From: [redacted]
Sent: 20 April 2009 10:25
To: Jeremy Powell
Cc: [redacted]
Subject: Rituximab for first line chronic lymphocytic leukaemia - ACD:

Dear Jeremy

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above single technology appraisal.

Comments received from my colleagues in the Department of Health are as follows:

"In our view, this is a reasonable decision to allow the use of rituximab with fludarabine and cyclophosphamide (F&C) as first line therapy in CLL.

F&C is certainly acknowledged as the best currently available first-line combination treatment in CLL for the younger group. Current evidence suggests that the addition of rituximab increases the rapidity and depth of the response.

We believe however that there are some provisos. The panel appear to have extrapolated from progression-free survival into overall survival. Whilst this may be the case, it has yet to be proven. In chemotherapy trials, comparing F&C with oral chlorambucil shows increased CR rate and PFS, but this did not translate into improved OS. However, a short course of treatment with improved response improves quality of life so that is perhaps, in the younger group a rationale for treatment. We belive that it is also the case that a better CR can then be followed with some form of stem cell transplant, and the results again are likely to be better because of the reduction in residual disease at the time of the transplant.

In the non-malignant setting (autoimmune disease), there appears to be some evidence of an increased rate of progressive multi-focal encephalopathy, with the combination of rituximab and cyclophosphamide. There has already been an FDA alert for rituximab alone and the association of PML, and there is increasing evidence that the additional immune suppression caused by cyclophosphamide exacerbates this. You may be aware that there is currently an exercise, trying to catch this data. We feel that it would be helpful if the company could carry out some post-marketing surveillance in this area, particularly if use will inevitably increase following confirmation of the appraisal.

In our view, it is disappointing that the combination of rituximab with chlorambucil in the elderly has not been accepted We feel that this is the group which has the highest incidence of CLL, and that F&C is not an appropriate treatment. Chlorambucil will contain the disease, but is rarely associated with CR and the potential benefits that PFS may bring of the potential impact on OS that you seem to accept.

We consider that rituximab is a relatively toxic-free drug to administer. In combination with chlorambucil, it would be potentially highly acceptable, and tolerated by the elderly. We feel that it is misfortunate that they will not be offered this possible effective treatment".

Many thanks and best wishes

[redacted]
Department of Health