total number of cycles of treatment received	783	733
Neutropenia/thrombocytopenia/leukopenia/lymphopenia:		
Granulocyte colony stimulating factors (GCSFs)	3% of cycles	0.3% of cycles
Erythropoietin	0.5% of cycles	0.3% of cycles
Red blood cells	5.7% of cycles	2.1% of cycles
Grade 1 – 2 nausea only (nausea – vomiting)	4.4% of patients. (18.7 – 14.3%)	6.6% of patients (13.2 – 6.6%)
Grade 1 – 2 nausea and vomiting	14.3% of patients	6.6% of patients
Grade 3 – 4 anaemia	2.5% of patients	0% of patients
Grade 3 – 4 pyrexia	1.9% of patients	1.3% of patients
Grade 3 – 4 pneumonia (infection)	1.9% of patients	0% of patients
Grade 1 – 2 diarrhoea	8.7% of patients	4% of patients

Source: 02CLLIII

Only data regarding the proportion of patients experiencing each adverse event are available (rather than the total number of adverse events experienced). The following assumptions were therefore made:

- Patients who experience grade 3 – 4 anaemia, grade 1 – 2 nausea, grade 1 – 2 nausea/vomiting or grade 1 – 2 diarrhoea experience these adverse events in every cycle in which they receive treatment.
- Patients who experience grade 3 – 4 pyrexia or grade 3 – 4 pneumonia experience these adverse events only once during the course of treatment.

It was assumed that the occurrence of adverse events is distributed across model cycles in proportion with the amount of the model cycle spent on treatment. Exactly the same data and approach were used to model first-line and re-treatment related adverse events.

Cost and quality of life implications of adverse events associated with second-line fludarabine treatment were also incorporated in to the model. Data were sourced from Robak *et al*[74] and are summarised in Table 6.14. Only adverse events included for bendamustine and chlorambucil were included, as these are the events for which utility values were available. As the study by Robak *et al* does not disaggregate all adverse events by grade, where this data were absent we assumed that the ratio of grade 1 – 2 to grade 3 – 4 events was as per the bendamustine arm of Study 02CLLIII. This may

underestimate the grade 3/4 adverse event rates for patients receiving FC, which would be likely to bias the cost-effectiveness of bendamustine downwards. The impact of increasing the cost and utility impact of FC-related adverse events was therefore explored as a sensitivity analysis. For the sensitivity analysis using data from O'Brien *et al*,[69] missing event rates were taken from Robak *et al*.

Table 6.14 Adverse events associated with second-line FC treatment

Adverse event	Base case[74]		Sensitivity analysis[69]
	Patients experiencing event		Patients experiencing event
	Grade 1-2	Grade 3-4	Specified grades
Nausea (grade 1 or 2 = nausea - nausea/vomiting)	45	-	44
Nausea/vomiting (grade 1 or 2)	51	-	-
Anaemia (grade 3 or 4)	-	35	-
Pyrexia (grade 3 or 4)	-	42	-
Pneumonia (grade 3 or 4)	-	17	10
Diarrhoea (grade 1 or 2)	32	-	6
n	272		128 (54 for infection)

Numbers of events per patient experiencing an event are assumed to be as for first-line treatment/re-treatment.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities were derived from the survival analysis parameter outputs using the following formula that relates transition probabilities to the survival function:

$tp(t_u) = 1 – S(t+u)/S(t)$

where $tp(t_u)$ denotes the probability of a transition occurring during the interval t to t + u; S(t) denotes the survival function at time t and u represents one cycle of the model (3 months).

Table 6.15 describes the survival analysis parameter outputs from SAS for each parametric distribution used and the survival function in terms of these parameters.

Table 6.15 Survival functions in terms of SAS parameter outputs

Parametric distribution	SAS parameters	Survival function
Exponential	μ = intercept	$\exp(-t \cdot \exp(-\mu))$
Weibull	μ = intercept σ = scale	$\exp(-\exp(-\mu/\sigma)*t^{1/\sigma})$
Log-logistic	μ = intercept σ = scale	$1/(1 + \exp(-\mu/\sigma) \cdot (t^{1/\sigma}))$
Log-normal	μ = intercept σ = scale	$1-\Phi((\ln(t)- \mu)/\sigma)$

Φ is the cumulative distribution function for the normal distribution

Where covariates were included in an analysis, 't', in the formulae above is divided by the exponent of the sum product of the vector of coefficients and the vector of covariable values.

The transition matrix is too large to present within the submission. However, it is clearly labelled and presented within the Excel model.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The time-to progression estimates used in the first-line part of the analysis and the overall survival estimates used throughout the model assume time-dependent hazards, as in all cases parametric models with time dependent hazards provided a superior fit to an exponential model (based on AIC and visual comparison of fitted and empirical survival curves).

Following progression, the probabilities of subsequent clinical events (transition from PD to new treatment, time to progression following re-treatment and time to progression following second-line treatment) were assumed to follow an exponential distribution. This is a simplification that avoids use of a more complex model structure (for example a patient level simulation approach).

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No surrogate outcomes were applied in the model (with the exception of utility values to calculate quality of life – see Section 6.4). Overall survival was modelled directly from the 02CLLIII trial data. Movement between health states was based on the 02CLLIII trial data or transitional probabilities estimated from the literature for transitions occurring after first line treatment.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]: the criteria for selecting the experts; the number of experts approached; the number of experts who participated; declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought; the background information provided and its consistency with the totality of the evidence provided in the submission; the method used to collect the opinions; the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?); the questions asked; whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 6.16 Summary of variables applied in the economic model

Parameter	Mean	Cross reference
Best overall response to first-line treatment(PD, SD, PR, CR)	Bendamustine SD = 16% PR = 29% CR + nPR = 45% PD = 10% Chlorambucil SD = 27% PR = 30% CR + nPR = 5% PD = 38%	6.3.1
Time to progression - SD	Intercept = 0.1052 Scale = 0.2600 Bendamustine = 0.0513 (Log logistic)	6.3.1
Time to progression - PR	Intercept 0.1259 Scale 0.4578 Bendamustine 0.5247 (Log normal)	6.3.1
Time to progression - CR	Intercept = 0.5795 Scale = 0.6047 Bendamustine = 0.4217 (Log-normal)	6.3.1
Time from progression to re-treatment	Intercept = 0.4097 Scale = 1.000 Bendamustine = -0.0445	6.3.1
Odds ratio, overall response rate in treatment-naïve *vs.* treatment-experienced patients (base-case)	0.70	6.3.1
% patients receiving fludarabine at re-treatment	50%	6.3.1
FC second-line therapy (PD or SD, PR, CR)	SD = 26% PR = 53% CR+ nPR = 15% PD = 6%	6.3.1
Overall survival	Intercept = 2.0203 Scale = 0.7106 Bendamustine = 0.3611	6.3.1
Adverse event probabilities first-line treatment/re-treatment	Grade 1 – 2 nausea only (nausea – vomiting)	6.3.1

Parameter	Mean	Cross reference
	Bendamustine 4.4% of patients. Chlorambucil 6.6% of patients Grade 1 – 2 nausea and vomiting Bendamustine 14.3% of patients Chlorambucil 6.6% of patients Grade 3 – 4 anaemia Bendamustine 2.5% of patients Chlorambucil 0% of patients Grade 3 – 4 pyrexia Bendamustine 1.9% of patients Chlorambucil 1.3% of patients Grade 3 – 4 pneumonia (infection) Bendamustine 1.9% of patients Chlorambucil 0% of patients Grade 1 – 2 diarrhoea Bendamustine 8.7% of patients Chlorambucil 4% of patients	
Proportion of cycles with GCSF/erythropoietin administration/red blood cells	Granulocyte colony stimulating factors (GCSFs) Bendamustine 3% of cycles Chlorambucil 0.3% of cycles Erythropoietin Bendamustine 0.5% of cycles Chlorambucil 0.3% of cycles Red blood cells Bendamustine 5.7% of cycles Chlorambucil 2.1% of cycles	6.3.1
Adverse event probabilities with second-line fludarabine/FC	Nausea (grade 1 or 2 = nausea - nausea/vomiting) 45% Nausea/vomiting (grade 1 or 2) 51% Anaemia (grade 3 or 4) 35% Pyrexia (grade 3 or 4) 42% Pneumonia (grade 3 or 4) 17% Diarrhoea (grade 1 or 2) 32%	6.3.1
Utilities	Baseline utility (used for both treatments during active treatment (time 0-4.9 months); used as baseline utility throughout model) 0.70 Complete Response 0.91 Partial Response 0.84 No Change NC 0.78	6.4.8

Parameter	Mean	Cross reference
	Progressive Disease 0.68	
	NC + 1-2 Nausea 0.73	
	NC + 1-2 Nausea/Vomiting 0.73	
	NC + 1-2 Diarrhoea 0.70	
	NC + 3-4 Anaemia 0.69	
	NC + 3-4 Pyrexia 0.67	
	NC + 3-4 Pneumonia 0.58	
	NC + Second-line Treatment 0.71	
Therapy treatment (including any relevant drug costs, infusion costs, blood count, biochemistry and antiemetic costs)	Bendamustine = £7,673.00 Chlorambucil = £1,136.60 FC (subsequent lines of therapy) =£2,232.51	6.5.5
Health state cycle costs (3 months)	Stable disease = £405.07 Partial response = £135.02 Complete response = £67.51 Progressive disease/BSC = £1,924.33	6.5.6
Adverse event health state costs (per episode)	Cytopenias GCSFs = £817.09 Cytopenias Erythropoietin = £1,188.61 Nausea (Grade 1 or 2) = £0.24 Nausea/vomiting (Grade 1 or 2) = £0.24 Anaemia = £453.12 Pyrexia = £3,076.99 Pneumonia = £2,188.00 Diarrhoea = £0.43	6.5.7
Discount rate	Costs = 3.5% Benefits = 3.5%	6.2.5

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator?

Extrapolation of long-term clinical outcomes was undertaken using the parametric survival curves described in Section 6.3.1 for the following endpoints:

- Time to disease progression.
- Time to retreatment.
- Overall survival.

As the overall survival data were relatively immature at the last trial follow-up, and log-log plots suggested that the underlying shape of the hazard function over time may be quite different for chlorambucil and bendamustine, sensitivity analyses were conducted where independent parametric curves where fitted to the chlorambucil and bendamustine arms of 02CLLIII separately. These analyses indicated that selection of the best fitting distributions for each arm based on the within trial data provides very unrealistic long-term predictions. Using a Weibull distribution for both arms provided more acceptable predictions and was therefore explored as a sensitivity analysis. However, as this analysis predicted that 2.7% of patients in the bendamustine arm would still be alive at 35 years (exceeding the predictions for members of the general population aged 63 years, the mean age of patients in 02CLLIII) it was not considered appropriate for the base-case.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The model made the following key assumptions:

<u>Treatment effects</u>
Bendamustine and chlorambucil *differ* with respect to:

- treatment acquisition and administration cost;
- best overall response;
- time to progression, conditional upon response;

- adverse event rates;
- overall survival;
- treatment pathway following first-line treatment: re-treatment is only possible with chlorambucil.

Bendamustine and chlorambucil are *equal* with respect to:

- health outcomes (response rates) and costs associated with subsequent health states and lines of therapy (FC and BSC);
- utility values in any specific health state including adverse events.

Time to best response

All patients start treatment with stable disease and transition to their best response state within the first cycle. As a half cycle correction is applied this is equivalent to assuming that median time to best response is 1.5 months. This was in line with patients being assessed for response at three cycles of treatment.

Extrapolation

Extrapolation was required in order to estimate costs and health outcomes over a patient's lifetime. The model extrapolates time to progression and overall survival using parametric survival curves as not all patients had experienced these events during trial follow-up. The model also extrapolates transitions through health states (FC and BSC) outside the period of trial follow-up based on data from Study 02CLLIII and the literature as again these transitions were not observed during the trial period.

Re-treatment efficacy

Chlorambucil is assumed to confer a positive but reduced benefit in the re-treatment setting. This assumption is made based on data from Robak *et al* (2005).[15]

Overall survival

- The model assumes that bendamustine offers an overall survival benefit over chlorambucil. This assumption is made based on the difference between arms observed in 02CLLIII. More recent data have supported this overall survival benefit with a statistically significant overall survival advantage in responders (see Section 6.10.5).
- The probability of transitioning to death depends only on time from treatment initiation and not health state. For example, a patient residing in a PD state does not face a higher mortality rate than a patient residing in a CR state at a given point in time. The time-dependence of the mortality rate will however allow the experience of the average patients' trajectory through the health states to be captured.

- With respect to implementation, the probability of death observed in the trial is applied directly and other probabilities are considered to express the probability of the events conditional upon a patient being alive. This is appropriate given that death is considered as a censoring event in the majority of the transition probability calculations.

Estimation of transition probabilities:

Where possible and appropriate transition probabilities are estimated to be time-dependent. This better reflects the underlying data from Study 02CLLIII and is an approach previously recommended in the context of CLL.[75]

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Being an incurable disease that patients can live with for a number of years, CLL impacts on patients' quality of life in a number of ways. Compared with healthy controls, patients with untreated CLL report:

- impaired physical, role, cognitive and social functioning;[19,20]
- more sleep disturbance;[20]

- more fatigue, nausea and vomiting, appetite loss and constipation.[19,20] In addition, CLL patients are prone to recurrent infections, some of which can be serious.[21]

For patients with more advanced disease, treatment status has an effect on quality of life. For example, an international, web-based survey of 1482 patients showed that those currently receiving treatment had lower scores for physical and functional wellbeing than patients not on treatment, but higher scores for social/family well-being.[77]

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As discussed in Section 2.1, there is increasing evidence demonstrating the relationship between PFS and improved quality of life. Recent studies have also demonstrated the impact of subsequent lines of therapy on a patient's quality of life. A patient's quality of life is also expected to decrease if they are suffering from adverse events/toxicity when receiving therapy.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

Study 02CLLIII collected quality of life data using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) EORTC-C30. These data were collected at baseline and at the end of each treatment cycle for both treatments (up to 6 cycles). Since the duration of follow-up was short, it was not possible to analyse the long-term consequences of treatment on patients' HRQL. Also, there were many missing data points – with many patients not having the EORTC-30 recorded for all 6 cycles.

Although there were insufficient data from Study 02CLLIII to provide health state-specific utility estimates, it was possible to estimate baseline utility from Study 02CLLIII using the EORTC-C30 data and a mapping algorithm described by McKenzie *et al*.[76] For details regarding the mapping algorithm, please see Section 6.4.4. Utility at baseline was estimated across both arms to be 0.6988 (standard error 0.01417; n = 242).This value was used to estimate utility for the treatment period (utility decrements associated with adverse events were also included within this period) and as the reference value to which utility decrements and increments associated with different clinical states were applied.

The results of the EORTC-C30 are shown in Section 5.5 and the results discussed in Section 5.10.3. In addition, a non-validated measure, the EORTC QLQ-CLL25 was also collected during Study 02CLLIII, but it was not possible to assess the results from this measure as the tools to assess the results of the questionnaire have not been published.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Utilities were generated from the EORTC-C30 data collected from Study 02CLLIII. This was achieved by using a published mapping function which maps from EORTC-C30 data to EQ-5D utilities.[76] The mapping algorithm was derived using data from 199 patients with inoperable oesophageal cancer. Two approaches to mapping were applied: the first approach uses ordinary least squares to regress EQ-5D utility values on EORTC-C30 responses, and the second uses ordered probit regression to independently predict the level of each EQ-5D dimension as a function of EORTC-C30 responses. Each mapping function was assessed using (i) statistical goodness of fit measures; (ii) predictive ability, assessed using a second data set of 254 breast cancer patients receiving post-operative radiotherapy and (iii) by comparing QALY estimates generated by the mapping function and the raw EQ-5D data. The oesophageal cancer data set is used as it provides good coverage of the different levels of the EQ-5D dimensions. The OLS mapping is found by the authors to outperform the ordered probit analysis and is therefore used as the basis for generating utilities from Study 02CLLIII.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data.

A search of utility literature was conducted in June 2010 in Medline, Medline in Process, Embase and EconLIT using OVID SP as the search provider. A search was also carried out in NHS EED. The Medline, Medline in Process and Embase search strategies combined CLL disease terms with utility search terms. The EconLIT and NHS EED databases were searched using disease terms only. The NICE website was also searched for technology appraisals (STAs) in CLL. All search syntaxes are provided in Section 9.12.

Retrieved abstracts and full text papers were assessed against the following inclusion criteria:

- Studies reporting utility values for health states or toxicities* associated with CLL and CLL treatment; or
- Cost-effectiveness analyses, health technology assessment reports, review papers potentially reporting relevant utilities
- English language only

* Toxicities to include; nausea, vomiting, diarrhoea, pyrexia, pneumonia and other infections

6.4.6 Provide details of the studies in which HRQL is measured.

The utility searches retrieved 315 entries in Medline and Medline in-Process, and 255 entries in Embase. NHS EED and EconLIT retrieved 69 and 14 hits, respectively. After removing duplicates from the search results, 380 abstracts were reviewed against our inclusion criteria. Of these, 13 references were ordered for full paper review. In addition, manufacturer submissions and evidence review group reports for five previous STAs in CLL were also reviewed (TA29 fludarabine second-line; TA119 fludarabine first-line; TA174 rituximab first-line; rituximab relapsed or refractory; ofatumumab double refractory).

Of the retrieved studies, one was deemed relevant for inclusion.[78] In addition, original research commissioned for this technology - but not available as a full publication at the time when the searches were conducted - was also included.[14] Six additional sources of utility weights were referenced in articles retrieved by the searches and the NICE appraisals.[22,23,52-54,79] It should be noted that one of these studies (Doorduijn et al)[79] reports on HRQL of NHL patients and would not therefore have met our inclusion criteria, it is however included in the discussion below as it has informed a previous NICE appraisal (TA119). Study methods and results for the eight included studies are summarised in Table 6.17.

The Wessex DEC report by Best[80] is also often referred to in the literature as a source for utility values. We were unable to obtain a copy of this report; however an article by Hyde, et al[54] describes the utility values reported by Best.

Table 6.17 Summary of HRQL studies identified

Identifier	Sample selection	Health state source	n	Response rate	Valuation	Utility data reported	Results	Analysis type	Use in appraisals
Beusterien 2010[14]	General population, recruited through "word of mouth"	Vignettes developed using literature, patient forums, 5 CLL patients, 4 CLL physicians	93	89/93 (4 excluded due to ≥3 illogical responses)	Standard gamble		Mean (SD)	Mean values	None to date
						Complete response	0.91 (0.11)		
						Partial response	0.84 (0.14)		
						No Change	0.78 (0.14)		
						Progressive disease	0.68 (0.20)		
						Second-line treatment	0.71 (0.17)		
						Third-line treatment	0.65 (0.22)		
						No change + grade 1 - 2 nausea	0.73 (0.17)		
						No change + grade 1 - 2 nausea/vomiting	0.73 (0.16)		
						No change + grade 1 - 2 diarrhoea	0.70 (0.19)		
						No change + grade 3 - 4 anemia	0.69 (0.18)		
						No change + grade 3 - 4 pyrexia	0.67 (0.17)		
						No change + grade 3 - 4 pneumonia	0.58 (0.19)		
Doorduijn 2005+[79]	NHL patients ≥65 years in chemotherapy RCT	EQ-5D	128	92% of questionnaires returned	Time trade-off based tariff	Baseline (n = 63)	0.74	Mean, Mean change	Used in fludarabine first-line
						Progression free (n = 31)	+ 0.04 Δ from baseline		
						Progressed (n = 13)	-0.24 Δ from baseline		
Ferguson 2008[23] (see also GSK 2010;[53] Hoyle 2010[81])	General population	Vignettes developed using literature, clinical guidelines, validation with specialist nurses and clinician	60	-	Time trade-off		Mean (se)	Mean values	Used in ofatumumab double refractory
						First-line alemtuzumab	0.619 (0.029)		
						First-line chlorambucil	0.623 (0.028)		
						First-line progression-free	0.777 (0.024)		
						First-line progressive	0.540 (0.026)		
						Second-line progression-free	0.650 (0.027)		
						Second-line progressive	0.470 (0.028)		
						Final treatment progression-free	0.428 (0.028)		
						Final treatment progressive	0.279 (0.027)		

GSK 2010;[53] Hoyle 2010[81]	General population	Vignettes, reviewed by 2 specialist clinicians	110	-	Time trade-off	Progression-free with response Progression-free non-response Disease progression Progression-free with response + thrombocytopenia Progression-free with response + neutropenia, no infection Progression-free with response + infection Progression-free no response + infection	Mean (SD) 0.671 (0.236) 0.394 (0.219) 0.214 (0.18) 0.563 (-) 0.508 (-) 0.476 (-) 0.333 (-)	Mean values	None (discussed in ofatumumab appraisal as ongoing)
Hyde 2002[54]	Expert opinion	Experts mapped health states on to Rosser index	-	-	Assume tariff, value set used not stated	Remission With disease During 6 months fludarabine treatment During 6 months CAP treatment	0.96 0.81 0.81 0.79	None	Used in fludarabine second line
Hancock 2003[22]	Expert opinion	Review of EORTC QLQ-C30 and FACT-G quality of life data from 418 cancer patients	-	-	Expert opinion	Progression-free Progressed	0.80 0.60	None	Used in fludarabine first line; rituximab first line; rituximab second line
Roche 2008; [52] Roche 2009[50]	Eight clinical sites in the UK	EQ-5D	11*	-	Assume time trade-off based tariff	Progression-free (n = 8, 1 missing value) Progressed (n = 2)	Mean (SD) 0.77 (0.32) 0.92 (0.11)	Mean values	None (discussed in rituximab 1st line; rituximab 2nd line)
Weeks 1991[78]	10 practicing oncologists	Description	10	-	Standard gamble	CLL without infection CLL with a trivial infection CLL with a moderate infection CLL with a major infection Intravenous immune globulin infusion	Mean (range): 0.87 (0.5,0.999) 0.86 (0.5,0.999) 0.81 (0.5,0.99) 0.46 (0.2,0.90) 0.66 (0.20,0.99)	Mean values	None

CAP = cyclophosphamide, doxorubicin, prednisolone; NHL = non-Hodgkin's lymphoma; +Utility values presented are those used in the first-line fludarabine submission (TA119), other utility values are also presented in this paper; *Ongoing study, target recruitment of 250 patients.

Two of the identified studies (Doorduijn 2005; Roche 2008) would meet the criteria of the NICE reference case.[52,79] However as mentioned above, Doorduijn 2005 measured HRQL in NHL patients, and thus was not deemed a suitable basis to inform the cost-effectiveness model. The Roche 2008 study would be an appropriate basis for estimating utilities for the cost-effectiveness model, however as this study has reported data for only 10 patients to date, the evidence available were not judged to be robust enough.

Two studies were of poor quality and did not meet any of the criteria for the reference case (Hyde 2002; Hancock 2003);[22,54] both were based on experts' opinions. Similarly, the Weeks 1991 study is also not in line with the reference case; this study elicited standard gamble valuations from 10 oncologists.[78]

The remaining three studies each took the form of "vignette" studies. By using vignettes these studies depart from the reference case (which states a preference for health states elicited from patients using a generic instrument), but do however meet the NICE requirements for using valuations elicited from the general public using a preference based measure (Beusterien 2010 uses the standard gamble; Ferguson 2008 and GSK 2010 use the time trade-off). The Ferguson 2008 and GSK 2010 studies are described briefly as an abstract and in a clarification letter to NICE, respectively. This makes it difficult to assess their methodological quality. In addition, unlike the Beusterien 2010 study, they provide minimal data regarding toxicities and do not differentiate between complete and partial response states. The Beusterien 2010 data are therefore used in the base case model, the study is described in further detail below.

Beusterien 2010

The study was commissioned by Napp Pharmaceuticals Limited because there is a shortage of suitable utility studies in the first-line setting. The utility values were elicited from general population participants in the UK through one-on-one, in-person interviews using the standard gamble method. The health states selected for valuation were intended to map to standard clinical endpoints reported in CLL trials, including Study 02CLLIII, and thus included CR, PR, NC (SD) and PD. Health states for second- and third-line treatment were added in the course of producing the vignettes to reflect feedback that, even when conditioning on response achieved, patients receiving latter line therapy were likely to experience worse health outcomes. Twelve vignette descriptions were therefore developed to reflect the major health states.

Because it would have been too cumbersome for respondents to value all possible combinations of clinical response status and adverse events, the treatment-related toxicities health states were done by modifying only one treatment outcome health state, the no change health state (see Table 6.18 in Section 6.4.9).

The health states descriptions were designed to describe the functional and patient-centered impacts of CLL and its treatment, rather than provide clinical descriptions of the disease, in line with published guidelines for health state development.[82,83] To ensure the validity of the health state descriptions, development involved an iterative process comprising incorporation of information from the literature and patient web-based discussion forums, and input from five UK CLL patients and four haematologists.

This process resulted in the selection of a number of key domains in CLL including the cancer description, “cancer of the blood”; treatment response category; swollen glands in neck, armpits, or groin; limitations in performing daily activities; level of fatigue; appetite; and trouble sleeping because of night sweats.

Ninety-three members of the UK general population were recruited for the study (62 from England, 31 from Scotland). In general, the samples were well matched to the demographic distributions of their target adult populations in Scotland and in England and Wales, based on the 2001 UK census.[25]

A decision rule was implemented for eliminating illogical responses. Specifically, participants who had at least three illogical responses (e.g. valuing no change plus toxicity as higher than the base state of no change) were eliminated from all analyses. This resulted in four participants (4.5%) being excluded from the final analysis.

The results of the utility elicitation study are presented in Section 6.4.9. The values elicited have face validity in terms of the ordering of the health states implied. No significant differences were found between values elicited from participants who reported extensive knowledge or experience of leukaemia and those who did not.

The results are not dissimilar to those used in previous appraisals with PD following first-line treatment being associated with a utility value of 0.68 and pre-progression status being associated with a utility of 0.78 – 0.91 depending on response achieved.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The baseline utility level across patients estimated by mapping from the EORTC-C30 to EQ-5D utilities, described in Sections 6.4.3 and 6.4.4, can be considered equivalent to the first-line stable disease state in Beusterien *et al*. Comparison of these values indicates that the mapped utility values from Study 02CLLIII (mean value of 0.70 across treatment groups at baseline) is somewhat lower than the stable disease estimate of 0.78 from Beusterien *et al*. The 02CLLIII data are therefore used to represent baseline utility throughout the model, as described in Section 6.4.3.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Quality of life was measured in Study 02CLLIII using the EORTC QLQ-C30. The results for some measures (fatigue, nausea and vomiting, dyspnoea, and appetite loss) favoured chlorambucil, which is consistent with the higher incidence of these adverse events in the bendamustine group. However, overall quality of life was modestly improved in both groups during treatment with no significant differences between the groups. A full description of the EORTC QLQ-C30 data can be found in Section 5.5 and a discussion on the quality of life data in Section 5.10.2.

6.4.9 Quality-of-life data used in cost-effectiveness analysis

Please summarise the values you have chosen for your cost-effectiveness analysis, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

The utility values shown in Table 6.18 were applied in the health economic model.

Table 6.18 Utility weights used in economic model

Health state	Mean ± SD	95% CI (lower, upper)	Reference in submission	Justification
Baseline utility (used for both treatments during active treatment (time 0 – 4.9 months); used as baseline utility throughout model)	0.70 +0.22	0.67, 0.73	Section 6.4.3	Best available estimate of baseline utility.
Complete response	0.91 ± 0.11	0.88, 0.93	6.4.6*	Best available estimate of differences between clinical health states (response, adverse events).
Partial response	0.84 ± 0.14	0.81, 0.87	6.4.6*	
No change	0.78 ± 0.14	0.75, 0.82	6.4.6*	
Progressive disease	0.68 ± 0.20	0.64, 0.72	6.4.6*	
NC + 1 – 2 nausea	0.73 ± 0.17	0.69, 0.76	6.4.6*	
NC + 1 – 2 nausea/vomiting	0.73 ± 0.16	0.69, 0.76	6.4.6*	
NC + 1 – 2 diarrhoea	0.70 ± 0.19	0.66, 0.74	6.4.6*	
NC + 3 – 4 anaemia	0.69 ± 0.18	0.65, 0.72	6.4.6*	
NC + 3 – 4 pyrexia	0.67 ± 0.17	0.63, 0.70	6.4.6*	
NC + 3 – 4 pneumonia	0.58 ± 0.19	0.54, 0.62	6.4.6*	
NC + second-line treatment	0.71 ± 0.17	0.68, 0.75	6.4.6*	

*All utility values came from Beusterien et al[14]

The utility values were used as follows in the model:

- For the first-line bendamustine and chlorambucil treatment period (on average 4.9 months), quality of life was set equal between the two groups, with both groups receiving the baseline utility value estimated from Study 02CLLIII. This reflects the similar quality of life observed between the two groups with respect to the EORTC QLQ-C30 data collected during the trial. Utility decrements associated with adverse events (taken from Beusterien *et al*) were also applied during this period.
- Patients with an adverse event experience a utility decrement equal to the difference between the 'No Change + adverse event' valuation and the 'No Change' valuation from Beusterien *et al* regardless of their health state.
- Beyond the 4.9 month treatment period, the 02CLLIII data were retained as the estimate of baseline utility. The impact of different response states on utility is applied as an increment or decrement to this. The increments and decrements are calculated from Beusterien *et al* as the difference between the SD state from Beusterien *et al* and the relevant response state from Beusterien *et al*. For example, a person achieving a CR to first line treatment would experience an absolute utility level of 0.70 (02CLLIII) + 0.91 – 0.78 (Beusterien *et al*) = 0.83.
- Patients re-treated with the same agent do not experience a decrement in utility conditional on them being in a given response state.
- During the re-treatment and second-line active treatment phases patients were assumed to experience the utility associated with the stable disease state.
- Patients receiving FC or BSC experience a utility decrement equal to the difference between the 'No Change + second-line treatment' valuation and the 'No Change' valuation, the same decrement is applied regardless of their response status.
- Patients in the BSC were all assumed to experience the PD response level.

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

Not applicable.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Within each response health state (CR, PR, SD, PD) there is potential variation in HRQL according to toxicity from therapies and line of therapy. The utility values are described in more detail in Section 6.4.8.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No major health effects were excluded as there was a comprehensive coverage of health effects in the health economic model with HRQL defined according to response, toxicity and line of therapy.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Data from Study 02CLLIII were used to estimate baseline utility in the model. The data used and the method for estimating and applying quality of life increments/decrements associated with different clinical events to this baseline are described in Sections 6.4.3 and 6.4.8.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Quality of life is a function of line of therapy and also depends on which health state the patient is in. It may also change over time with respect to toxicity if the patient receives a new active therapy. However, conditional upon health state (including adverse events), no time dependence of utility values was incorporated in to the model.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology**.**

Not applicable.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The clinical management of CLL includes regular visits to clinical specialists (haematologists) and regular testing and follow-up (e.g. full blood count, biochemistry, infusion cost, and blood transfusion). Hospitalisation may be required in some cases with outpatient visits for chemotherapy administration. The appropriate HRG groups for these categories are described in the subsequent sections.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

There are no HRG costs specific to bendamustine, however, non-drug specific administration costs can be applied from the NHS reference costs.[40] Bendamustine is administered on Days 1 and 2 of each cycle. For the first day of the first cycle, the most appropriate HRG category is to 'Deliver simple Parenteral Chemotherapy at first attendance' (SB12Z) (outpatient attendance). For subsequent cycles the most appropriate HRG category is 'Deliver subsequent elements of a Chemotherapy cycle' (SB15Z) (outpatient attendance).

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK.

A search for literature relating to the costing and economic burden of CLL was conducted in June 2010, using Medline and Medline in Process, Embase and EconLIT via OVID SP as the search provider. A search was also carried out in NHS EED. The Medline, Medline in Process and Embase search strategies combined CLL disease terms with cost and resource use search terms. The EconLIT and NHS EED databases were searched using disease terms only. The NICE website was also searched for cost data used in previous STAs in CLL. All search syntaxes are shown in Section 9.13.

Retrieved abstracts and full text papers were assessed against the following inclusion criteria:

- Studies reporting empirical cost or resource use estimates for health states or toxicities* associated with CLL and CLL treatment;
- Cost-effectiveness analyses, health technology assessment reports, review papers potentially reporting relevant data
- Cost and resource use estimates pertaining to the UK
- English language only.

*Toxicities to include; nausea, vomiting, diarrhoea, pyrexia, pneumonia and other infections

The searches retrieved 194 entries in Medline and Medline in Process, and 333 entries in Embase. NHS EED and EconLIT retrieved 69 and 14 hits, respectively. After removing duplicates from the search results, 422 abstracts were reviewed against our inclusion criteria. Of these, 13 references were ordered for full paper review. In addition, manufacturer submissions and evidence review group reports for five previous STAs in CLL were also reviewed (TA29 fludarabine second-line; TA119 fludarabine first-line; TA174 rituximab first-line; rituximab in relapsed/refractory CLL; ofatumumab in double-refractory CLL patients).

None of the studies met our inclusion criteria. We also looked at the cost data used in the previous CLL appraisals and found that there are limited empirical published data to inform estimates of resource usage linked to the management of CLL patients. Only the fludarabine submission (TA119)[51] based a substantial proportion of resource use estimates on empirical data. The cost inputs used in that submission, derived from a subset of patients from the CLL4 trial, have not however been made publically available.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]: the criteria for selecting the experts; the number of experts approached; the number of experts who participated; declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought; the background information provided and its consistency with the totality of the evidence provided in the submission; the method used to collect the opinions; the medium used to collect opinions; the questions asked; whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

An advisory board was conducted in London in January 2010 with UK haematologists to obtain clinical information regarding the treatment of CLL. The two main topics discussed at the advisory board were the CLL treatment pathway and resource use. The experts selected were working in the UK NHS and dealing with CLL patients on a daily basis. Eight experts were contacted and five agreed to attend. Background slides, on both the clinical data and the proposed health economic model, were provided at the advisory board.

We are not aware of any conflicts of interest; however, a formal declaration was not signed.

Specific questions were presented to the advisory board members including:

- resource use when managing CLL patients in specific health states (SD, PR, CR and PR);
- administration costs;
- growth factor use;
- adverse events resource use.

Questions were also asked about the treatment pathway, estimated patient numbers, the chlorambucil dose used in the UK, and how to determine which patients are not appropriate for fludarabine. The responses were summarised and sent around to the attendees after the advisory board for confirmation. One comment was received that suggested reducing the number of haematologist visits when costing SD; however, this was not changed given the majority of the advisory board attendees accepted this input, and it was very unlikely to have a substantial impact on the model results.

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Data and sources used to estimate treatment acquisition costs for treatment with bendamustine and chlorambucil are presented in Table 6.19. The cost of FC (which patients can receive in the model in subsequent lines of therapy, but is not a comparator) is also included. Treatment costs for chlorambucil are assumed to be equivalent for first-line and re-treatment. In line with clinical experts' opinion, it is assumed that all patients receiving bendamustine and FC are prescribed prophylactic anti-emetics. The cost linked to the management of patients in the BSC health state are described in Section 6.5.6.

Drug costs are calculated assuming full wastage at the body surface area/Broca's weight for the average patient in Study 02CLLIII. Sensitivity analyses around patient weight and the associated variable levels of wastage are also provided. For bendamustine, the average price per mg across the three product formulations is used for the cost calculations, as this is very similar across formulations.

Table 6.19 Unit costs associated with the technology in the economic model, comparator costs and subsequent lines of therapy

Items	Bendamustine	Ref.	Chlorambucil (comparator)	Ref.	FC (subsequent lines of therapy in model)	Ref.
Technology cost	25 mg x 5 = £347.26 25 mg x 20 = £1379.04 100 mg x 5 = £1379.04 100 mg/m^2 body surface area on Days 1 and 2, every 4 weeks Average BSA 1.72m^2 Mean no. cycles 4.9	See Section 1.10	2 mg x 25 = £8.36 0.8 mg/kg Broca's weight Days 1 and 15, every 4 weeks Broca's weight 68.73 Mean no. cycles 4.9	See Section 5.3.2	F: 10 mg x 20 = £357.49 C: 50 mg x 100 = £13.85 F: 25 mg/m^2 3 days per cycle; C: 250mg/m^2 3 days per cycle; Average BSA 1.72m^2 Mean no. cycles 4.6	See Section 6.3.1
Mean cost of technology treatment	Course therapy: **£4,741.54**	See Section 1.10	Course therapy: **£91.76**	See Section 5.3.2	Course therapy **£1,250.54**	See Section 1.10
Infusion cost	First infusion= £272.10 Subsequent infusions (cost per infusion) =£226.88	Deliver simple Parenteral Chemotherapy at first attendance, Outpatient (SB12Z); Deliver subsequent elements of a Chemotherapy cycle, Outpatient (SB15Z)[40]	Not applicable	Not applicable	Not applicable	Not applicable
Haematologist outpatient visit	One per cycle = £130.71	Resource use: advisory board (see Section 6.5.2) Cost: Consultant Led: Follow up Attendance Non-Admitted Face to Face: Clinical Haematology 303[40]	One per cycle = £208.92	Resource use: advisory board (see Section 6.5.2) Cost: Deliver exclusively Oral Chemotherapy, Outpatient (SB11Z)[40]	One per cycle = £208.92	Resource use: advisory board (see Section 6.5.4) Cost: Deliver exclusively Oral Chemotherapy, Outpatient (SB11Z)[40]

Items	Bendamustine	Ref.	Chlorambucil (comparator)	Ref.	FC (subsequent lines of therapy in model)	Ref.
Blood count	One per month = £2.97	Resource use: advisory board (see Section 6.5.2) Cost: Direct Access: Pathology Services: Haematology (excluding anti-coagulant services) (DAP823)[40]	One per month = £2.97	Resource use: advisory board (see Section 6.5.2) Cost: Direct Access: Pathology Services: Haematology (excluding anti-coagulant services) DAP823[40]	One per month = £2.97	Resource use: advisory board (see Section 6.5.4) Cost: Direct Access: Pathology Services: Haematology (excluding anti-coagulant services) DAP823[40]
Biochemistry	One per month = £1.34	Resource use: advisory board (see Section 6.5.2) Direct Access: Pathology Services: Biochemistry (DAP841)[40]	One per month = £1.34	Resource use: advisory board (see Section 6.5.2) Direct Access: Pathology Services: Biochemistry (DAP841)[40]	One per month = £1.34	Resource use: advisory board (see Section 6.5.4) Direct Access: Pathology Services: Biochemistry (DAP841)[40]
Antiemetic cost per cycle	50% Maxolon (87.5 mg/cycle) and 50% domperidone (70mg/cycle) £0.24	Resource use: advisory board (see Section 6.5.2) and Herrstedt, et al[84] Cost: BNF 59[85]	None – except when having an AE	Advisory board (see Section 6.5.4)	50% Maxolon (87.5 mg/cycle) and 50% domperidone (70mg/cycle) £0.24	Assumed equal to bendamustine
Total	**£7,673.00**		**£1,136.60**		**£2,232.51**	

Pharmaceutical prices taken from BNF 59 (excluding bendamustine);[85] FC dosage taken from Robak *et al* 2010;[74] mean cycles of FC taken from Catovsky *et al*.[49]

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Unit costs for the different health states are summarised in Table 6.20. Note that patients do not receive the health state costs if they are receiving active therapy and instead receive the therapy acquisition, administration and monitoring costs as outlined in Table 6.19. These were based on consultation with clinical experts. Patients in the best supportive care health state receive the progressive disease cost.

Table 6.20 List of health states and associated costs in the economic model

Health states	Items	Unit cost	Reference – Cost	Reference – Resource use
Stable disease (costs incurred every month)	Consultant haematologist	£130.71	Consultant Led: Follow up Attendance Non-Admitted Face to Face: Clinical Haematology 303[40]	Advisory board (see Section 6.5.4)
	Full blood count	£2.97	Direct Access: Pathology Services: Haematology (excluding anti-coagulant services) DAP823[40]	Advisory board (see Section 6.5.4)
	Routine biochemistry	£1.34	Direct Access: Pathology Services: Biochemistry DAP841[40]	Advisory board (see Section 6.5.4)
	Total (per 3 month model cycle)	£405.07	-	-
Partial response (costs incurred every 3 months)	Consultant haematologist	£130.71	As above	As above
	Full blood count	£2.97	As above	As above
	Routine biochemistry	£1.34	As above	As above
	Total (per 3 month model cycle)	£135.02	-	-
Complete response (costs incurred every 6 months)	Consultant haematologist	£130.71	As above	As above
	Full blood count	£2.97	As above	As above
	Routine biochemistry	£1.34	As above	As above
	Total (per 3 month model cycle)	£67.51	-	-
Progressive disease/BSC (costs incurred every 3 weeks)	Consultant haematologist	£130.71	As above	As above
	Full blood count	£2.97	As above	As above
	Routine biochemistry	£1.34	As above	As above
	Blood transfusion	Blood transfusion – transfusion administration £84.60 Blood transfusion - red blood cells (2 x units) £261.46 Total: £346.06	Non-Consultant Led: Follow-up attendance Non-Admitted Face to Face: Blood transfusion 821[40] NHS Blood and Transplant Annual Review 2008-09[86]	Advisory board (see Section 6.5.4)
	Total (per 3 month model cycle)	£1,924.33		

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

The adverse events costs are shown in Table 6.21. Note that for anaemia the proportion of patients experiencing an event along with an assumption of one event per cycle is used to calculate the utility impact of the event. For costing purposes however, the number of red blood cell administrations from Study 02CLLIII is used.

Table 6.21 List of adverse events and summary of costs included in the economic model

Adverse event	Treatment type	Treatment	% patients receiving treatment	Total unit cost	Total units (mg/appointments /admission days)	Total cost per adverse event episode	Reference
Cytopenias - GCSF	i.v. infusion	Haematologist consultation	100%	£130.71	1.00	£817.09	Section 6.5.5
	GCSF	Neulasta (Pegfilgrastin)	100%	£686.38	1.00		BNF 59[85]
Cytopenias - Erythropoietin	Erythropoietin	Erythropoietin treatment	100%	£1,188.61	1.00	£1,188.61	Wilson, et al 2007[87] (inflated to 2009)
Nausea (grade 1 or 2)	Anti emetics	Metoclopramide	50%	£0.004	87.5	£0.24	Section 6.5.6
		Domperidone	50%	£0.002	70		Section 6.5.6
Nausea/vomiting (grade 1 or 2)	Anti emetics	Metoclopramide	50%	£0.004	87.5	£0.24	Section 6.5.6
		Domperidone	50%	£0.002	70		Section 6.5.6
Anaemia (grade 3 or 4)	Transfusion	Blood transfusion	100%	£346.06	1	£453.12	Section 6.5.6
	Consultation	Nurse	50%	£83.40	1		Non-consultant Led: Follow up Attendance Non-Admitted Face to Face: Clinical Haematology 303[40]
		Consultant	50%	£130.71	1		Section 6.5.5
Pyrexia (grade 3 or 4)	i.v. antibiotics	Tazocin	100%	£0.003	126000	£3,076.99	BNF 59[85]
	Hospital care	Inpatient admission	100%	£2,652.23	1		Reference costs*
Pneumonia (grade 3 or 4)	i.v. antibiotics	Tazocin	100%	£0.003	126000	£2,188.00	BNF 59[85]
	Hospital care	Inpatient admission	100%	£1,763.24	1		Reference costs**
Diarrhoea (grade 1 or 2)	Anti-diarrhoeal	Loperamide	50%	£0.018	21	£0.43	BNF 59[85]
		Codeine	50%	£0.002	270		BNF 59[85]

Prices taken from BNF 59, except erythropoietin cost which was from Wilson 2007

* NHS Reference costs 2008-09 Non-Elective Inpatient (Long Stay) HRG Data: Fever unspecified with complications and co-morbidities PA20A (£1,699.47) and NHS Reference costs 2008-09 Non-Elective Inpatient (Long Stay) HRG Data: Febrile Neutropenia with Malignancy PA45Z (£3,569.55)., weighted by activity (906 and 941 respectively).

** NHS Reference costs 2008-09 Non-Elective Inpatient (Long Stay) HRG Data: Lobar, Atypical or Viral Pneumonia with complications and co-morbidities DZ11B (£1,750.98) and NHS Reference costs 2008-09 Non-Elective Inpatient (Long Stay) HRG Data: Bronchopneumonia with complications and co-morbidities DZ23B (£1,941.40), weighted by activity (44,114 and 3,306 respectively).

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Not applicable.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The following sensitivity analyses around the model structural assumptions were undertaken:

Treatment effects

The current analysis includes a treatment covariate when extrapolating the parametric survival curves. The treatment covariates were included to make use of all available data; however, in some cases they were not statistically significant. We have therefore explored the impact of removing each covariate as a sensitivity analysis.

Survival distributions

Uncertainty around the assumed forms of the parametric survival functions used in the base case analysis was explored by fitting different survival functions to the 02CLLIII data and assessing the impact of this on cost-effectiveness. Treatment covariates were included as per the base case analysis. The parameter estimates for each endpoint, for each survival distribution (exponential, Weibull, log-normal and log-logistic) are provided in the model. A sensitivity analysis was also undertaken where individual Weibull distributions were fitted for overall survival to both the bendamustine and chlorambucil groups separately.

Treatment pathway following first-line therapy

The treatment algorithm in the base-case assumes that patients receiving bendamustine do not receive retreatment with bendamustine. However, consultation with clinical experts indicated that some clinicians may consider retreating patients who had a long duration of remission (24 months or more). This re-treatment scenario has therefore been included as a sensitivity analysis. Given the uncertainty regarding re-treatment patterns and re-treatment efficacy the following scenarios were also run:

a. The first involves patients receiving bendamustine retreatment *ad infinitem* if they achieve a remission time of greater than or equal to 24 months – the 24 month assumption was based on feedback from the advisory board.

b. Patients on bendamustine who achieve a remission of at least 12 months are treated with chlorambucil (and re-treated *ad infinitem* with chlorambucil using this criteria) before they progress to FC/BSC. Treatment with chlorambucil is associated with the chlorambucil re-treatment efficacy, safety and cost parameters. Chlorambucil patients treated as normal.

c. Chlorambucil and bendamustine patients are re-treated and re-treatment efficacy set so response and time to progression equal to first-line efficacy for both comparators.

d. Patients are re-treated with bendamustine and re-treatment criteria and efficacy for bendamustine is equal to chlorambucil re-treatment (although bendamustine costs are retained).

Consultation with clinicians also indicated that the duration of remission required for patients to be considered eligible for re-treatment may also vary. The following scenario analyses were therefore run:

- Chlorambucil patients re-treated if remission is 6 months or more.
- Chlorambucil patients re-treated if remission is 24 months or more.
- Bendamustine re-treatment if remission is 6 months or more.
- Bendamustine re-treatment if remission is 12 months or more.

Data sources for subsequent line therapies

Alternative data sources were trialled for re-treatment efficacy [Robak *et al* (2005) is replaced by Montserrat *et al*] and for FC efficacy and safety [Robak, *et al* (2010) is replaced by O'Brien, *et al*].

Utilities

Although the utilities included in the current submission are believed to represent the best estimates available at the time of writing, sensitivity analyses were run to explore the impact of using the utilities used in the recent NICE appraisals of fludarabine and rituximab in CLL.[51,52]

For the sensitivity analysis using the fludarabine TA119 utilities, the on-treatment utility of 0.74 was applied to patients receiving treatment at any position in the treatment pathway; the 0.80 response value was applied to patients with SD, PR or CR at any treatment point and the 0.60 value was applied to patients with progressive disease at any treatment point. Adverse event disutility is not included in this analysis as it is assumed that this is captured by the on-treatment decrement.

For the sensitivity analysis using the rituximab TA174 utilities the pre-progression utility of 0.80 is applied to the SD, PR and CR states associated with initial treatment and the 0.60 post-progression utility is applied to all states entered following progression after the first treatment. Adverse event disutilities are as per the base case analysis.

Sensitivity analysis was also undertaken whereby patients achieve response-specific utility levels as soon as they enter the response states rather than at the end of the 4.9 month treatment period.

Decision maker parameters

Sensitivity analysis was undertaken on:

- Discount rate was tested at 0% and 6%
- Time horizon:
    - Trial duration (68 months)
    - 10 years
    - 15 years
    - 20 years
    - 25 years
    - 30 years
- 35 years (base case)

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic parameter sensitivity analyses were also run; the parameters varied are described below:

Patient body surface area

A sensitivity analysis is conducted to explore the impact of patients being in different body surface area bands. This sensitivity analysis explores the impact of patients having a BSA of 1.26 – 1.50m^2; 1.76 – 2.0m^2 and 2.01 – 2.25m^2 as these patients will require 150 mg, 200 mg and 225 mg of bendamustine per infusion, assuming full vial wastage.

Time to re-treatment

Time to re-treatment was estimated from Study 02CLLIII in the absence of alternative data sources. However, this estimate may be influenced by treatment practices in the European centres where the trial was carried out. Sensitivity analysis was therefore carried out varying the hazard for re-treatment from its base case value using the lower and upper bounds of the confidence interval on the intercept and treatment coefficient parameters. These values used are provided in the model.

Sensitivity analysis on response rates

Sensitivity analyses were run using the 02CLLIII confidence intervals around overall response rates for chlorambucil and bendamustine and the 02CLLIII confidence intervals around CR as a proportion of all responses for chlorambucil and bendamustine. The values used are provided in the model.

Costs

Sensitivity analyses were carried out varying the following cost parameters in the model:

- Setting all health state costs to zero and varying by +/-20%
- Excluding the cost of FC treatment and varying it by +/-20%
- Excluding adverse event costs for bendamustine and chlorambucil and varying these by +/-20%
- Excluding adverse event costs for FC and varying these by +/-20%
- Varying bendamustine administration cost by +/-20%
- Exclusion of GCSF and erythropoietin costs

Utilities

Sensitivity analyses were carried out varying the following cost parameters in the model:

- Excluding adverse event utility decrements for bendamustine and chlorambucil and varying these by +/-20%
- Excluding adverse event utility decrements for FC and varying these by +/-20%

Subsequent line therapy efficacy

Another area of uncertainty is around patient performance on FC therapies. Sensitivity analyses were therefore conducted by altering the overall response rates and time to progression associated with FC by +/- 15%.

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of ‘priors’. If any

parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

The distributions used in the probabilistic sensitivity analysis and their parameterisation are presented in Table 6.22. Where possible, distributions were parameterised using empirical data; where these were not available, wide confidence intervals were assigned to represent the lack of knowledge regarding parameter uncertainty.

Table 6.22 Distributions used in probabilistic sensitivity analysis

Parameter	Distribution	Uncertainty parameter estimates	Uncertainty parameter sources
Best initial response (PD, SD, PR, CR)	Dirichlet	Directly parameterised using counts presented in Table 6.2	02CLLIII
Time to progression – SD, survival curve parameters	Multivariate normal	Parameters in Table 6.3 as well as the variance-covariance matrix parameters: var(intercept) = 0.021514 var(scale) = 0.002977 var(tx) = 0.083809 covar(intercept, scale) = 0.002841 covar(intercept, tx) = -0.018232 covar(scale,tx) = 0.000598	02CLLIII
Time to progression - PR, survival curve parameters	Multivariate normal	Parameters in Table 6.4 as well as the variance-covariance matrix parameters: var(intercept) = 0.005676 var(scale) = 0.001779 var(tx) = 0.011749 covar(intercept, scale) = 0.00018 covar(intercept,tx) = -0.00563 covar(scale, tx) = 0.000239	02CLLIII
Time to progression - CR, survival curve parameters	Multivariate normal	Parameters in Table 6.5 as well as the variance-covariance matrix parameters: var(intercept) = 0.064766 var(scale) = 0.00507 var(tx) = 0.070757 covar(intercept, scale) = 0.001912 cov(intercept, tx) = -0.064024 cov(scale,tx) = 0.00005754	02CLLIII
Time from progression to re-treatment, survival curve parameters	Normal	Parameters in Table 6.6 as well as the variance-covariance matrix parameters: var(intercept) = 0.016129 var(tx) = 0.034648 cov(intercept, tx) = -0.016129	02CLLIII

Parameter	Distribution	Uncertainty parameter estimates	Uncertainty parameter sources
Odds ratio, overall response rate in re-treated versus treatment-naïve patients	Log-normal	Parameters in Table 6.7.	Robak 2005[15]
Time to progression following re-treatment - PR *vs*. SD hazard ratio	Log-normal	Parameters in Table 6.8.	02CLLIII
Time to progression following re-treatment - CR *vs*. SD hazard ratio	Log-normal	As above.	02CLLIII
Time to progression following re-treatment - CR *vs*. PR hazard ratio	Log-normal	As above.	02CLLIII
Time to progression bendamustine (used to estimate re-treatment time to progression)	Beta distribution for median survival proportion	Median survival time = 21.6 months, n = 162	02CLLIII
Time to progression chlorambucil (used to estimate re-treatment time to progression)	Beta distribution for median survival proportion	Median survival time = 8.3 months, n = 157	02CLLIII
Time to progression first line Robak 2005 (used to derive hazard ratio for re-treatment *vs*. first line)	Beta distribution for median survival proportion	Median survival time = 17 months, n = 103	Robak 2005[15]
Time to progression re-treatment Robak 2005 (used to derive hazard ratio for re-treatment *vs*. first line)	Beta distribution for median survival proportion	Median survival time = 12 months, n = 19	Robak 2005[15]
Best response to FC (PD or SD, PR, CR)	Dirichlet	Directly parameterised using counts presented in Table 6.10.	Robak 2010[74]
Proportion patients treated with FC/BSC at second line	Beta	Assumed proportion derived from 100 patients.	Assumption
Median time to progression FC – responders	Beta distribution for median survival proportion	Median survival time = 27.7, n = 160	
Median time to progression FC – all patients	Beta distribution for median survival proportion	Median survival time = 20.6, n = 236	

Parameter	Distribution	Uncertainty parameter estimates	Uncertainty parameter sources
Adverse event probabilities initial treatment/re-treatment	Beta	Parameters in Table 6.13.	02CLLIII
Proportion of cycles with GCSF/erythropoietin red blood cell administration	Beta	Parameters in Table 6.13.	02CLLIII
Adverse event probabilities FC	Beta	Parameter in Table 6.14.	Robak 2005;[15] 02CLLIII
Utilities	Beta	Parameters in Table 6.18	02CLLIII; Beusterien 2010[14]
Bendamustine/chlorambucil treatment cycles	Normal (restricted to be positive)	Parameters in Table 6.19 as well as the standard errors: s.e.(mean cycles chlor) = 0.14 s.e.(mean cycles bend) = 0.13	02CLLIII
FC treatment cycles	Normal (restricted to be positive)	Parameters in Table 6.19 as well as the standard error estimate of 0.20	Assumption
Resource use estimates (counts)	Gamma	Assume s.e. = 0.50*mean	Assumption
Resource use estimates (proportions)	Beta	Assumed expert opinion equivalent to sample size of 100	Assumption
Unit costs	Gamma	Assumed lower and upper quartiles in reference costs represent 50 % confidence interval.	NHS Reference Costs 2008-9[40]
Unit cost – blood transfusion / erythropoietin treatment	Gamma	Assume s.e. = 0.50 mean	Assumption

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over).

Table 6.23 Summary of model results compared with clinical data

Outcome	Bendamustine		Chlorambucil	
	Clinical trial result	Model result	Clinical trial result	Model result
Response rates	Input directly from trial			
Median PFS	21.6 months	21 months	8.3 months	9 months*
PFS at 12 months	80%	74%	33%	31%
PFS at 24 months	48%	42%	3%	6%
PFS at 36 months	31%	21%	1%	1%
Median OS	Not yet reached	99 months	66 months	69 months
OS at 30 months	88%	88%	83%	81%
OS at 60 months	73%	71%	54%	57%
Adverse events	Input directly from trial			

*Median occurs at between 6 and 9 months.

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Distributions of patients across model health states over time for bendamustine and chlorambucil are provided as Table 6.24 and 6.25. The health states are aggregated for subsequent therapy lines for ease of interpretation; the full Markov traces are available from the Excel model.

Table 6.24 Distribution of patients across health states: bendamustine (greyed out states not used in base-case)

Time (years)	1st treatment				Re-tx	Retreatment				FC	FC				BSC	Death
	SD	PR	CR	PD		SD	PR	CR	PD		SD	PR	CR	PD		
6 months	14%	29%	45%	10%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	1%	1%
12 months	7%	26%	42%	17%	0%	0%	0%	0%	0%	1%	0%	1%	0%	0%	3%	3%
30 months	0%	7%	22%	30%	0%	0%	0%	0%	0%	2%	2%	5%	2%	2%	15%	12%
68 months	0%	0%	4%	9%	0%	0%	0%	0%	0%	1%	2%	7%	3%	6%	36%	32%
10 years	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	2%	1%	2%	34%	59%
15 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	20%	79%
20 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	9%	91%
25 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	4%	96%
30 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%	99%
35 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%	99%

Table 6.25 Distribution of patients across health states: chlorambucil

Time (years)	1st treatment				Re-tx	Retreatment				FC	FC				BSC	Death
	SD	PR	CR	PD		SD	PR	CR	PD		SD	PR	CR	PD		
6 months	24%	28%	5%	35%	0%	0%	0%	0%	0%	3%	0%	0%	0%	0%	3%	2%
12 months	10%	17%	4%	46%	0%	0%	0%	0%	0%	3%	1%	3%	1%	1%	8%	6%
30 months	0%	1%	1%	28%	5%	4%	5%	1%	16%	1%	1%	3%	1%	2%	11%	19%
68 months	0%	0%	0%	3%	1%	1%	2%	1%	11%	1%	1%	4%	2%	4%	22%	47%
10 years	0%	0%	0%	0%	0%	0%	0%	0%	2%	0%	0%	1%	1%	1%	17%	77%
15 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	7%	93%
20 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	98%
25 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
30 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
35 years	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs accrued overtime using a Markov trace. Utility values are assigned accordingly for each health state, with disutility from toxicities also accounted for (see Section 6.4.8).

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 6.26 Model outputs by clinical outcomes

Outcome	LY		QALY		Cost (£)	
	Bend	Chlor	Bend	Chlor	Bend	Chlor
Progression-free survival	1.96	0.75	1.53	0.54	£7,785	£1,218
Post-progression survival	5.86	5.08	3.30	3.01	£40,685	£32,296
Adverse events	n/a	n/a	-0.01	-0.01	£529	£307

LY, life years; QALY, quality-adjusted life year

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 6.27 Summary of QALY gain by health state

Health state	QALY intervention (Bendamustine)	QALY comparator (Chlorambucil)	Increment	% absolute increment
Progression-free survival	1.53	0.54	0.98	77%
Post-progression survival	3.30	3.01	0.29	23%
Adverse events	-0.01	-0.01	0.00	0%
Total	4.82	3.55	1.27	100%

QALY, quality-adjusted life year
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 6.28 Summary of costs by health state

Health state	Cost intervention (Bendamustine)	Cost comparator (Chlorambucil)	Increment	% absolute increment
Progression-free survival	£7,785	£1,218	£6,567	43%
Post-progression survival	£40,685	£32,296	£8,389	55%
Adverse events	£529	£307	£222	1%
Total	£49,000	£33,821	£15,179	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 6.29 Summary of predicted resource use by category of cost

Item	Cost intervention (Bendamustine)	Cost comparator (Chlorambucil)	Increment	% absolute increment
Treatment acquisition	£4,726	£150	£4,576	30%
Treatment administration/monitoring	£2,922	£1,706	£1,216	8%
FC acquisition, administration/monitoring	£780	£592	£188	1%
Adverse events B/C	£375	£190	£185	1%
Adverse events FC	£155	£117	£37	0%
Routine follow-up costs	£40,043	£31,065	£8,978	59%
Total	£49,000	£33,821	£15,179	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The base-case results are summarised in Table 6.30.

Table 6.30 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) *vs.* baseline (QALYs)
Bendamustine	£49,000	7.81	4.82	£15,179	1.99	1.27	£11,960
Chlorambucil	£33,821	5.83	3.55	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Table 6.31 Results of sensitivity analyses

Variable	Base case	Sensitivity Analysis	ICER
Distribution used for survival analysis			
SD TTP	Loglogistic	Exponential	£12,111
		Weibull	£11,756
		Lognormal	£11,892
PR TTP	Lognormal	Exponential	£11,246
		Weibull	£11,473
		Loglogistic	£12,025
CR TTP	Lognormal	Exponential	£11,007
		Weibull	£12,263
		Loglogistic	£11,933
Overall survival	Weibull	Exponential	£12,858
		Loglogistic	£12,295
		Lognormal	£12,603
		Weibull separate[+]	£12,535
Treatment covariate			
SD TTP	Included	Excluded	£12,007
PR TTP	Included	Excluded	£13,387
CR TTP	Included	Excluded	£12,382
Time to re-treat	Included	Excluded	£11,982
Overall survival	Included	Excluded	£10,997
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
Chlorambucil CR / OR	Base case	Upper CI	£12,319
		Lower CI	£11,741
Bendamustine CR / OR	Base case	Upper CI	£11,473

Variable	Base case	Sensitivity Analysis	ICER
		Lower CI	£12,454
Re-treatment			
Re-treatment algorithm	Base case	Bend re-treatment	£8,722
		All chlor re-tx	£9,641
		1st line efficacy for re-tx	£8,030
		Bend re-tx efficacy equals chlor	£12,427
Cut-off duration of response for re-treat CLB	12 months	6 months	£12,915
		24 months	£10,769
Cut-off duration of response for re-treat Bend	No re-tx	6 months	£6,698
		12 months	£7,510
Efficacy re-treatment	Robak (2005)[15]	Montserrat[66]	£11,450
Time to re-treatment	Base case	Upper confidence intervals	£12,154
		Lower confidence intervals	£11,684
FC efficacy			
FC data source	Robak (2010)[74]	O'Brien[69]	£11,152
FC response rate	Base case	+15%	£11,842
		-15%	£12,071
FC time to progression	Base case	+15%	£11,779
		-15%	£12,156
Costs			
Patient BSA	1.51-1.75m^2	1.26-1.50	£11,412
		1.76-2.00	£12,492
		2.01-2.25	£13,041
Health state costs	Include	Exclude	£4,886
		+20%	£13,375
		-20%	£10,545
Costs of FC acquisition and administration	Include	Exclude	£11,812
		+20%	£11,990
		-20%	£11,931
AE costs (B / C)	Include	Exclude	£11,815
		+20%	£11,989
		-20%	£11,931
AE costs (FC)	Include	Exclude	£11,931
		+20%	£11,966
		-20%	£11,954
Cost of bendamustine administration	Base Case	+20%	£12,851
		-20%	£11,069
GCSF / erythropoietin cost	Include	Exclude	£11,881
Utilities			

Variable	Base case	Sensitivity Analysis	ICER
Source	Beusterien[14]	Fludarabine (TA119)[51]	£11,024
		Rituximab (TA174)[52]	£10,607
Remove benefit in tx period	Yes	No	£11,803
AE utilities (B / C)	Include	Exclude	£11,815
		+20%	£11,989
		-20%	£11,931
AE 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
Time horizon	35 years	Trial duration (68 months)	£8,551
		10 years	£10,371
		15 years	£11,379
		20 years	£11,755
		25 years	£11,895
		30 years	£11,944

[+]Separate parametric curves fitted to each trial arm.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 6.8 Distribution of simulations on cost-effectiveness plane (5,000 simulations)

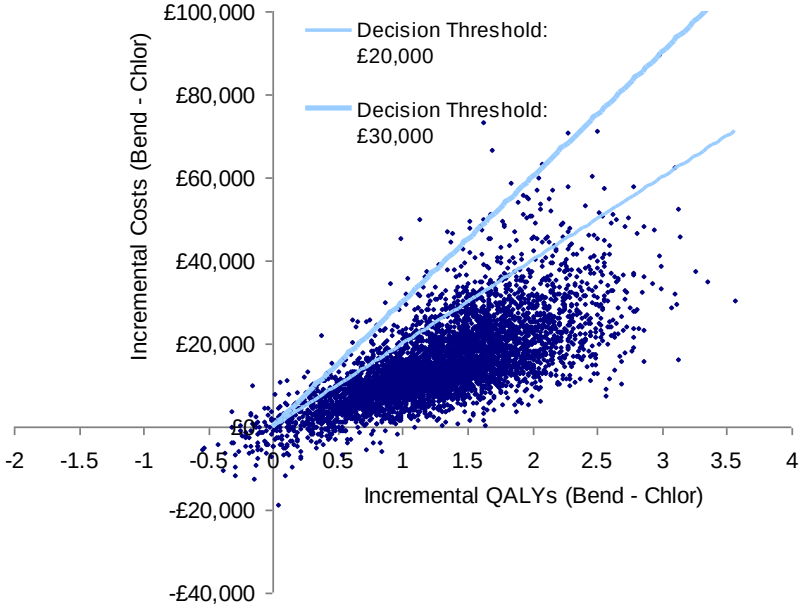


Figure 6.9 Cost-effectiveness acceptability curves (5,000 simulations)

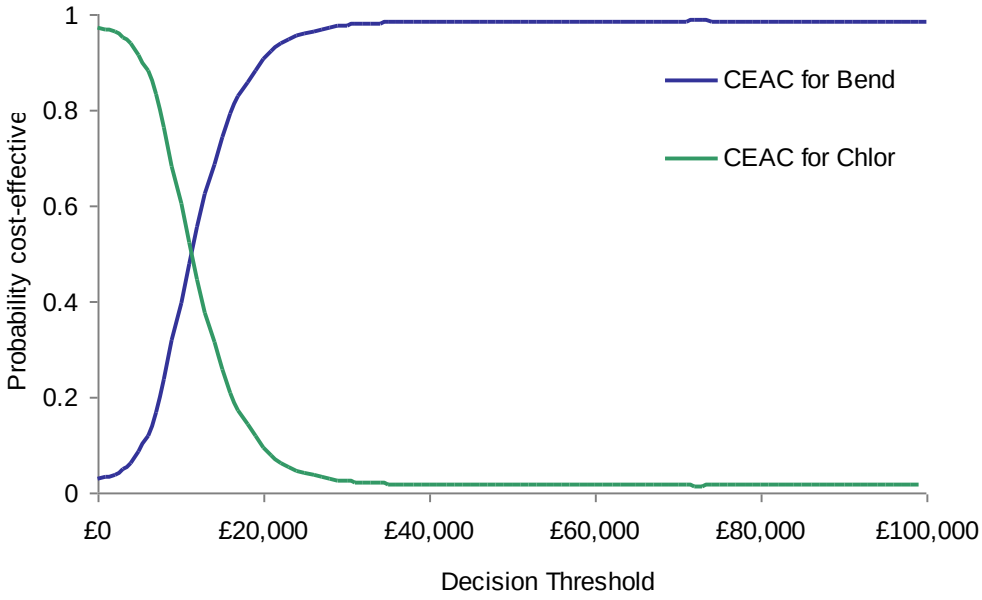


Table 6.32 Probability of cost-effectiveness at specific thresholds (5,000 simulations)

Threshold	% simulations cost-effective	
	Bendamustine	Chlorambucil
£10,000	40%	60%
£15,000	74%	26%
£20,000	90%	10%
£25,000	96%	4%
£30,000	98%	2%
£35,000	98%	2%
£40,000	98%	2%

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Results of all the deterministic sensitivity analysis (parameter and structural) are described in Section 6.7.7. No additional scenario analysis was undertaken.

6.7.10 What were the main findings of each of the sensitivity analyses?

The sensitivity analyses suggest that the base-case results are robust to variations in parameter estimates and structural assumptions. None of the sensitivity analyses increased the ICER by more than £2,000 per QALY. Of interest is the result

generated when the treatment effect on overall survival is removed. A detailed breakdown of this analysis is presented below.

Table 6.33 Base-case results excluding treatment effect on overall survival

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) *vs*. baseline (QALYs)
Bendamustine	£41,334	6.70	4.19	£1,668	0.00	0.15	£10,997
Chlorambucil	£39,666	6.70	4.04	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

These results indicate that although removal of the treatment effect on overall survival substantially decreases the QALY advantage of bendamustine, this is offset by a reduction in the incremental costs due to the removal of the additional cost of extending life in the bendamustine arm. The net effect on the ICER of these changes is small.

6.7.11 What are the key drivers of the cost-effectiveness results?

The main drivers of the cost-effectiveness results are the quality of life and survival advantage of bendamustine over chlorambucil, the higher acquisition cost of bendamustine and the high cost associated with the progressive disease health state.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

As described in Section 6.7.1, the model distribution of patients across response rates and disease progression, was closely matched to the outcomes of the Study 02CLLIII. An academic group audited the Excel model and a consulting firm also audited an earlier version of the model The overall survival benefit estimated in the model is similar to what patients would receive in the real life setting.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Three subgroups are analysed in the model:

- Age ≥65 years
- WHO physical status ≥1
- WHO physical status ≥1 and age ≥65 years

The objective of these sensitivity analyses was to explore the impact of these characteristics to test the cost-effectiveness of bendamustine across the heterogeneous patient group that is likely to be receiving it.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

See Section 6.9.1.

6.9.3 Please describe how the statistical analysis was undertaken.

Two alterations to the model were made to simulate long-term costs and health outcomes in these subgroups. Firstly, the distributions of patients across response categories were obtained from the relevant subgroup. Secondly, a dummy covariable for the subgroup was included in all the survival analyses. The subgroup covariable was retained in all analyses regardless of significance as Study 02CLLIII was not powered to detect differences with respect to these covariables. All survival analyses were run using the parametric distributions used in the base case. Treatment effects were included as per the base case analysis.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

The associated odds ratios for overall response for the base-case population and each subgroup are presented in Table 6.34. The mean estimates indicate that the treatment effect of bendamustine is maintained across subgroups although uncertainty around the treatment effects is high (due to the smaller sample sizes).

Table 6.34 Odds ratios for overall response

Patient group	Absolute response probability (Chlor.), mean (95% CI)	Odds ratio for overall response (Bend. *vs*. Chlor.), mean (95% CI)
Base case (ITT)	35% (27%, 43%)	5.38 (3.26, 9.05)
Age≥65	36% (26%, 47%)	4.57 (2.25, 9.60)
WHO≥1	24% (13%, 38%)	4.67 (1.83, 12.65)
Age≥65 & WHO≥1	24% (11%, 43%)	3.94 (1.17, 14.71)

Results for each subgroup are provided in Tables 6.35 – 6.37.

Table 6.35 Age≥65

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) *vs.* baseline (QALYs)
Bendamustine	£40,451	6.56	4.09	£12,771	1.56	1.01	£12,617
Chlorambucil	£27,680	5.00	3.08	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 6.36 WHO≥1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) *vs.* baseline (QALYs)
Bendamustine	£42,924	6.51	3.97	£13,921	1.64	1.03	£13,452
Chlorambucil	£29,002	4.87	2.94				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 6.37 Age≥65 & WHO≥1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) *vs.* baseline (QALYs)
Bendamustine	£37,292	5.72	3.53	£12,948	1.48	0.95	£13,567
Chlorambucil	£24,344	4.24	2.57	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

All relevant subgroups were considered.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Not applicable. No other cost-effectiveness studies of bendamustine in CLL have been identified.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

No subjects included in Study 02CLLIII were excluded in the model used to support the present economic evaluation, which is reflective of the heterogeneous group of untreated CLL patients expected to be eligible for bendamustine in clinical practice.

In addition, the three subgroup analyses also confirmed that bendamustine appears cost-effective even if the patient population is restricted to elderly patients (≥65 years old); patients with a lesser global physical status (WHO status ≥1) or patients who fulfil both of these criteria. This demonstrates that bendamustine is cost-effective across the heterogeneous patients group that is likely to receive it.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of the analysis are that the model was principally based on the RCT, Study 02CLLIII, which incorporated the appropriate comparator (chlorambucil). Subsequent lines of therapy were included in the model meaning it was realistic to a real world treatment setting, where patients can receive a response to a future therapy after entering a progressive disease health state. The model was also conservative in terms of how overall survival was estimated, with parametric survival curves estimated by extrapolating the survival benefit found in Study 02CLLIII and no adjustment made for the greater number of follow-up therapies received by patients in the chlorambucil group. Including time dependent transitional probabilities, where possible, increased the model's accuracy.

The main weakness of the analysis is that the quality of life data from Study 02CLLIII were not able to inform the utility differences between different health states (though utility values estimated from EORTC data were applied during the treatment period only). These utility differences between health states were instead estimated using vignette based utility values – an approach that is at variance with the NICE reference case but that has been applied in all five of the previous CLL submissions made to NICE.

The ICER of £11,960 indicates that although bendamustine is associated with higher acquisition and administration costs compared to chlorambucil, the health benefits (increased HRQL and OS) generated by better and more durable response rates would be considered to be good value at conventional decision thresholds (£20 - 30,000/QALY). Extensive sensitivity analysis was undertaken and the ICER remained under £14,000 in all cases. Probabilistic sensitivity analyses indicate that bendamustine is a cost-effective treatment option with probability 90% at a decision threshold of £20,000/QALY and 98% at a decision threshold of £30,000/QALY.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Analysis could be undertaken looking at the effect of subsequent lines of therapy and cross-over on the overall survival benefit. This may be of interest as the chlorambucil patients received a greater number of therapies than the bendamustine group.

6.10.5 Recent supporting evidence

A few days before the submission deadline for this report, the authors of Study 02CLLIII shared an academic in confidence abstract for selection to this year's American Society of Hematology annual meeting (4 - 7 December 2010).[88] The abstract reports on the latest trial analyses after a median observation time of 54 months (rather than the 35 months reported in the main publication used in this submission). The results for the primary outcomes confirm that bendamustine offers significantly greater response rates and PFS, and a much longer time to next treatment than chlorambucil. The relationship between initial clinical response and improved overall survival benefit was further supported, with patients achieving a CR experiencing a statistically significant longer overall survival than patients not in CR (median not reached *vs*. 76.2 months, respectively; $P = 0.002$). Also, patients with any response (CR + PR) after either bendamustine or chlorambucil has a longer overall survival than non-responders (median not reached *vs*. 68.3 months; $P<0.0001$). The overall survival benefit for bendamustine between the two treatment groups was also confirmed, but the result was still not statistically significant (hazard ratio = 1.3 in favour of bendamustine, $P = 0.24$). While this recent cut of data supports the existing analysis, 54 months is still a relatively short time period to measure outcomes like overall survival given the indolent nature of CLL.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The reported incidence of CLL varies, with robust values of true incidence unknown. Cancer Research UK reports the overall incidence to be approximately 3 per 100,000 per year based on 2007 estimates.[2] From the pool of all new cases of CLL it is difficult to determine the number of cases which will then go on to require treatment. Bendamustine has a clear position on the treatment pathway, i.e. as an alternative to chlorambucil. Therefore, the most accurate way to estimate the number of patients eligible for bendamustine was to first of all determine the number of patients currently being treated with chlorambucil in the UK.

Data from IMS Oncology Analyzer[24] provided estimates on the number of CLL patients currently treated in the UK, and also the percent of these patients using chlorambucil as first-line treatment. IMS Health's Oncology Analyzer monitors hospital usage of chemotherapy, with data collected on a quarterly basis. Physicians are asked to complete patient medical records for the 15 first patients during an estimated reporting period. Data are projected at a national level to estimate treated prevalence. The IMS Oncology Analyzer estimated that in 2009, approximately 2,552 patients received first-line treatment for CLL in the UK and 1,323 patients were using chlorambucil.

These estimates are in line with the Decision Resources Database which estimated that there were 2,065 ‘drug treated’ patients for first line CLL in 2010.[89]

The IMS data are based on UK projections for 2009. Using the latest published population estimates for the UK[90] the percentage of patients using chlorambucil as

first-line treatment is calculated as 0.0021%. This percentage is applied to population estimates for England and Wales between 2010 and 2014 obtained from 2008-based population projections from the Office for National Statistics.[25] Therefore the projected number of first-line CLL patients that would receive chlorambucil in 2010 is 1,182.

An advisory board was asked to estimate the patient numbers likely to receive bendamustine. The advisory board estimated that 90% of patients, who would otherwise receive chlorambucil, would be eligible for bendamustine, i.e. only 10% of chlorambucil patients would be contra-indicated or otherwise unsuitable for bendamustine (see Section 6.5.4 for a description of the advisory board). The number of patients eligible for bendamustine in England and Wales for 2010 to 2014 is therefore as follows:

Table 7.1 Patients eligible for bendamustine

	2010	2011	2012	2013	2014
Total population	55209000	55601000	55994000	56388000	56781000
Patients currently receiving chlorambucil as first-line	1182	1190	1199	1207	1216
Patients eligible for bendamustine	**1064**	**1071**	**1079**	**1087**	**1094**

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

Bendamustine is anticipated to replace a percentage of the patients currently treated with chlorambucil. The uptake of bendamustine is discussed in the next section.

7.3 What assumption(s) were made about market share (when relevant)?

The participants of the advisory board estimated that of those who are eligible for chlorambucil, clinicians would choose bendamustine for 70% of these patients (i.e. clinician choice/preference would be *not* to use bendamustine in 30% of all eligible patients). This 70% uptake is assumed to take place in Year 5 and therefore a linear growth (14% increase every year) is assumed over the next 5 years. The number of patients in which bendamustine will be used over the next 5 years is presented in Table 7.2.

Table 7.2 Estimated number of patients treated with bendamustine

	2010	2011	2012	2013	2014
Untreated CLL patient eligible for bendamustine	1064	1071	1079	1087	1094
Market share	14%	28%	42%	56%	70%
Untreated CLL patients treated with bendamustine	149	300	453	608	766

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Bendamustine is administered on two days per cycle; these administration costs were included in the calculation described in the next section. There are no other significant costs associated with bendamustine.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit costs assumed were the same as used in the modelling (see Section 6.5.5), and are presented in the table below. Costs related to the management of adverse events were derived directly from the economic model.

Table 7.3 Costs for budget impact

	Bendamustine	Chlorambucil	Cross-reference
Treatment cost	£7673	£1136	6.5.5
AEs related costs	£376.01	£116.35	Economic model
Total cost per course of therapy (4.9 cycles)	£8049.01	£1252.95	Calculated

7.6 Were there any estimates of resource savings? If so, what were they?

Any other savings that might occur in subsequent lines of therapy were excluded from the analysis for simplicity. This was potentially biased against bendamustine, as for the first five years of the health economic model other health care costs were greater with chlorambucil than with bendamustine.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Based on the assumptions above regarding number of patients eligible for treatment with bendamustine, the estimate for budget impact for bendamustine over the next five years is presented below:

Table 7.4 Net budget impact

	2010	2011	2012	2013	2014
Number of patients receiving bendamustine	149	300	453	608	766
Costs of patients receiving bendamustine	£1,198,810	£2,414,645	£3,647,568	£4,897,645	£6,164,724
Costs of patients receiving chlorambucil	£186,613	£375,876	£567,799	£762,392	£959,632
Net budget impact	**£1,012,197**	**£2,038,769**	**£3,079,769**	**£4,135,252**	**£5,205,092**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable.

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9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levact 2.5 mg/ml powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 25 mg bendamustine hydrochloride.

One vial contains 100 mg bendamustine hydrochloride.

1 ml of the concentrate contains 2.5 mg bendamustine hydrochloride when reconstituted according to section 6.6.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White, microcrystalline powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.

Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment.

4.2 Posology and method of administration

For intravenous infusion over 30 - 60 minutes (see section 6.6).

Infusion must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Poor bone marrow function is related to increased chemotherapy-induced haematological toxicity. Treatment should not be started if leukocyte and/or platelet values have dropped to < 3,000/µl or < 75,000/µl, respectively (see section 4.3).

Monotherapy for chronic lymphocytic leukaemia
100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab
120 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks.

Multiple myeloma
120 - 150 mg/m² body surface area bendamustine hydrochloride on days 1 and 2, 60 mg/m² body surface area prednisone i.v. or per os on days 1 to 4; every 4 weeks.

Treatment should be terminated or delayed if leukocyte and/or platelet values have dropped to < 3,000/µl or < 75,000/µl, respectively. Treatment can be continued after leukocyte values have increased to > 4,000/µl and platelet values to > 100,000/µl.

The leukocyte and platelet Nadir is reached after 14-20 days with regeneration after 3-5 weeks. During therapy free intervals strict monitoring of the blood count is recommended (see section 4.4).

In case of non-haematological toxicity dose reductions have to be based on the worst CTC grades in the preceding cycle. A 50% dose reduction is recommended in case of CTC grade 3 toxicity. An interruption of treatment is recommended in case of CTC grade 4 toxicity.
If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

For preparation and administration instructions see section 6.6.

Hepatic impairment
On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2 mg/dl). A 30% dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2 - 3.0 mg/dl).
No data is available in patients with severe hepatic impairment (serum bilirubin values of >3.0 mg/dl) (see section 4.3).

Renal impairment
On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of > 10 ml/min. Experience in patients with severe renal impairment is limited.

Paediatric patients
There is no experience in children and adolescents with Levact.

Elderly patients
There is no evidence that dose adjustments are necessary in elderly patients (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1)

During breast feeding

Severe hepatic impairment (serum bilirubin > 3.0 mg/dl)

Jaundice

Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3,000/µl or < 75,000/µl, respectively)

Major surgery less than 30 days before start of treatment

Infections, especially involving leukocytopenia

Yellow fever vaccination

4.4 Special warnings and precautions for use

Myelosuppression
Patients treated with bendamustine hydrochloride may experience myelosuppression. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4,000/µl or > 100,000/µl, respectively.

Infections
Infection, including pneumonia and sepsis, has been reported. In rare cases, infection has been associated with hospitalization, septic shock and death. Patients with neutropenia and/or lymphopenia following treatment with bendamustine hydrochloride are more susceptible to infections. Patients with myelosuppression following bendamustine hydrochloride treatment should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms.

Skin reactions
A number of skin reactions have been reported. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, Levact should be withheld or discontinued. For severe skin reactions where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued.

Patients with cardiac disorders
During treatment with bendamustine hydrochloride the concentration of potassium in the blood must be closely monitored and potassium supplement must be given when K^+ <3.5 mEq/l, and ECG measurement must be performed.

Nausea, vomiting
An antiemetic may be given for the symptomatic treatment of nausea and vomiting.

Tumour lysis syndrome
Tumour lysis syndrome associated with Levact treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of Levact and, without intervention, may lead to acute renal failure and death. Preventive measures include adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. The use of allopurinol during the first one to two weeks of Levact therapy can be considered but not necessarily as standard. However, there have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol were administered concomitantly.

Anaphylaxis
Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions.
Patients who experienced Grade 3 or worse allergic-type reactions were typically not re-challenged.

Contraception
Bendamustine hydrochloride is teratogenic and mutagenic.
Women should not become pregnant during treatment. Male patients should not father a child during and up to 6 months after treatment. They should seek advice about sperm conservation prior to treatment with bendamustine hydrochloride because of possible irreversible infertility.

Extravasation
An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.

4.5 Interaction with other medicinal products and other forms of interaction

No *in-vivo* interaction studies have been performed.

When Levact is combined with myelosuppressive agents, the effect of Levact and/or the co-administered medicinal products on the bone marrow may be potentiated. Any treatment reducing the patient's performance status or impairing bone marrow function can increase the toxicity of Levact.

Combination of Levact with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.

Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection which may lead to fatal outcome. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme (see section 5.2). Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exists.

4.6 Pregnancy and lactation

Pregnancy
There are insufficient data from the use of Levact in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic (see section 5.3). During pregnancy Levact should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with Levact is absolutely necessary during pregnancy or if pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

Women of childbearing potential/contraception
Women of childbearing potential must use effective methods of contraception both before and during Levact therapy.
Men being treated with Levact are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Levact.

Breast feeding
It is not known whether bendamustine passes into the breast milk, therefore, Levact is contraindicated during breast feeding (see section 4.3). Breast feeding must be discontinued during treatment with Levact.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, ataxia, peripheral neuropathy and somnolence have been reported during treatment with Levact (see section 4.8). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

4.8 Undesirable effects

The most common adverse reactions with bendamustine hydrochloride are hematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

The table below reflects the data obtained with bendamustine hydrochloride in clinical trials.

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1, 000**	**Very rare <1/10, 000**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Infection NOS*			Sepsis	Pneumonia primary atypical	
Neoplasms benign, malignant		Tumour lysis syndrome				
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombocytopenia	Haemorrhage, Anaemia, Neutropenia			Haemolysis	
Immune system disorders		Hypersensitivity NOS*		Anaphylactic reaction, Anaphylactoid reaction	Anaphylactic shock	
Nervous system disorders		Insomnia		Somnolence, Aphonia	Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders, Ataxia, Encephalitis	
Cardiac disorders		Cardiac dysfunction, such as palpitations, angina pectoris, Arrhythmia	Pericardial effusion		Tachycardia, Myocardial infarction, Cardiac failure	
Vascular disorders		Hypotension, Hypertension		Acute circulatory failure	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Pulmonary dysfunction			Pulmonary fibrosis	
Gastrointestinal disorders	Nausea, Vomiting	Diarrhoea, Constipation, Stomatitis			Haemorrhagic oesophagitis, Gastrointestinal haemorrhage	
Skin and subcutaneous tissue disorders		Alopecia, Skin disorders NOS*		Erythema, Dermatitis, Pruritus, Macular-papular rash, Hyperhidrosis		
Reproductive system and breast disorders		Amenorrhea			Infertility	
General disorders and administration site conditions	Mucosal inflammation, Fatigue, Pyrexia	Pain, Chills, Dehydration, Anorexia			Multi organ failure	

MedDRA system organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1, 000	Very rare <1/10, 000	Not known (cannot be estimated from the available data)
Investigations	Haemoglobin decrease, Creatinine increase, Urea increase	AST increase, ALT increase, Alkaline phosphatase increase, Bilirubin increase, Hypokalemia				

NOS = Not otherwise specified

A small number of cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported in patients using bendamustine in combination with allopurinol or in combination with allopurinol and rituximab.

The CD4/CD8 ratio may be reduced. A reduction of the lymphocyte count was seen. In immuno-suppressed patients, the risk of infection (e.g. with herpes zoster) may be increased.

There have been isolated reports of necrosis after accidental extra-vascular administration and toxic epidermal necrolysis, tumour lysis syndrome and anaphylaxis.

There are reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma. The association with Levact therapy has not been determined.

4.9 Overdose

After application of a 30 min infusion of Levact once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m². Cardiac events of CTC grade 2 which were compatible with ischaemic ECG changes occurred which were regarded as dose limiting.

In a subsequent study with a 30 min infusion of Levact at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m^2. The dose limiting toxicity was grade 4 thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

Counter measures
There is no specific antidote. Bone marrow transplantation and transfusions (platelets, concentrated erythrocytes) may be made or haematological growth factors may be given as effective countermeasures to control haematological side effects.
Bendamustine hydrochloride and its metabolites are dialyzable to a small extent.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents,
ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumour agent with unique activity. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. The antitumour effect of bendamustine hydrochloride has been demonstrated by several *in vitro* studies in different human tumour cell lines (breast cancer, non-small cell and small cell lung cancer, ovarian carcinoma and different leukaemia) and *in vivo* in different experimental tumour models with tumours of mouse, rat and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukaemia and small cell lung cancer).

Bendamustine hydrochloride showed an activity profile in human tumour cell lines different to that of other alkylating agents. The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms at least in part due to a comparatively persistent DNA interaction. Additionally, it was shown in clinical studies that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab. However, the number of assessed patients is small.

Chronic lymphocytic leukaemia
The indication for use in chronic lymphocytic leukaemia is supported by a single open label study comparing bendamustine with chlorambucil. In the prospective, multi-centre, randomised study, 319 previously untreated patients with chronic lymphocytic leukaemia stage Binet B or C requiring therapy were included. The first line therapy with bendamustine hydrochloride 100 mg/m² i.v. on days 1 and 2 (BEN) was compared to treatment with chlorambucil 0.8 mg/kg days 1 and 15 (CLB) for 6 cycles in both arms. Patients received allopurinol in order to prevent tumour lysis syndrome. Patients with BEN had a significantly longer median progression free survival than patients with CLB treatment (21.5 versus 8.3 months, $p < 0.0001$ in the latest follow-up). Overall survival was not statistically significantly different (median not reached). The median duration of remission was 19 months with BEN and 6 months with CLB treatment ($p < 0.0001$). The safety evaluation in both treatment arms did not reveal any unexpected undesirable effects in nature and frequency. The dose of BEN was reduced in 34% of the patients. Treatment with BEN was discontinued in 3.9% of patients due to allergic reactions.

Indolent non-Hodgkin's lymphomas
The indication for indolent non-Hodgkin's lymphomas relied on two uncontrolled phase II trials. In the pivotal prospective, multi-centre, open study 100 patients with indolent B-cell non-Hodgkin´s lymphomas refractory to rituximab mono- or combination therapy were treated with BEN single agent. Patients had received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses was 2. The patients had had no response or there had been progression within 6 months after rituximab treatment. The dose of BEN was 120 mg/m² i.v. on days 1 and 2 planned for at least 6 cycles. Duration of treatment depended on response (6 cycles planned). The overall response rate was 75% including 17% complete (CR and CRu) and 58% partial response as assessed by independent review committee. The median duration of remission was 40 weeks. BEN was generally well tolerated when given in this dose and schedule. The indication is further supported by another prospective, multi-centre, open study including 77 patients. The patient population was more heterogeneous including: indolent or transformed B-cell non-Hodgkin's lymphomas refractory to rituximab mono- or combination therapy. The patients had no response or there had been progression within 6 months or had had an untoward reaction to prior rituximab treatment. Patients had received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses had been 2. The overall response rate was 76% with a median duration of response of 5 months (29 [95% CI 22.1, 43.1] weeks).

Multiple myeloma
In a prospective, multi-centre, randomised, open study 131 patients with advanced multiple myeloma (Durie-Salmon stage II with progression or stage III) were included. The first line therapy with bendamustine hydrochloride in combination with prednisone (BP) was compared to treatment with melphalan and prednisone (MP). Neither transplant-eligibility nor the presence of specific co-morbidities played a role for inclusion into the trial. The dose was bendamustine hydrochloride 150 mg/m² i.v. on days 1 and 2 or melphalan 15 mg/m² i.v. on day 1 each in combination with prednisone. Duration of treatment depended on response and averaged 6.8 cycles in the BP and 8.7 cycles in the MP group. Patients with BP treatment had a longer median progression free survival than patients with MP (15 [95% CI 12-21] versus 12 [95% CI 10-14] months) ($p=0.0566$). The median time to treatment failure was 14 months with BP and 9 months with MP treatment. The duration of remission was 18 months with BP and 12 months with MP treatment. The difference in overall survival was not significantly different (35 months BP versus 33 months MP). Tolerability in both treatment arms was in line with the known safety profile of the respective medicinal products with significantly more dose reductions in the BP arm.

5.2 Pharmacokinetic properties

Distribution
The elimination half-life $t_{1/2ß}$ after 30 min i.v. infusion of 120 mg/m^2 area to 12 subjects was 28.2 minutes.
Following 30 min i.v. infusion the central volume of distribution was 19.3 l. Under steady-state conditions following i.v. bolus injection the volume of distribution was 15.8-20.5 l.
More than 95% of the substance is bound to plasma proteins (primarily albumin).

Metabolism
A major route of clearance of bendamustine is the hydrolysis to monohydroxy- and dihydroxy-bendamustine. Formation of N-desmethyl-bendamustine and gamma-hydroxy-bendamustine by hepatic metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Another major route of bendamustine metabolism involves conjugation with glutathione. In-vitro bendamustine does not inhibit CYP 1A4, CYP 2C9/10, CYP 2D6, CYP 2E1 or CYP 3A4.

Elimination
The mean total clearance after 30 min i.v. infusion of 120 mg/m^2 body surface area to 12 subjects was 639.4 ml/minute. About 20% of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine > oxidised metabolite > N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Hepatic impairment
In patients with 30 - 70% tumour infestation of the liver and mild hepatic impairment (serum bilirubin < 1.2 mg/dl) the pharmacokinetic behaviour was not changed. There was no significant difference to patients with normal liver and kidney function with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Renal impairment
In patients with creatinine clearance > 10 ml/min including dialysis dependent patients, no significant difference to patients with normal liver and kidney function was observed with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance.

Elderly subjects
Subjects up to 84 years of age were included in pharmacokinetic studies. Higher age does not influence the pharmacokinetics of bendamustine.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Histological investigations in dogs showed macroscopic visible hyperaemia of the mucosa and haemorrhagia in the gastrointestinal tract. Microscopic investigations showed extensive changes of the lymphatic tissue indicating an immunosuppression and tubular changes of kidneys and testis, as well as atrophic, necrotic changes of the prostate epithelium.

Animal studies showed that bendamustine is embryotoxic and teratogenic.

Bendamustine induces aberrations of the chromosomes and is mutagenic *in vivo* as well as *in vitro*. In long-term studies in female mice bendamustine is carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.
The powder should be reconstituted immediately after opening of the vial.
The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution.

Solution for infusion
After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 ºC/ 60% RH and 2 days at 2 ºC to 8 ºC in polyethylene bags.

From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted or diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I brown glass vials of 26 ml or 60 ml with rubber stopper and an aluminium flip-off cap.

26 ml-vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 5, 10 and 20 vials.

60 ml-vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

When handling Levact, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes!). Contaminated body parts should be carefully rinsed with water and soap, the eyes should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid-impermeable, absorbent disposable foil. Pregnant personnel should be excluded from handling cytostatics.

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Reconstitution
Reconstitute each vial of Levact containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking;
Reconstitute each vial of Levact containing 100 mg bendamustine hydrochloride in 40 ml water for injection by shaking.
The reconstituted concentrate contains 2.5 mg bendamustine hydrochloride per ml and appears as a clear colourless solution.

2. Dilution
As soon as a clear solution is obtained (usually after 5-10 minutes) dilute the total recommended dose of Levact immediately with 0.9% NaCl solution to produce a final volume of about 500 ml.

Levact must be diluted with 0.9% NaCl solution and not with any other injectable solution.

3. Administration
The solution is administered by intravenous infusion over 30-60 min.

The vials are for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 14427/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/08/2010

10 DATE OF REVISION OF THE TEXT

03/08/2010

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Embase, Medline and Medline In-Process were searched using the OVID search platform, The Cochrane Library Cochrane Central Register of Controlled Trials (CENTRAL) database was also searched.

9.2.2 The date on which the search was conducted.

All searches were carried out on 22nd April 2010.

9.2.3 The date span of the search.

The date span of the Embase search was 1988 to 2010 Week 15. The date span of the Medline search was from 1950 to April Week 2 2010. The date span of the Medline In-Process search was up to 21st April 2010. The date span for the Cochrane CENTRAL search was 1800 to 2010.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search terms for each search are stated with the database title at the start of the search strategy.

Embase

1	Clinical trial/	574605
2	Randomized controlled trial/	176722
3	Randomization/	27904
4	Single blind procedure/	9266
5	Double blind procedure/	72558
6	Crossover procedure/	22753
7	Placebo/	115323
8	Randomi?ed control* trial*.tw.	39548
9	Rct.tw.	3321
10	Random*.tw.	403055
11	Random* allocation.tw.	735
12	Random* allocat*.tw.	10616
13	Allocat* random*.tw.	1299
14	(allocat* adj2 random*).tw.	12485
15	Single blind$.tw.	6980
16	Double blind$.tw.	74751
17	((treble or triple) adj blind$).tw.	134
18	Placebo$.tw.	103099

19	Prospective study/	92821
20	or/1-19	906156
21	Case study/	5220
22	Case report.tw.	112509
23	Abstract report/ or letter/	462550
24	or/21-23	577676
25	20 not 24	880681
26	Chronic Lymphatic Leukemia/	10828
27	Leukemia, Lymphocytic, Chronic, B-Cell/	10828
28	CLL.tw.	5929
29	Chronic$ lymph$ leukaem$.tw.	1823
30	(Chronic$ and lymph$ and leukaem$).tw.	2630
31	Chronic$ lymph$ leucaem$.tw.	3
32	(Chronic$ and lymph$ and leucaem$).tw.	4
33	Chronic$ lymph$ leukem$.tw.	7067
34	(Chronic$ and lymph$ and leukem$).tw.	10812
35	Chronic$ lymph$ leucem$.tw.	3
36	(Chronic$ and lymph$ and leucem$).tw.	9
37	or/26-36	16903
38	Bendamustine.mp.	496
39	bendamustin?.mp.	496
40	(cytostasan or imet 3393 or cimet 3393).mp.	29
41	Ribomustin.mp.	26
42	ribomustin*.mp.	28
43	Treanda.mp.	53
44	Treand*.mp.	55
45	(cytostasan? or zimet 3393).mp.	25
46	levact.mp.	0
47	or/38-46	499
48	37 and 47	179
49	25 and 48	115

Medline

1	Randomized controlled trials as Topic/	66078
2	Randomized controlled trial/	288559
3	Random allocation/	67885
4	Double blind method/	105955
5	Single blind method/	13834
6	Clinical trial/	460228
7	exp Clinical Trials as Topic/	226617
8	or/1-7	732901
9	(clinic$ adj trial$1).tw.	140573

10	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	102938
11	Placebos/	28712
12	Placebo$.tw.	122245
13	Random$ allocat$.tw.	12813
14	random$.tw.	477518
15	rct.tw.	3768
16	(allocat$ adj2 random$).tw.	15198
17	or/9-16	649801
18	8 or 17	1017504
19	Case report.tw.	148754
20	Letter/	675760
21	Historical article/	263281
22	Review of reported cases.pt.	0
23	Review, multicase.pt.	0
24	or/19-23	1078744
25	18 not 24	992838
26	Chronic Lymphatic Leukemia.tw.	856
27	Leukemia, Lymphocytic, Chronic, B-Cell/	9208
28	cll.tw.	7685
29	Chronic$ lymph$ leukaem$.tw.	2846
30	(Chronic$ and lymph$ and leukaem$).tw.	3999
31	Chronic$ lymph$ leucaem$.tw.	3
32	(Chronic$ and lymph$ and leucaem$).tw.	6
33	Chronic$ lymph$ leukem$.tw.	10087
34	(Chronic$ and lymph$ and leukem$).tw.	15483
35	Chronic$ lymph$ leucem$.tw.	4
36	(Chronic$ and lymph$ and leucem$).tw.	14
37	or/26-36	22137
38	Bendamustine.mp.	161
39	Bendamustin$.mp.	162
40	(cytostasan or imet 3393 or cimet 3393).mp.	27
41	Ribomustin.mp.	3
42	ribomustin*.mp.	4
43	Treanda.mp.	6
44	treanda*.mp.	6
45	cytostasan*.mp.	25
46	zimet 3393.mp.	4
47	levact.mp.	0
48	or/38-47	176
49	37 and 48	46
50	25 and 49	23

Medline in-Process

1	Randomized controlled trials as Topic/	5
2	Randomized controlled trial/	476
3	Random allocation/	0
4	Double blind method/	1
5	Single blind method/	0
6	Clinical trial/	334
7	exp Clinical Trials as Topic/	8
8	or/1-7	538
9	(clinic$ adj trial$1).tw.	5883
10	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	2218
11	Placebos/	0
12	Placebo$.tw.	3111
13	Random$ allocat$.tw.	492
14	random$.tw.	25730
15	rct.tw.	366
16	(allocat$ adj2 random$).tw.	542
17	or/9-16	30965
18	8 or 17	31031
19	Case report.tw.	7036
20	Letter/	12575
21	Historical article/	6
22	Review of reported cases.pt.	0
23	Review, multicase.pt.	0
24	or/19-23	19480
25	18 not 24	30871
26	Chronic Lymphatic Leukemia.tw.	6
27	Leukemia, Lymphocytic, Chronic, B-Cell/	0
28	cll.tw.	174
29	Chronic$ lymph$ leukaem$.tw.	30
30	(Chronic$ and lymph$ and leukaem$).tw.	41
31	Chronic$ lymph$ leucaem$.tw.	0
32	(Chronic$ and lymph$ and leucaem$).tw.	0
33	Chronic$ lymph$ leukem$.tw.	188
34	(Chronic$ and lymph$ and leukem$).tw.	265
35	Chronic$ lymph$ leucem$.tw.	0
36	(Chronic$ and lymph$ and leucem$).tw.	0
37	or/26-36	353
38	Bendamustine.mp.	9
39	Bendamustin$.mp.	9
40	(cytostasan or imet 3393 or cimet 3393).mp.	0
41	Ribomustin.mp.	0

42	ribomustin*.mp.	0
43	Treanda.mp.	1
44	treanda*.mp.	1
45	cytostasan*.mp.	0
46	zimet 3393.mp.	0
47	levact.mp.	0
48	or/38-47	9
49	37 and 48	4
50	25 and 49	1

CENTRAL

1	MeSH descriptor **Leukemia, Lymphocytic, Chronic, B-Cell** explode all trees	156
2	cll:ti,ab,kw in Clinical Trials	258
3	(chronic* and lymph* and leukem*):ti,ab,kw in Clinical Trials	440
4	(chronic* and lymph* and leukaem*):ti,ab,kw in Clinical Trials	67
5	(chronic* and lymph* and leucem*):ti,ab,kw in Clinical Trials	0
6	(chronic* and lymph* and leucaem*):ti,ab,kw in Clinical Trials	1
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	536
8	(bendamustin* or imet 3393 or cimet 3393 or ribomustin* or treanda or cytostasan* or zimet 3393 or levact):ti,ab,kw in Clinical Trials	29
9	(#8 AND #7)	5

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

No additional searches were carried out.

9.2.6 The inclusion and exclusion criteria.

	Clinical effectiveness
Inclusion criteria	Population: CLL
	Interventions: bendamustine compared with any other treatment
	Outcomes: any
	Study design: RCTs
	Language restrictions: English only
Exclusion criteria	Population: non-CLL patients
	Interventions: don't include bendamustine-based treatment as one of the comparators
	Outcomes: no exclusion by outcomes
	Study design: non-RCTs
	Language restrictions: non English

9.2.7 The data abstraction strategy.

Only one relevant study was identified (Study 02CLLIII) so a data abstraction strategy was not necessary.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym: 02CLLIII Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Yes. See Section 5.3.2 for details.	Yes
Was the concealment of treatment allocation adequate?	The study was open-label. A blinded study was not appropriate given the different methods of administration of bendamustine (i.v. infusion) and chlorambucil (oral).	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. As described in Section 5.3.4, patients' baseline characteristics were well balanced between the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients and carers were not blinded to treatment allocation as this was an open-label study. However, the independent response assessors were blinded to treatment allocation.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No, the number of patients withdrawing from the study was similar between treatment groups.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Quality of life was measured during the study. It is not reported in the published paper, but is fully documented in the study report.	Yes

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the efficacy analyses were carried out on the ITT population. See Section 5.3.6 for information on handling of missing data.	Yes

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

Not applicable as no indirect or mixed treatment comparisons were undertaken.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

Not applicable as no indirect or mixed treatment comparisons were undertaken.

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The following information should be provided.

9.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Embase, Medline, Medline In-Process, BIOSYS and the Cochrane CENTRAL database were searched using Dialog DataStar.

9.6.2 The date on which the search was conducted.

All searches were conducted on 2nd July 2010

9.6.3 The date span of the search.

The date span of the Medline search was 1949 to the present and that of the Embase search was 1947 to the present. The Medline in-Process search covered the eight weeks up to 2nd July 2010. Biosys was searched from 1996 to the present. The Cochrane CENTRAL cearch was from 1800 to 2010.

9.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline

1	randomized ADJ controlled ADJ trial	362876
2	RANDOMIZED-CONTROLLED-TRIALS-AS-TOPIC.DE.	67108
3	random ADJ allocation	69169
4	double ADJ blind ADJ method	106007
5	single ADJ blind ADJ method	13972
6	clinical ADJ trial	664543
7	clinical ADJ trial	664543
8	CLINICAL-TRIALS-AS-TOPIC#.DE.	228755
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8	836132
10	(clinic$ ADJ trial$1).TI.	32633
11	(clinic$ ADJ trial$1).AB.	129572
12	10 OR 11	150323
13	((single$ OR doubl$ OR treb$ OR tripl$) ADJ blind$3 OR mask$3).TI.	35766
14	((single$ OR doubl$ OR treb$ OR tripl$) ADJ blind$3 OR mask$3).AB.	132999
15	13 OR 14	146313
16	placebos$	30041
17	placebo$.TI.	19983
18	placebo$.AB.	123114
19	17 OR 18	127074
20	(random$ ADJ allocat$).TI.	42
21	(random$ ADJ allocat$).AB.	13562
22	20 OR 21	13589
23	random$.TI.	79146
24	random$.AB.	501416
25	23 OR 24	514492

26	rct.TI.	414
27	rct.AB.	8500
28	26 OR 27	8804
29	12 OR 15 OR 19 OR 22 OR 25 OR 28	721770
30	9 OR 29	1113351
31	case ADJ report$	1520140
32	letter	947864
33	observation$ ADJ study	26188
34	propesctive ADJ study	0
35	prospective ADJ study	309613
36	historical ADJ article	264901
37	retrospective ADJ study	365490
38	31 OR 32 OR 33 OR 35 OR 36 OR 37	3222964
39	30 OR 38	4163158
40	(chronic ADJ lymphatic ADJ leukemia).TI.	623
41	(chronic ADJ lymphatic ADJ leukemia).AB.	383
42	40 OR 41	916
43	chronic ADJ lymphatic ADJ leukemia	918
44	LEUKEMIA-LYMPHOCYTIC-CHRONIC-B-CELL.DE.	9241
45	cll.TI.	1041
46	cll.TI.	1041
47	cll.AB.	7687
48	46 OR 47	8024
49	(chronic$ ADJ lymph$ ADJ leukaem$).TI.	0
50	(chronic$ ADJ lymph$ ADJ leukaem$).AB.	0
51	chronic$ AND lymph$ AND leukaem$	346
52	chronic$.TI. AND lymph$.TI. AND leukaem$.TI.	17
53	chronic$.AB. AND lymph$.AB. AND leukaem$.AB.	235
54	52 OR 53	241
55	(chronic$ ADJ lymph$ ADJ leucaem$).TI.	0
56	(chronic$ ADJ lymph$ ADJ leucaem$).AB.	0
57	chronic$.TI. AND lymph$.TI. AND leucaem$.TI.	0
58	chronic$.AB. AND lymph$.AB. AND leucaem$.AB.	2
59	55 OR 56	0
60	57 OR 58	2
61	(chronic$ ADJ lymph$ ADJ leukem$).TI.	0
62	(chronic$ ADJ lymph$ ADJ leukem$).AB.	0
63	61 OR 62	0
64	chronic$.TI. AND lymph$.TI. AND leukem$.TI.	117
65	chronic$.AB. AND lymph$.AB. AND leukem$.AB.	882
66	64 OR 65	958
67	(chronic$ ADJ lymph$ ADJ leucem$).TI.	0
68	(chronic$ ADJ lymph$ ADJ leucem$).AB.	0
69	chronic$.TI. AND lymph$.TI. AND leucem$.TI.	0
70	chronic$.AB. AND lymph$.AB. AND leucem$.AB.	0
71	42 OR 43 OR 44 OR 48 OR 51 OR 54 OR 59 OR 60 OR 63 OR 66	13510
72	bendamustine	182
73	bendamustin$	183
74	cytostasan OR imet ADJ '3393' OR cimet ADJ '3393' OR zimet ADJ '3393'	29
75	ribomustin*	0
76	ribomustin	4
77	ribomustin$	5
78	76 OR 77	5
79	treanda	8
80	treand$	14
81	levact	0
82	72 OR 73 OR 74 OR 76 OR 77 OR 79 OR 80 OR 81	202

83	71 AND 82	51
84	83 AND 39	32

Medline in-Process

85	randomized ADJ controlled ADJ trial	1685
86	RANDOMIZED-CONTROLLED-TRIALS-AS-TOPIC.DE.	0
87	random ADJ allocation	18
88	double ADJ blind ADJ method	3
89	single ADJ blind ADJ method	0
90	clinical ADJ trial	4614
91	clinical ADJ trial	4614
92	CLINICAL-TRIALS-AS-TOPIC#.DE.	0
93	85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92	6082
94	(clinic$ ADJ trial$1).TI.	684
95	(clinic$ ADJ trial$1).AB.	4083
96	94 OR 95	4451
97	((single$ OR doubl$ OR treb$ OR tripl$) ADJ blind$3 OR mask$3).TI.	629
98	((single$ OR doubl$ OR treb$ OR tripl$) ADJ blind$3 OR mask$3).AB.	2509
99	97 OR 98	2667
100	placebo$.TI.	433
101	placebo$.AB.	2364
102	100 OR 101	2418
103	(random$ ADJ allocat$).TI.	1
104	(random$ ADJ allocat$).AB.	324
105	103 OR 104	325
106	random$.TI.	2509
107	random$.AB.	13605
108	106 OR 107	13866
109	rct.TI.	18
110	rct.AB.	515
111	109 OR 110	527
112	96 OR 99 OR 102 OR 105 OR 108 OR 111	18398
113	93 OR 112	18521
114	case ADJ report$	4159
115	letter	14122
116	observation$ ADJ study	1306
117	prospective ADJ study	2093
118	historical ADJ article	2
119	retrospective ADJ study	1746
120	114 OR 115 OR 116 OR 117 OR 118 OR 119	23111
121	113 OR 120	40645
122	(chronic ADJ lymphatic ADJ leukemia).TI.	0
123	(chronic ADJ lymphatic ADJ leukemia).AB.	3
124	122 OR 123	3
125	chronic ADJ lymphatic ADJ leukemia	3
126	LEUKEMIA-LYMPHOCYTIC-CHRONIC-B-CELL.DE.	0
127	cll.TI.	39
128	cll.AB.	189
129	127 OR 128	204
130	chronic$ AND lymph$ AND leukaem$	54
131	chronic$.TI. AND lymph$.TI. AND leukaem$.TI.	32
132	chronic$.AB. AND lymph$.AB. AND leukaem$.AB.	40
133	131 OR 132	54
134	(chronic$ ADJ lymph$ ADJ leucaem$).TI.	0

135	(chronic$ ADJ lymph$ ADJ leucaem$).AB.	1
136	chronic$.TI. AND lymph$.TI. AND leucaem$.TI.	0
137	chronic$.AB. AND lymph$.AB. AND leucaem$.AB.	1
138	134 OR 135	1
139	136 OR 137	1
140	(chronic$ ADJ lymph$ ADJ leukem$).TI.	143
141	(chronic$ ADJ lymph$ ADJ leukem$).AB.	175
142	140 OR 141	211
143	chronic$.TI. AND lymph$.TI. AND leukem$.TI.	149
144	chronic$.AB. AND lymph$.AB. AND leukem$.AB.	236
145	143 OR 144	274
146	124 OR 125 OR 126 OR 129 OR 130 OR 133 OR 138 OR 139 OR 142 OR 145	353
147	bendamustine	8
148	bendamustin$	8
149	cytostasan OR imet ADJ '3393' OR cimet ADJ '3393' OR zimet ADJ '3393'	1
150	ribomustin	1
151	ribomustin$	1
152	treanda	1
153	treand$	1
154	levact	0
155	147 OR 148 OR 149 OR 150 OR 151 OR 152 OR 153 OR 154	8
156	146 AND 155	2
157	156 AND 127	1
158*	combined sets 84, 157	33
159*	dropped duplicates from 158	1
160*	unique records from 158	32

*Medline plus Medline in-Process

Embase

161	randomized ADJ controlled ADJ trial	281676
162	RANDOMIZED-CONTROLLED-TRIALS-AS-TOPIC.DE.	0
163	random ADJ allocation	1024
164	double ADJ blind ADJ method	683
165	single ADJ blind ADJ method	76
166	clinical ADJ trial	899624
167	clinical ADJ trial	899624
168	CLINICAL-TRIALS-AS-TOPIC#.DE.	0
169	161 OR 162 OR 163 OR 164 OR 165 OR 166 OR 167 OR 168	916446
170	(clinic$ ADJ trial$1).TI.	14
171	(clinic$ ADJ trial$1).AB.	103
172	170 OR 171	117
173	((single$ OR doubl$ OR treb$ OR tripl$) ADJ blind$3 OR mask$3).TI.	44324
174	((single$ OR doubl$ OR treb$ OR tripl$) ADJ blind$3 OR mask$3).AB.	157532
175	173 OR 174	175504
176	placebo$.TI.	24114
177	placebo$.AB.	142429
178	176 OR 177	148504
179	(random$ ADJ allocat$).TI.	50
180	(random$ ADJ allocat$).AB.	1306
181	179 OR 180	1342
182	random$.TI.	85508
183	random$.AB.	412729

184	182 OR 183	437641
185	rct.TI.	498
186	rct.AB.	9598
187	185 OR 186	9964
188	172 OR 175 OR 178 OR 181 OR 184 OR 187	587840
189	169 OR 188	1218730
190	case ADJ report$	1791810
191	letter	982530
192	observation$ ADJ study	35274
193	prospective ADJ study	209363
194	historical ADJ article	117
195	retrospective ADJ study	237480
195	190 OR 191 OR 192 OR 193 OR 194 OR 195	3071933
196	189 OR 196	4153216
197	(chronic ADJ lymphatic ADJ leukemia).TI.	829
198	(chronic ADJ lymphatic ADJ leukemia).AB.	982
199	197 OR 198	1613
200	chronic ADJ lymphatic ADJ leukemia	17300
201	LEUKEMIA-LYMPHOCYTIC-CHRONIC-B-CELL.DE.	0
202	cll.TI.	1227
203	cll.AB.	8424
204	202 OR 203	8908
205	chronic$ AND lymph$ AND leukaem$	762
206	chronic$.TI. AND lymph$.TI. AND leukaem$.TI.	19
207	chronic$.AB. AND lymph$.AB. AND leukaem$.AB.	377
208	206 OR 207	387
209	(chronic$ ADJ lymph$ ADJ leucaem$).TI.	0
210	(chronic$ ADJ lymph$ ADJ leucaem$).AB.	0
211	chronic$.TI. AND lymph$.TI. AND leucaem$.TI.	0
212	chronic$.AB. AND lymph$.AB. AND leucaem$.AB.	2
213	209 OR 210	0
214	211 OR 212	2
215	(chronic$ ADJ lymph$ ADJ leukem$).TI.	0
216	(chronic$ ADJ lymph$ ADJ leukem$).AB.	0
217	215 OR 216	0
218	chronic$.TI. AND lymph$.TI. AND leukem$.TI.	96
219	chronic$.AB. AND lymph$.AB. AND leukem$.AB.	903
220	218 OR 219	964
221	199 OR 200 OR 201 OR 204 OR 205 OR 208 OR 213 OR 214 OR 217 OR 220	20150
222	bendamustine	603
223	bendamustin$	604
224	cytostasan OR imet ADJ '3393' OR cimet ADJ '3393' OR zimet ADJ '3393'	75
225	ribomustin	28
226	ribomustin$	30
227	treanda	60
228	treand$	70
229	levact	0
230	222 OR 223 OR 224 OR 225 OR 226 OR 227 OR 228 OR 229	624
231	221 AND 230	202
232	231 AND 196	155
233*	combined sets 84, 157, 232	188
234*	dropped duplicates from 233	31
235*	unique records from 233	157

*Medline + Medline in-Process + Embase

BIOSYS

1	meeting ADJ abstract	2229809
2	meeting ADJ poster	781566
3	1 OR 2	2502659
4	bendamustin$ OR cytostasan OR imet ADJ '3393' OR cimet ADJ '3393' OR zimet ADJ '3393' OR ribomustin$ OR treanda OR levact	232
5	chronic ADJ lymphatic ADJ leukemia OR CLL OR chronic$ ADJ lymph$ ADJ leukaem$ OR chronic$ ADJ lymph$ ADJ leucaem$	9511
6	chronic ADJ lymphatic ADJ leukaemia	64
7	CHRONIC-LYMPHATIC-LEUKEMIA.DS. OR CHRONIC-LYMPHOCYTIC-LEUKEMIA.DS.	6075
8	5 OR 6 OR 7	11424
9	5 OR 6 OR 7	11424
10	3 AND 4 AND 9	51
11	10 AND HUMANS# AND ABSTRACT=YES	35
12	dropped duplicates from 11	2
13	unique records from 11	33

CENTRAL

1	MeSH descriptor Leukemia, Lymphocytic, Chronic, B-Cell, this term only	158
2	(CLL):ti,ab,kw	265
3	(Chronic* and lymph* and leukem*):ti,ab,kw	484
4	(Chronic* and lymph* and leukaem*):ti,ab,kw	94
5	(Chronic* and lymph* and leucem*):ti,ab,kw	0
6	(Chronic* and lymph* and leucaem*):ti,ab,kw	1
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	587
8	(bendamustin* or imet 3393 or cimet 3393 or ribomustin* or treanda* or cytostasan* or zimet 3393 or levact):ti,ab,kw	33
9	(#8 AND #7)	7

9.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were carried out.

9.6.6 The inclusion and exclusion criteria.

	Clinical effectiveness
Inclusion criteria	Population: patients aged ≥18 years with CLL; no restriction on race or gender Interventions: bendamustine compared with or combined with: rituximab alemtuzumab chlorambucil cyclophosphamide methylprednisolone ofatumumab placebo no treatment All combinations of regimens of the above. No restrictions in dose, formulation or mode of delivery Outcomes: overall survival, event-free survival, PFS, response rates, duration of response, time to response Study design: prospective and retrospective studies. Non-RCTs, including single arm, observational, and cohort and case series. Language restrictions: English only
Exclusion criteria	Population: non-CLL patients Interventions: fludarabine. Bendamustine-based treatment as a comparator Outcomes: no exclusions Study design: RCTs Language restrictions: non-English

9.6.7 The data abstraction strategy.

Not applicable.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

9.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Medline and Medline In-Process were searched using a combination of MeSH term and free-text strategy in PubMed to identify all the relevant publications.

Medline and Medline in-Process

1	Randomized controlled trials as Topic/	66078
2	Randomized controlled trial/	288559
3	Random allocation/	67885
4	Double blind method/	105955
5	Single blind method/	13834
6	Clinical trial/	460228
7	exp Clinical Trials as Topic/	226617
8	or/1-7	732901
9	(clinic$ adj trial$1).tw.	140573
10	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	102938
11	Placebos/	28712
12	Placebo$.tw.	122245
13	Random$ allocat$.tw.	12813
14	random$.tw.	477518
15	rct.tw.	3768
16	(allocat$ adj2 random$).tw.	15198
17	or/9-16	649801
18	8 or 17	1017504
19	Case report.tw.	148754

20	Letter/	675760
21	Historical article/	263281
22	Review of reported cases.pt.	0
23	Review, multicase.pt.	0
24	or/19-23	1078744
25	18 not 24	992838
26	Bendamustine.mp.	161
27	Bendamustin$.mp.	162
28	(cytostasan or imet 3393 or cimet 3393).mp.	27
29	Ribomustin.mp.	3
30	ribomustin*.mp.	4
31	Treanda.mp.	6
32	treanda*.mp.	6
33	cytostasan*.mp.	25
34	zimet 3393.mp.	4
35	levact.mp.	0
36	or/26-35	176
37	25 and 36	**139**

Embase

2	Bendamustine.W..DE. OR Bendamustine.W..DE. OR Bendamustine.W..DE.	521
3	TREANDA	62
4	LEVACT	0
5	RIBOMUSTINE	2
6	SDX-105	8
7	CYTOSTASAN	5
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	525
9	dropped duplicates from 8	19
10	unique records from 8	506
11	10 AND CLINICAL-TRIAL#	292

Cochrane

1	(bendamustine) or (levact) or (treanda) or (cytostasan) or (ribomustine)	**31**

In addition, the databases of the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) were searched using the same free-text terms as for the Cochrane database. The searches returned:

- **61** hits from the ASH database
- **12** from the ASCO database.

Thus the total number of hits from searches was 535.

9.8.2 The date on which the search was conducted.

All searches were carried out on 9th July 2010

9.8.3 The date span of the search.

The date span of the Embase search was from1996 until 9th July 2010.

There was no date limit for the other searches.

9.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See above.

9.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The abstract databases for ASH and ASCO meetings were also searched (see Section 9.9.1).

9.8.6 The inclusion and exclusion criteria.

	Clinical effectiveness
Inclusion criteria	Interventions: bendamustine compared with any other treatment
	Outcomes: contains AEs/safety
	Study design: RCTs
	Language restrictions: English only
Exclusion criteria	Interventions: does not include bendamustine-based treatment as one of the comparators
	Outcomes: does not contain AEs/safety as an outcome
	Study design: non-RCTs
	Language restrictions: non English

From the 535 hits returned, 91 duplicates were removed (using Reference Manager and by hand), the remaining 444 were screened based on title and abstracts:

- 17 were included
- 425 were excluded, including
    - 83 non-RCT (Phase I - III, dose escalation, others) clinical studies
    - 14 hits not in English
    - 65 hits concerned with *in vitro*/animal studies, or not concerned with bendamustine
    - 265 were commentaries, reviews, editorials or opinions

The 17 abstracts included related to four Phase III RCTs:

- 11 hits relating to a study of bendamustine/prednisone *vs.* melphalan/prednisone in first-line treatment of multiple myeloma (Pösnich *et al*.
- Four hits relating to a study of bendamustine/rituximab vs. CHOP-R (Rummel *et al*).
    - Full data not available yet
- One hit relating to a study of bendamustine, vincristine and prednisone (BOP) *vs.* COP cyclophosphamide, vincristine and prednisone (Herold *et al*).
- One hit relating to a study of bendamustine hydrochloride, methotrexate and 5-fluorouracil *vs.* cyclophosphamide, methotrexate and 5-fluorouracil in metastatic Breast Cancer (Von Minckwitz *et al*).

Summary of RCTs identified:

Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone - a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO)
Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany)
Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma: results of a randomised phase III trial (OSHO# 19)
Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC

None of these RCTs contain information on the adverse events experienced with bendamustine in relation to the decision problem. None of the studies identified were in CLL.

Within the 83 hits classified as non RCT, eight results were returned when the subset was searched for chlorambucil. Out of these eight results, six were connected to the Study 02CLLIII, the other two were not concerned with comparing bendamustine and chlorambucil.

9.8.7 The data abstraction strategy.

Not applicable.

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

9.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable.

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED

Embase, Medline, Medline In-Process and EconLIT were searched using the OVID serach platform. NHS EED was searched using the CRD website.

9.10.2 The date on which the search was conducted.

All searches were carried out on 4th June 2010.

9.10.3 The date span of the search.

The Medline and Medline In-Process searches date span was 1950 to the present. For the Embase search, the date range was 1988 to Week 21, 2010. For EconLIT, the date range was 1969 to May 2010. There was no date restriction for the NHS EED search.

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline and Medline in-Process

1	Leukemia, Lymphocytic, Chronic, B-Cell/	9323
2	cll.tw.	7972
3	(chronic$ and lymph$ and leuk?em$).tw.	19691
4	(chronic$ and lymph$ and leuc?em$).tw.	22
5	or/1-4	22729
6	(bendamustin? or imet 3393 or cimet 3393 or ribomustin or treanda or cytostasan? or zimet 3393 or levact).mp.	189
7	"costs and cost analysis"/ or cost-benefit analysis/	84879
8	quality-adjusted life years/	4384
9	markov chains/	6374
10	monte carlo method/	13889
11	Decision Trees/ec	1
12	(cost$ adj1 (estimate? or variable? or effective$ or unit?)).ti,ab.	56748
13	(qol or qoly? or hrqol or hrql or qaly? or qale?).ti,ab.	19449
14	(economic$ or price$ or pricing or pharmacoeconomic$).ti,ab.	125022
15	(sensitivity adj analys?s).ti,ab.	8663
16	(willing$ adj2 pay).ti,ab.	1711
17	quality adjusted life.ti,ab.	3646
18	(decision adj1 (tree$ or analy$ or model$)).ti,ab.	7154
19	monte carlo.ti,ab.	19742
20	markov chain$.ti,ab.	2296
21	or/7-20	275993
22	5 and 6 and 21	1

Embase

1	chronic lymphatic leukemia/	10995
2	cll.tw.	6019
3	(chronic$ and lymph$ and leuk?em$).tw.	13444
4	(chronic$ and lymph$ and leuc?em$).tw.	13
5	or/1-4	17138
6	(bendamustin? or imet 3393 or cimet 3393 or ribomustin or treanda or cytostasan? or zimet 3393 or levact).mp.	519
7	"cost benefit analysis"/ or "cost effectiveness analysis"/	90395
8	quality adjusted life year/	5074
9	probability/	28715
10	monte carlo method/	9156
11	(cost$ adj1 (estimate? or variable? or effective$ or unit?)).ti,ab.	47148
12	(qol or qoly? or hrqol or hrql or qaly? or qale?).ti,ab.	17830
13	(economic$ or price$ or pricing or pharmacoeconomic$).ti,ab.	84463
14	(sensitivity adj analys?s).ti,ab.	7883

15	(willing$ adj2 pay).ti,ab.	1510
16	quality adjusted life.ti,ab.	3388
17	(decision adj1 (tree$ or analy$ or model$)).ti,ab.	5943
18	monte carlo.ti,ab.	13069
19	markov chain$.ti,ab.	1503
20	or/7-19	235142
21	5 and 6 and 20	2

EconLIT

1	(leuk?em$ or leuc?em$ or cll).mp.	14
2	(leuk?em$ or leuc?em$ or cll).tw.	14
3	(leuk?em$ or leuc?em$ or cll).kw.	0
4	1 or 2 or 3	14

NHS EED

1	MeSH Leukemia, Lymphocytic, Chronic, B-Cell EXPLODE 1 2 3	33
2	cll	19
3	chronic* AND lymph* AND leukem*	27
4	chronic* AND lymph* AND leukaem*	47
5	chronic* AND lymph* AND leucaem*	0
6	chronic* AND lymph* AND leucem*	0
7	#1 or #2 or #3 or #4 or #5 or #6	69

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were carried out.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

Not applicable.

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED

Embase, Medline, Medline In-Process and EconLIT were searched using the OVID serach platform. NHS EED was searched using the CRD website.

9.12.2 The date on which the search was conducted.

All searches were carried out on 2nd June 2010.

9.12.3 The date span of the search.

The Medline and Medline In-Process searches date span was 1950 to the present. For the Embase search, the date range was 1988 to Week 21, 2010. For EconLIT, the date range was 1969 to May 2010. There was no date restriction for the NHS EED search.

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline and Medline in-Process

1	Leukemia, Lymphocytic, Chronic, B-Cell/	9297
2	cll.tw.	7955
3	(chronic$ and lymph$ and leuk?em$).tw.	19658
4	(chronic$ and lymph$ and leuc?em$).tw.	22
5	or/1-4	22693
6	quality-adjusted life years/	4364
7	quality adjusted life.tw.	3630
8	quality of well being.tw.	268
9	quality of wellbeing.tw.	5
10	qwb.tw.	138
11	index of wellbeing.tw.	1
12	index of well being.tw.	61
13	(health related quality adj2 life$).tw.	12978
14	classification of illness state$.tw.	1
15	(standard gamble or sg).tw.	4443
16	(timetradeoff or time tradeoff or time trade off or tto).tw.	838
17	(health adj3 (indicator? or status)).tw.	34789
18	(qaly? or qale? or hrqol? or hrql).tw.	8461
19	(euroquol or euroqol or euro qol or eq 5d or eq5d).tw.	1954
20	(hui2 or hui 2 or hui3 or hui 3 or hui).tw.	632
21	(sf 36 or sf36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or short form thirty six or short form thirtysix or short form thirty six).tw.	10392
22	(sf 6d or sf6d or short form 6d or shortform 6d or sf six$ or shortform six$ or short form six$).tw.	196
23	(fact adj1 leu).tw.	1
24	functional assessment of cancer therapy.tw.	673
25	(qlq c30 or qlq c 30).tw.	1221
26	qlq leu.tw.	1
27	exp Health Status Indicators/	139578
28	(cost$ adj1 (effective$ or benefit$)).tw.	59328
29	Pain Measurement/	43581
30	visual analogue scale$.tw.	9992
31	vas.tw.	17503
32	"Activities of Daily Living"/	40112
33	utilit$.tw.	81275
34	or/6-33	406704
35	5 and 34	336
36	35	336
37	limit 36 to english language	315

Embase

1	chronic lymphatic leukemia/	10995
2	cll.tw.	6019
3	(chronic$ and lymph$ and leuk?em$).tw.	13444
4	(chronic$ and lymph$ and leuc?em$).tw.	13
5	or/1-4	17138
6	quality adjusted life year/	5074
7	quality adjusted life.tw.	3388
8	quality of well being.tw.	227
9	quality of wellbeing.tw.	7
10	qwb.tw.	121
11	index of wellbeing.tw.	0
12	index of well being.tw.	36
13	(health related quality adj2 life$).tw.	11796
14	classification of illness state$.tw.	1
15	(standard gamble or sg).tw.	3476
16	wellbeing/	17962
17	time trade off/	13
18	(timetradeoff or time tradeoff or time trade off or tto).tw.	787
19	(health adj3 (indicator? or status)).tw.	22933
20	(qaly? or qale? or hrqol? or hrql).tw.	7825
21	(euroquol or euroqol or euro qol or eq 5d or eq5d).tw.	1850
22	(hui2 or hui 2 or hui3 or hui 3 or hui).tw.	502
23	(sf 36 or sf36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or short form thirty six or short form thirtysix or short form thirty six).tw.	9665
24	(sf 6d or sf6d or short form 6d or shortform 6d or sf six$ or shortform six$ or short form six$).tw.	187
25	(fact adj1 leu).tw.	0
26	functional assessment of cancer therapy.tw.	598
27	(qlq c30 or qlq c 30).tw.	1180
28	qlq leu.tw.	1
29	European quality of life questionnaire 5D/	24
30	european quality of life 5 dimension/	5
31	short form 36/	5287
32	exp health status/	56087
33	(cost$ adj1 (effective$ or benefit$)).tw.	49000
34	visual analog scale/	15902
35	visual analogue scale$.tw.	9002
36	vas.tw.	14130
37	daily life activity/	24713
38	utilit$.tw.	68299
39	or/6-38	256454
40	5 and 39	269
41	40	269
42	limit 40 to english language	255

EconLIT

1	(leuk?em$ or leuc?em$ or cll).mp.	14
2	(leuk?em$ or leuc?em$ or cll).tw.	14
3	(leuk?em$ or leuc?em$ or cll).kw.	0
4	1 or 2 or 3	14

NHS EED

1	MeSH Leukemia, Lymphocytic, Chronic, B-Cell EXPLODE 1 2 3	33
2	cll	19
3	chronic* AND lymph* AND leukem*	27
4	chronic* AND lymph* AND leukaem*	47
5	chronic* AND lymph* AND leucaem*	0
6	chronic* AND lymph* AND leucem*	0
7	#1 or #2 or #3 or #4 or #5 or #6	69

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The reference lists of ordered papers were manually reviewed to check for additional studies that may have met the inclusion criteria. In addition, a manual search of the NICE website was undertaken to identify relevant STAs.

9.12.6 Inclusion and exclusion criteria

Retrieved abstracts and full text papers were assessed against the following inclusion criteria:

- Studies reporting utility values for health states or toxicities* associated with CLL and CLL treatment; or
- Cost-effectiveness analyses, health technology assessment reports, review papers potentially reporting relevant utilities
- English language only

* Toxicities to include; nausea, vomiting, diarrhoea, pyrexia, pneumonia and other infections

9.12.7 The data abstraction strategy.

The following data were extracted for each study:

- Author, year
- Method of sample selection
- Source of health states
- Sample size
- Response rate
- Valuation method

- Health states utility values
- Utility estimates with measure of uncertainty
- Analysis methods
- Use of utility values in previous appraisals.

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED

Embase, Medline, Medline In-Process and EconLIT were searched using the OVID search platform. NHS EED was searched using the CRD website.

9.13.2 The date on which the search was conducted.

All searches were carried out on 4th June 2010.

9.13.3 The date span of the search.

The Medline and Medline In-Process searches date span was 1950 to the present. For the Embase search, the date range was 1988 to Week 21, 2010. For EconLIT, the date range was 1969 to May 2010. There was no date restriction for the NHS EED search.

9.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline and Medline in-Process

1	Leukemia, Lymphocytic, Chronic, B-Cell/	9323
2	cll.tw.	7972
3	(chronic$ and lymph$ and leuk?em$).tw.	19691
4	(chronic$ and lymph$ and leuc?em$).tw.	22
5	or/1-4	22729
6	exp "Costs and Cost Analysis"/	150170
7	quality-adjusted life years/	4384
8	markov chains/	6374
9	monte carlo method/	13889
10	Decision Trees/ec	1
11	(qol or qoly? or hrqol or hrql or qaly? or qale?).ti,ab.	19449
12	(economic$ or price$ or pricing or pharmacoeconomic$).ti,ab.	125022
13	(sensitivity adj analys?s).ti,ab.	8663
14	(resourc$ adj2 use$).ti,ab.	7204
15	(resourc$ adj2 utili?ation).ti,ab.	3796
16	(willing$ adj2 pay).ti,ab.	1711
17	quality adjusted life.ti,ab.	3646
18	(decision adj1 (tree$ or analy$ or model$)).ti,ab.	7154
19	monte carlo.ti,ab.	19742
20	markov chain$.ti,ab.	2296
21	cost$4.ti,ab.	244003
22	Health Resources/	6854
23	Economics, Nursing/	3815
24	exp Economics, Hospital/	16582
25	exp Economics Pharmaceutical/	2102
26	exp Economics Medical/	12947
27	exp "Fees and Charges"/	24751
28	or/6-27	491442
29	5 and 28	224
30	29	224
31	limit 30 to english language	194

Embase

1	chronic lymphatic leukemia/	10995
2	cll.tw.	6019
3	(chronic$ and lymph$ and leuk?em$).tw.	13444
4	(chronic$ and lymph$ and leuc?em$).tw.	13
5	or/1-4	17138
6	"cost benefit analysis"/ or "cost effectiveness analysis"/	90395
7	quality adjusted life year/	5074
8	probability/	28715
9	monte carlo method/	9156
10	(qol or qoly? or hrqol or hrql or qaly? or qale?).ti,ab.	17830
11	(economic$ or price$ or pricing or pharmacoeconomic$).ti,ab.	84463
12	(resourc$ adj2 use$).ti,ab.	5624
13	(resourc$ adj2 utili?ation).ti,ab.	3128
14	(sensitivity adj analys?s).ti,ab.	7883
15	(willing$ adj2 pay).ti,ab.	1510
16	quality adjusted life.ti,ab.	3388
17	(decision adj1 (tree$ or analy$ or model$)).ti,ab.	5943
18	monte carlo.ti,ab.	13069
19	markov chain$.ti,ab.	1503
20	cost$4.ti,ab.	177119
21	health care planning/	23974
22	health economics/ or fee/ or "health care cost"/ or pharmacoeconomics/	80665
23	hospital billing/ or hospital charge/ or medical fee/	6593
24	or/6-23	387516
25	5 and 24	368
26	25	368
27	limit 26 to english language	333

EconLIT

1	(leuk?em$ or leuc?em$ or cll).mp.	14
2	(leuk?em$ or leuc?em$ or cll).tw.	14
3	(leuk?em$ or leuc?em$ or cll).kw.	0
4	1 or 2 or 3	14

1	MeSH Leukemia, Lymphocytic, Chronic, B-Cell EXPLODE 1 2 3	33
2	cll	19
3	chronic* AND lymph* AND leukem*	27
4	chronic* AND lymph* AND leukaem*	47
5	chronic* AND lymph* AND leucaem*	0
6	chronic* AND lymph* AND leucem*	0
7	#1 or #2 or #3 or #4 or #5 or #6	69

9.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The reference lists of ordered papers were manually reviewed to check for additional studies that may have met the inclusion criteria. In addition, a manual search of the NICE website was undertaken to identify relevant STAs.

9.13.6 The inclusion and exclusion criteria.

Retrieved abstracts and full text papers were assessed against the following inclusion criteria:

- Studies reporting empirical cost or resource use estimates for health states or toxicities* associated with CLL and CLL treatment; or
- Cost-effectiveness analyses, health technology assessment reports, review papers potentially reporting relevant data
- Cost and resource use estimates pertaining to the UK
- English language only.

* Toxicities to include; nausea, vomiting, diarrhoea, pyrexia, pneumonia and other infections

9.13.7 The data abstraction strategy.

Not applicable as no studies were identified.

9.14 Appendix 14: Search strategy for subsequent lines of therapy

Details of this search strategy are available on request from the manufacturer.