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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).

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)

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).

A4. Please provide details of the EORTC data from study 02CLLIII (section 5.5, p62).

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?

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).

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

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)).

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)).

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

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).

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)).

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