National Institute for Health and Clinical Excellence

NICE
Level 1A
City Tower
Piccadilly Plaza
Manchester
M1 4BD

Tel: +44 0161 870 3152
Fax: (0)20 7061 9764

Email: Lori.Farrar@nice.org.uk

www.nice.org.uk

Dear [redacted]

**Re: Single Technology Appraisal – Bendamustine for the treatment of chronic lymphocytic leukaemia**

The Evidence Review Group (ERG; Peninsula Technology Assessment Group (PenTAG)) and the technical team at NICE have now had an opportunity to take a look at the submission received on the 12 August 2010 from Napp Pharmaceuticals. In general terms they felt that it was well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, Monday 13 September 2010**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Helen Starkie – Technical Lead (Helen.Starkie@nice.org.uk). Any procedural questions should be addressed to Lori Farrar – Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

**Points for clarification**

Detailed below are comments/points of clarification on the submission. Please note that all questions are priority questions.

**Section A: Clarification on effectiveness data**

*A1. Please provide baseline information for the additional need-to-treat criteria specified (section 5.3.3, p43).*

A breakdown of the number of patients meeting the need-to-treat criteria is shown on the next page.

**Study and indication specific inclusion criteria**

| | Number (%) of patients | | | | | |
|---|---|---|---|---|---|---|
| | Bendamustine (n = 162) | | Chlorambucil (n = 157) | | Total (n = 319) | |
| Haemopoietic insufficiency with non-haemolysis-induced haemoglobin <10 g/dL | 159 | (98) | 148 | (94) | 307 | (96) |
| Thrombocytopenia <100 x $10^9$/L | 34 | (21) | 30 | (19) | 64 | (20) |
| B symptoms | 80 | (49) | 79 | (50) | 159 | (50) |
| Persistent or recurrent pyrexia of unknown origin >38°C | 15 | (9) | 27 | (17) | 42 | (13) |
| Night sweats | 74 | (46) | 75 | (48) | 149 | (47) |
| Unexplained weight loss >10% weight loss in the last 6 months | 44 | (27) | 39 | (25) | 83 | (26) |
| Rapidly progressive disease | 53 | (33) | 47 | (30) | 100 | (31) |
| Risk of organ complications from bulky lymphomas | 0 | - | 3 | (2) | 3 | (<1) |
| Comment not classifiable – need to treat: increasing pleural effusion with B-CLL tumour cells | 0 | - | 1 | (<1) | 1 | (<1) |
| Comment not classifiable – need to treat: abdominal lymph node conglomerate may cut port arteria to kidney | 1 | (<1) | 0 | - | 1 | (<1) |
| Criteria not specified | 1 | (<1) | 6 | (4) | 7 | (2) |

*A2. Please clarify the median figures cited e.g. bendamustine, median 23.9 (TTP, ITT population) vs bendamustine, median 21.6 (PFS, ITT population): as TTP is more likely to happen we would expect the median figures for TTP to be lower than for PFS. (Figure 5.5, page 57 and Figure 5.7, page 60)*

The definitions of progression-free survival (PFS) and time to progression (TTP) applied in the study were:

> Progression-free survival (PFS)
> The time from randomisation to first PD or relapse after inter-current remission or death for any cause.
>
> Time to progression (TTP)
> The time from randomisation to first PD or relapse after inter-current remission or CLL-related death.

The median times for PFS and TTP in the report are correct.

The reason median PFS was shorter than median TTP is because non CLL-related deaths were included with PFS (but not with TTP). Therefore median time until an event would have been shorter with PFS than with TTP.

*A3. The figures cited in Table 5.8 for 'Time to onset of event' are incorrect, they are identical to the figures cited in Table 5.7 (PFS) on page 58. Please provide the correct figures (table 5.8, page 61).*

Thank you for drawing this to our attention - you are correct that there was an error. The correct tables are included on the next page.

**Progression-free survival based on ICRA – Kaplan-Meier estimates (intention-to-treat population)**

| Analysis<br>Statistic | Bendamustine | | Chlorambucil | | Hazard ratio (95% CI)* (chlorambucil/bendamustine) | *P*-value |
|---|---|---|---|---|---|---|
| **All patients**, n (%) | 162 | | 157 | | 4.37 (3.14 – 6.07) | <0.0001 |
| Patients with events | 86 | (53.1) | 101 | (64.3) | | |
| Censored patients | 76 | (46.9) | 56 | (35.7) | | |
| Quartiles (95% CI), months: | | | | | | |
| 25. percentile | 13.1 | (9.6 – 17.0) | 5.6 | (4.2 – 5.6) | | |
| 50. percentile | 21.6 | (18.6 – 31.0) | 8.3 | (5.9 – 11.3) | | |
| 75. percentile | 40.4 | (33.2 – NA) | 14.0 | (12.0 – 15.9) | | |
| Time to onset of event:† | | | | | | |
| 12 months | 78.6 | (94) | 34.9 | (31) | | |
| 24 months | 47.9 | (54) | 3.0 | (2) | | |
| 36 months | 30.9 | (23) | 1.5 | (1) | | |
| 48 months | 22.2 | (7) | 0.0 | (0) | | |
| 54 months | 17.8 | (3) | 0.0 | (0) | | |

*Hazard ratios and their 95% confidence intervals are adjusted for Binet stage and based on the Cox regression proportional hazard model).
†Time to onset of event is summarized with Kaplan-Meier estimates and (number at risk)

**Overall survival – Kaplan-Meier estimates (intention-to-treat population)**

A4. Please provide details of the EORTC data from study 02CLLIII (section 5.5, p62).
As these data total 60 pages, we have provided them as a separate pdf document.

## Section B: Clarification on cost-effectiveness data

*B1. Please clarify the following: "The average dose applied in the chlorambucil group reached 95% of the planned dose whereas 90% was achieved in the bendamustine group". Are the 95% and 90% figures "dose intensities"? i.e. 95% = total dosage actually received over all chlorambucil patients over entire duration of the trial divided by total dosage over all chlorambucil patients over entire duration of the trial if all chlorambucil patients took their planned dose (0.8mg/kg on days 1 and 15 of 28 day cycle) whilst in PFS ? Expressed another way, in the model, the total average dose for patients on chlorambucil over the entire trial is 549mg (cell D12, worksheet "Costs"). If PenTAG's understanding of the 95% figure above is correct, then the average total dose of chlorambucil actually taken in the trial should be 549mg * 95% = 521mg. Similarly the average total dose for patients on bendamustine over the entire trial is quoted as 1,715mg (cell C12, worksheet "Costs"). If PenTAG's understanding of the 90% figure above is correct, then the average total dose should be 1,715mg * 90% = 1,544mg (page 80). If the 95% and 90% figures are not "dose intensities", please specify what these numbers represent?*

In the economic model, the cost of bendamustine and chlorambucil was based on the planned dose. As noted, this does not account for the fact that some patients did not receive the planned dose within each treatment cycle. The relative dose of the patient measures the extent to which patients received the planned dose. The formula applied to calculate the relative dose is presented below:

$$\frac{\text{Total dose received}}{\text{Planned dose}}$$

The exclusion of this relative dose was a simplifying modelling assumption, which was reasonable given patients received close to the planned dose (95% and 90%).

The base case model was rerun assuming that the relative dose (dose intensities) matched those seen in the trial, 95% for chlorambucil and 90% for bendamustine, rather than the planned doses. The results are as below:

**Model results with relative dose**

| | QALYs | Costs |
|---|---|---|
| Bendamustine | 4.82 | £48,527 |
| Chlorambucil | 3.55 | £33,814 |
| Bend. - Chlor. | 1.27 | £14,714 |
| ICER (Bend. *vs.* Chlor.) | £11,594 | |

*B2. If patients progress within the first three months they are out of the trial, please clarify how this is dealt with in the model (Section 6.3.1, Figure 6.1 (page 87) and Figure 6.2 (page 88) with reference to CSR, page 25).*

Patients who progress within the first 3 months are not removed from the trial analyses completely; they continue to be followed up for overall survival and start of antineoplastic therapy.

These patients were included in the 02CLLIII analyses that inform post-progression parameters in the model i.e. the analysis of time to re-initiation of antineoplastic therapy and the overall survival analysis.

Following progression these patients are treated in the same way as patients who progress after a period of response (partial or complete) or stable disease.

*B3. Please clarify the number of retreatment cycles permitted in the model before subsequent treatments are given (section 6.2, p88).*

The total number of cycles were not limited but were determined by the probability of attaining a sufficient response to the previous course of therapy (>12 months) and the influence of competing events such as death (absorbing health state). The net effect of these led to 63.1% of chlorambucil patients receiving one or more retreatment cycles and the mean number of cycles for those patients who were retreated was 1.13.

*B4. Please explain how mortality for patients in the best supportive care state is dealt with in the model (Section 6.3.1, Page 105, also Figure 6.1 (page 87) and Figure 6.2 (page 88)).*

Mortality for patients receiving chlorambucil and bendamustine was modelled directly from the 02CLIII trial data using parametric survival analysis; it was not extrapolated from other surrogate endpoints such as response or progression. Endpoints such as response and progression were used solely to estimate costs and utilities for surviving patients. The model design was essentially that of a partitioned survival model. That is, overall survival was calculated independent of the health state through extrapolation of survival curves; which is in contrast to a standard Markov model where mortality rates are assigned to each health state. Partitioned survival models have been submitted to NICE in a number of recent technology appraisals.[1]

This method explicitly links mortality rates to time in model rather than to specific health states. As mortality data are taken directly from the trial, the correlation between the distribution of patients across health states and the mortality rate at different points of time in the 02CLLIII trial will be captured. This method also ensures

1. GlaxoSmithKline UK. Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab. Manufacturer's NICE STA Submission 2010. Available from: http://www.nice.org.uk/nicemedia/live/12264/49445/49445.pdf (**see pages 91 -93)**

that the model predictions closely match the overall survival data observed in 02CLLIII.

*B5. Please describe how background mortality; e.g. death from stroke, is dealt with in the model (Section 6.3.1, Figure 6.1 (page 87) and Figure 6.2 (page 88)).*

As above, the mortality rate was estimated by extrapolating the overall survival data in the model by applying parametric techniques. Therefore, the 'background' mortality was the non CLL-related deaths present in the trial population. Of the 72 deaths reported in the trial, 13 patients in the bendamustine group and 21 patients in the chlorambucil group reported CLL deaths; conversely there were 18 non CLL-related deaths in the bendamustine group and 20 non CLL-related deaths in the chlorambucil group (including some patients with unknown cause). Note that only 65 death events are included in the parametric overall survival analysis (Bendamustine: 26; Chlorambucil: 39). This is because we excluded patients, who were not examined, from all the analyses for the economic model. The CLL deaths in this patient group are Bendamustine: 11; Chlorambucil: 20. Non-CLL deaths are Bendamustine: 12; Chlorambucil: 13 and unknown causes are Bendamustine: 3 and Chlorambucil: 6.

*B6. Please explain the basis of 50% / 50% split between fludarabine + cyclophosphamide and best supportive care (BSC) (section 6.2, p88).*

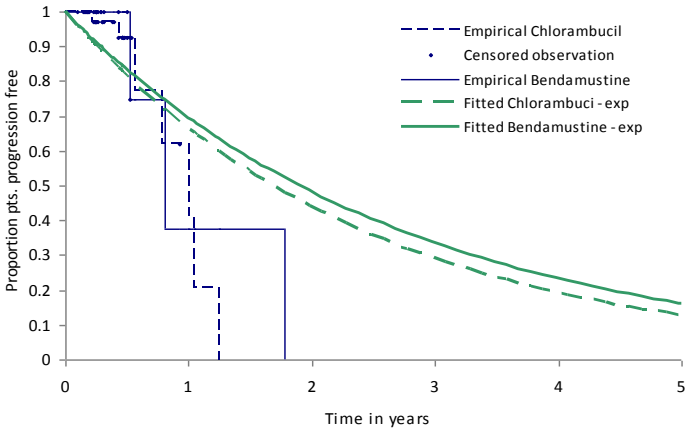
The 50%/50% split between treatment with fludarabine + cyclophosphamide and BSC was based on feedback from the advisory board as representing UK clinical practice. A full description of the advisory board can be found in Section 6.5.4 (Page 131) of the original report.

*B7. In your submission it is stated 'To be conservative the log-logistic, which appears to provide the best fit by visual inspection, is therefore used'. Please provide us with plots for alternative survival functions and associated AIC data (section 6.3, p96).*

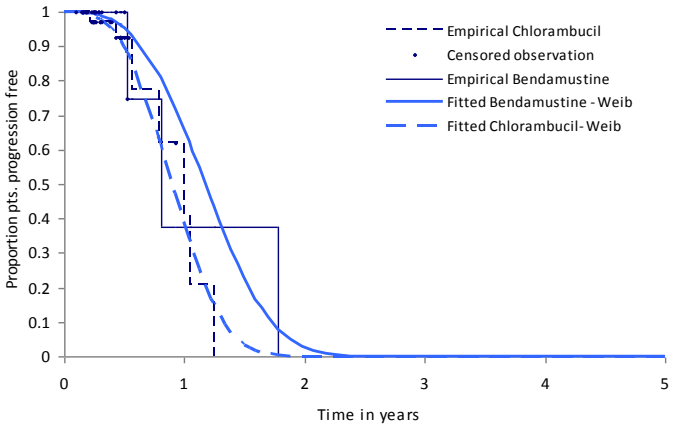
The survival curves and AIC data are presented below.

Figure: Different parametric functions used for time to progression from stable disease

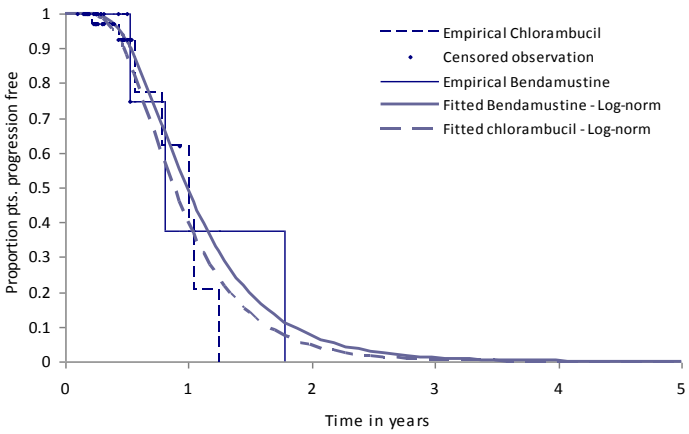
(a) Exponential




(b) Weibull




(c) Log-normal




(d) Log-logistic (base case)

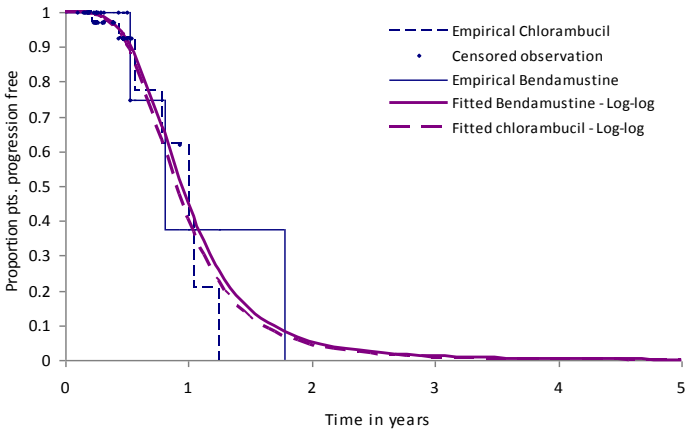



Table: AIC for different parametric functions used for time to progression from stable disease

| Distribution | AIC |
|---|---|
| Exponential | 50.98 |
| Weibull | 32.28 |
| Log-logistic | 33.37 |
| Log-normal | 33.94 |

*B8. Please explain how utilities are handled in relation to the utilities from the general public (Kind et al, BMJ, 1998)? (Section 6.4.6, Pages 124-125 (Beusterien 2010)).*

The utilities presented in Beusterein 2010 have been adjusted to reflect the utility derived by mapping from the EORTC QLQ C-30 data collected in 02CLLIII. This was achieved by assuming that the 02CLLIII baseline utility value could be used to represent the stable disease state. For example, this resulted in utility estimates for

use in the model of 0.83 for complete response; 0.76 for partial response; 0.70 for stable disease and 0.60 for progressive disease (health states following first line treatment). The utility values should therefore reflect the age composition of the 02CLLIII patients at baseline. No further adjustments were made for cohort age.

*B9. Please provide the health state descriptions for the utility study, Beusterien et al (section 6.4, p177).*

**Stable disease**

| **Health State: ∗** |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened.<br><br>• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.<br><br>• Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities.<br><br>• Much of the time, you don't feel hungry or you feel full after eating a little.<br><br>• You often have trouble sleeping because of night sweats that wake you up. |

**Partial response**

| **Health State: ϕ** |
| --- |

• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.

• Your symptoms have improved with treatment.

• Your swollen glands in your neck, armpits, or groin are smaller than they were before treatment.

• Daily activities may take more effort than usual, and you feel a little fatigued (tired and weak). You may feel short of breath during normal activities.

• Sometimes, you don't feel hungry or you feel full after eating a little.

• You occasionally have trouble sleeping because of night sweats that wake you up.

**Complete response**

| Health State: ♣ |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• Your symptoms have improved with treatment.<br><br>• You do not have swollen glands in your neck, armpits, or groin.<br><br>• Daily activities do not take more effort than usual, but you feel slightly fatigued (tired and weak). You do not feel short of breath during normal activities.<br><br>• Your appetite is normal.<br><br>• You do not have trouble sleeping because of night sweats. |

**Progressive disease**

| Health State: ▲ |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• Your symptoms are getting worse.<br><br>• Your swollen glands in your neck, armpits, or groin are bigger and visible. They may be uncomfortable.<br><br>• Daily activities require a lot of effort, and you are almost always fatigued (tired and weak). You feel short of breath during normal activities.<br><br>• Almost always, you don't feel hungry or you feel full after eating a little.<br><br>• Most of the time, you have trouble sleeping because of night sweats that wake you up. |

**No change plus grade I/II nausea**

| **Health State: ♦** |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened.<br><br>• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.<br><br>• Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities.<br><br>• Much of the time, you don't feel hungry or you feel full after eating a little.<br><br>• You often have trouble sleeping because of night sweats that wake you up.<br><br>• Once a month when you receive treatment, you experience nausea for 24-48 hours, during which time you don't feel like eating, and food may have a funny metallic taste. Most of the time, this can be relieved with medication. |

**No change plus grade I/II nausea/vomiting**

| **Health State: ∞** |
| --- |

• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.

• Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened.

• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.

• Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities.

• Much of the time, you don't feel hungry or you feel full after eating a little.

• You often have trouble sleeping because of night sweats that wake you up.

• Once a month when you receive treatment, you experience nausea and vomiting for 24-48 hours, during which time you don't feel like eating, and food may have a funny metallic taste. Most of the time, this can be relieved with medication.

**No change plus grade III/IV anaemia**

**Health State:** ▼

• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.

• Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened.

• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.

• You experience substantial fatigue (tiredness/weakness), and your ability to exercise (walking or shopping, etc.) is substantially limited. You feel short of breath during normal activities. You receive a 6-hour blood transfusion at the clinic, which relieves the fatigue for 2-3 weeks.

• Much of the time, you don't feel hungry or you feel full after eating a little.

• You often have trouble sleeping because of night sweats that wake you up.

**No change plus grade III/IV pyrexia**

| Health State: Ω |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened.<br><br>• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.<br><br>• Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities.<br><br>• Much of the time, you don't feel hungry or you feel full after eating a little.<br><br>• You often have trouble sleeping because of night sweats that wake you up.<br><br>• Once a month, you develop a fever due to infection, and this requires treatment in the hospital for 4 to 5 days. |

**Second-line treatment**

| Health State: ◘ |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• This is your second time on treatment because your symptoms worsened.<br><br>• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.<br><br>• Daily activities require quite a bit of effort, and you are fatigued (tired and weak) much of the time. You feel short of breath during normal activities.<br><br>• Much of the time, you don't feel hungry or you feel full after eating a little.<br><br>• You often have trouble sleeping because of night sweats that wake you up. |

**No change plus grade III/IV pneumonia**

| **Health State: ✚** |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened.<br><br>• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.<br><br>• Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities.<br><br>• Much of the time, you don't feel hungry or you feel full after eating a little.<br><br>• You often have trouble sleeping because of night sweats that wake you up.<br><br>• Once a month, you have pneumonia, which causes coughing, chest pain, fever, and breathlessness. This requires you to stay in the hospital for 7-10 days and receive intravenous antibiotics. |

**No change plus grade I/II diarrhoea**

| **Health State: ●** |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened.<br><br>• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.<br><br>• Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities.<br><br>• Much of the time, you don't feel hungry or you feel full after eating a little.<br><br>• You often have trouble sleeping because of night sweats that wake you up.<br><br>• Once a month when you receive treatment, you experience 3 to 4 episodes per day of diarrhoea (watery stools) that lasts for 3 to 4 days. |

**Third-line treatment**

| Health State: ♠ |
| --- |
| • You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections.<br><br>• This is your third time on treatment because your symptoms worsened.<br><br>• You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable.<br><br>• Daily activities require a lot of effort, and you are almost always fatigued (tired and weak). You feel short of breath during normal activities.<br><br>• Much of the time, you don't feel hungry or you feel full after eating a little.<br><br>• You often have trouble sleeping because of night sweats that wake you up. |

**Full health**

| Health State: § |
| --- |
| • You are in full health<br><br>• You have no medical conditions; you are considered healthy |

**Dead**

| Health State: ♫ |
| --- |
| • You are dead |

## Additional questions received from NICE via email correspondence

**Received: Wed 01/09/2010 13:43**

1. Please could you provide an accessible reference source for the price of bendamustine cited in the submission (see Table 6.19, page 133). Within the submission the reference is: British National Formulary 59 available from http://www.medicinescomplete.com/mc/bnf/current but the ERG are not able to access this reference without paying for a subscription, and the information isn't in the BNF 59.

Bendamustine has only recently launched therefore it is still waiting to be included in external sources such as MIMS and BNF.

The closest we have to a formal source for the bendamustine price is an internal Trade Price List (September 2010), which includes the price of all Napp products. We hope this is sufficient for now. We have attached this document to the email.