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Dear Mr Powell

Rituximab for maintenance treatment of people with advanced follicular non-Hodgkin's lymphoma in first remission

On behalf of NHS Camden, I would like to submit our comments on the appraisal consultation document for Rituximab for maintenance treatment of people with advanced follicular non-Hodgkin's lymphoma in first remission.

- **The provisional recommendations extend the use of rituximab in patients with follicular non-Hodgkin's lymphoma as maintenance treatment following first line chemotherapy.** After review of the manufacturer's evidence submission and cost-effectiveness modelling, NICE recommends rituximab as an option for maintenance treatment in patients with advanced follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy. This recommendation is questionable as there is no evidence to demonstrate improvements in overall survival, and there are uncertainties about the use of salvage chemotherapy following disease progression. The manufacturer's model was based over a 6 year time period, despite only 4 years' follow up in the PRIMA study.
- **The provisional recommendations could increase the use and therefore the overall cost of this drug for a PCT population.** According to manufacturer's estimates, the cost of treating a person with an average body surface area of $1.8m^2$ with rituximab maintenance treatment for 2 years is £14,669. Implementing this guidance could carry additional annual drug costs of approximately £300,000 for NHS Camden, with an estimated 42 people receiving maintenance treated with rituximab for this indication per year. It is difficult to see how this can be justified in the absence of evidence of improved overall survival, and with very limited (and indirect) evidence suggesting improved quality of life – which is itself confounded by failure to take account of the effects of salvage chemotherapy after relapse following either observation or rituximab maintenance. Direct estimates of quality of life would have been useful.
- **Substantial amounts of data have been redacted in this ERG report.** The most relevant RCT is a phase III study called the PRIMA trial and this forms the basis of the manufacturer's submission. Data from the post-study observational follow-up period, which had a median follow-up of 38 months, were submitted to the ERG as 'academic in confidence' and will become more generally available when and if they are published. We note that the ERG cautioned that the data were immature and that the early closure of the trial might have led to an overestimation of the clinical benefits of rituximab maintenance treatment.

- **The PRIMA study (phase III, open-label, multicentre)** randomized 1019 people with previously untreated advanced follicular lymphoma who had responded to treatment with rituximab in combination with CVP, CHOP or FCM, to maintenance rituximab treatment or to observation. After 25 months median follow up, rituximab maintenance halved the risk of disease progression (HR 0.50, 95% CI 0.39 to 0.64). Progression-free survival was said to have been improved by treatment after 38 months median follow-up but data is not publically available. Any difference in overall survival could not be established because of the low number of deaths at that time. Longer-term data are not available from the PRIMA trial so the manufacturer modelled the expected survival outcomes using data from a separate study - the EORTC 20981 study (conducted in a different population), which was also used to help estimate the transition probabilities between health states and death in the economic model. It is important to note that study evidence did not show a statistically significant improvement in survival after 5 years in EORTC 20981.

- **There is no convincing evidence of improved survival or quality of life and this calls into question the assumptions in the cost-effectiveness model.** NICE should also note that in the PRIMA trial, there was no statistically significant difference in measured quality of life (using FACT-G and EORTC QLQ-C30 questionnaires developed to assess the quality of life of cancer patients) between those receiving rituximab maintenance or observation. With no evidence of statistically significant improvements of overall survival or quality of life, it is difficult to understand how a prolongation of progression-free survival can be worthwhile in its own right. This also calls into question the utility assumptions that were included in the cost-effectiveness model.

- **While there are side effects to treatment, the appraisal committee decided that overall these are not severe and that the use of rituximab as a maintenance treatment may delay the need for further chemotherapy.** Although the appraisal committee agreed that rituximab maintenance is likely to prolong survival, the extent of any such survival benefit is unclear, and the study evidence did not show a statistically significant improvement in survival after 5 years in EORTC 20981). The committee appears to have assumed that the delay to requiring further chemotherapy in people with advanced follicular non-Hodgkin's lymphoma (that has responded to first-line induction treatment with rituximab in combination with chemotherapy) translates into overall improved survival. Without assessing the impact of salvage chemotherapy after relapse, such an assertion is unfounded. The committee appears to have given weight to the assumption that patients' quality of life is improved by the more manageable side effects of rituximab maintenance therapy compared with side effects of salvage chemotherapy, but this was not clearly demonstrated and rituximab maintenance was associated with a higher rate of Grade III/IV infections in EORTC 20981.

- **Rituximab is not convincingly demonstrated to be a cost-effective use of NHS resources for this indication.** In the manufacturer's base case analysis, rituximab maintenance was cost effective compared with observation when the benefits of rituximab are assumed to last for 6 years (ICER £15,978/QALY). In sensitivity analyses undertaken by the ERG, ICERs ranged from £21,000 to £26,000 per QALY when the benefit was assumed to be sustained for the first 3 to 4 years. However, the lack of evidence of improvement in overall survival and the failure to demonstrate improved quality of life by rituximab maintenance, calls into question the fundamental assumptions in the cost-effectiveness model.

- **The ERG agreed to the manufacturer's small changes to the decision problem,** i.e. by considering the treatment in people who had responded to first-line treatment with rituximab plus chemotherapy rather than as specified in 'adults with advanced follicular lymphoma that has responded to first-line chemotherapy'. There are two effects of this. One of the comparators that was originally specified in the scope, ibritumomab tiuxetan, has been excluded from analysis. The determination has also pre-empted the findings of the review of TA 110 'Rituximab for the first-line treatment of stage III-IV follicular lymphoma' which will report in 2011 and considers a wider range of rituximab containing regimens for first

induction. This could have an important impact on the interpretation of the results from EORTC 20981, which have proved highly influential in this appraisal.

Yours sincerely

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