European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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Subject: Your letter of 16 August 2007 regarding Mabthera (rituximab) for the treatment of recurrent or refractory Stage III or IV follicular non-Hodgkin's lymphoma

Dear Mr. Boysen,

Thank you for your letter requesting the Agency's views on the Marketing Authorisation of Mabthera (rituximab) for the treatment of recurrent or refractory Stage III or IV follicular non-Hodgkin's lymphoma.

Your letter has been discussed internally within the EMEA and shared with the Rapporteur for Mabthera.

With reference to the specific queries on the two indications which currently undergo appraisal by NICE, please find the requested clarifications - using the identical point system for ease of reference- as follows:

1. "MabThera maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera."

Questions:

- Does the 2006 EMEA marketing authorisation confer a single authorised indication for the use of rituximab as maintenance in patients responding to induction therapy? Or, does it confer two separate authorised indications for (i) the use of rituximab as maintenance therapy for responding patients and (ii) the use of rituximab in combination with chemotherapy as induction therapy at first relapse?

The indication of maintenance therapy is interpreted in line with the data from the pivotal trial (EORTC 20981) which formed the basis of this authorisation. This trial was conducted in patients with relapsed or refractory follicular lymphoma treated with or without rituximab maintenance after achieving a complete or partial remission following induction therapy (chemotherapy with or without Mabthera). The efficacy results of both parts of the trial are described in section 5.1 "Pharmacodynamic Properties" of the Summary of Product Characteristics, tables 8, page 23 *Induction phase* and table 9, page 24 *Maintenance phase*. Safety data are reported under section 4.8 (Undesirable effects) from the two parts of the trial in table 2, page 13: *Induction phase* and table 3, page 14: *Maintenance phase*. Therefore the above indication should be viewed as the (i) identification of those patients where the use of rituximab as maintenance therapy is appropriate- i.e. responders to prior induction therapy (ii) the possibility to use rituximab in combination with chemotherapy as induction therapy at relapse.

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- Can rituximab be used for induction at first relapse independently of being used for maintenance therapy?

As discussed previously, the final efficacy analysis of EORTC 20981 trial included all patients randomised to both parts of the study. Data from the first part (induction phase) are provided in section 5.1 of the Summary of Product Characteristics. The results after a median observation time of 31 months for patients randomised to the induction phase, showed that R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP- in terms of complete response rates (29% vs 16%, p= 0.0005). Only responding patients should receive maintenance treatment.

If so, we would like you to clarify how to interpret the indication for the treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. We are aware that this may become more clear if the answer to question 2 below is that the indication is limited to monotherapy.

2. "MabThera is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy."

Question:

- Does this limit the use of rituximab to monotherapy – or can rituximab be used in combination with chemotherapy at second and subsequent relapse?

Initially this indication had been approved as monotherapy following the results of a pivotal study, in patients with relapsed or chemoresistant low-grade or follicular B cell NHL. These results were the basis of the first Marketing Authorisation of Mabthera in 1998.

However with the evolution of the knowledge with the product, the option to use rituximab in combination with chemotherapy at second relapse (and further treatment with rituximab as maintenance) is available to the clinician and is covered by the data analysed above which formed the basis of the indication authorised in July 2006. Looking at the charasteristics of patients enrolled in the EORTC 20981 trial, while the majority (82%) were in their first relapse, there were a number of patients (18%) in their second relapse. Patients in a subsequent to the second relapse were not included. PFS was analyzed in subgroups defined by baseline prognostic factors. The subgroup of patients who were in their second relapse derived equal benefit as other subgroups both from treatment with R-CHOP as induction –in terms of response - and subsequent maintenance treatment with rituximab, in terms of progression-free survival. These results were statistically significant.

I trust the above satisfactorily addresses your queries. If you should have any additional questions, please do not hesitate to contact me directly.

Sincerely yours,

[redacted],
Head of Post-Authorisation Human Unit,
EMEA