HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

8 November 2006

**MABTHERA 100 mg, concentrate for solution for infusion (CIP 560 600-3)**
**Pack of 2**
**MABTHERA 500 mg, concentrate for solution for infusion (CIP 560 602-6)**
**Pack of 1**

**Applicant: ROCHE**

rituximab

List I
Medicinal product requiring hospital prescription. Prescription restricted to oncology or haematology specialists or doctors with cancer training, rheumatology or internal medicine specialists. Medicinal product requiring specific monitoring during treatment.
Initial administration must be carried out in a hospital environment.

Date of European Marketing Authorisation (centralised procedure) and amendments: June 2, 1998; March 21, 2002; August 2, 2004; July 6, 2006

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the extension of indication: MabThera® maintenance therapy is indicated for patients with relapsed or refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera®.

Health Technology Assessment Division

## 1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient
rituximab

### 1.2. Background
Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody.

### 1.3. Indications

Non-Hodgkin's lymphomas
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.

MabThera® is indicated in combination with CVP chemotherapy for the treatment of previously untreated patients with stage III-IV follicular lymphoma.

**MabThera® maintenance therapy is indicated for patients with relapsed or refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera®.**

MabThera® in combination with CHOP chemotherapy is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma.

Rheumatoid arthritis (*)
MabThera®, in combination with methotrexate, is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying treatments (DMRAD), including one or more TNF (tumour necrosis factor) inhibitor therapies.
*(*) This indication has not yet been assessed by the Transparency Committee.*

### 1.4. Dosage

Maintenance therapy:
Patients who have responded to induction treatment may receive maintenance therapy with MabThera® given at 375 mg/m$^2$ body surface area once every 3 months until disease progression or for a maximum period of two years.

The safety and efficacy of MabThera® have not been demonstrated in combination with other forms of chemotherapy.

## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC classification (2004)

| | |
|---|---|
| L | Antineoplastic and immunomodulating agents |
| L01 | Antineoplastic agents |
| L01X | Other antineoplastic agents |
| L01XC | Monoclonal antibodies |
| L01XC02 | Rituximab |

### 2.2. Medicines in the same therapeutic category

Comparable medicinal products
None

### 2.3. Medicines with a similar therapeutic aim

Monotherapy
- chlorambucil (CHLORAMINOPHENE)
- cyclophosphamide (ENDOXAN)
- fludarabine (FLUDARA)
- ibritumomab tiuxetan (ZEVALIN)

Combinations of cytotoxic agents, particularly the CHOP protocol (cyclophosphamide, doxorubicin, vincristine, prednisone), the CHVP protocol (cyclophosphamide, doxorubicin, etoposide, prednisolone) alone or in combination with interferon alpha, and the CVP protocol (cyclophosphamide, vincristine, prednisolone).

## 3. ANALYSIS OF AVAILABLE DATA

### 3.1. Efficacy

One study was provided in the dossier.

EORTC 20981 study
Phase III, randomised, open-label study evaluating MabThera® maintenance therapy against no treatment in 465 patients with relapsed or refractory follicular lymphoma (stage III or IV) after a maximum of 2 non-anthracycline chemotherapy regimens and who have never taken MabThera®.

**Methods**
Randomisation was performed in the 2 stages of the study:

- First randomisation, for the induction therapy:
CHOP (reference group) against R-CHOP (CHOP + MabThera® 375 mg/m$^2$ on day 1 of each course). The induction design provides for 6 courses 21 days apart. Tumour response is assessed after 3 courses. Disease progression or stability is considered a failure of the treatment. Patients showing an objective response (clinically and radiologically) receive 3 additional courses.

- Second randomisation, for the maintenance therapy in responders (defined as partial response or complete response, with immunoglobulin G levels > 3 g/l):
No treatment (observation group) against maintenance therapy with MabThera® 375 mg/m$^2$ every 3 months until there is disease progression or for a maximum of 2 years.

The second randomisation, in which the maintenance treatment is assessed, was stratified according to research centre, induction therapy received (CHOP or R-CHOP), and quality of the response obtained (PR or CR).

Primary endpoints:
- Induction stage: global response rate (sum of complete responses [CR] and partial responses [PR])
- Maintenance stage: progression-free survival, defined as the time elapsing between the 2nd randomisation and objective disease progression or death.

Secondary endpoints:
- Induction stage: progression-free survival after the first randomisation
- Maintenance stage: overall survival.

**Results:**
The median age of the patients randomised for maintenance therapy was 55 years in the untreated group and 53 years in the MabThera® group. Approximately 1/3 of patients had a FLIPI[1] score of 3-5 and approximately 80% of patients had responded inadequately to a single previous chemotherapy regimen.

Induction therapy
The results derive from a median 31 month follow-up after the initial randomisation.

The overall response level (primary endpoint) was higher in the R-CHOP group (87%) than in the CHOP group (74%, p = 0.0003). The same was true for the complete response rate: 29% vs. 16%, p = 0.0005.

Median progression-free survival was longer in the R-CHOP group (33.2 months) than in the CHOP group (19.4 months), corresponding to a 38% reduction in the risk of progression or death (p = 0.0001).

Maintenance therapy
The results derive from a median 28.3 month follow-up after the second randomisation.

334 patients that had a complete or partial response to the induction therapy were randomised to either MabThera® maintenance therapy (n = 167) or no therapy (n = 167).

Median progression-free survival (primary endpoint) after the second randomisation was longer in the MabThera® group than in the untreated group (42.2 months vs. 14.3 months, p < 0.0001).

The percentage of patients showing disease progression or dying was lower in the group receiving MabThera® maintenance treatment compared with the untreated group (37.1% vs. 62.3%), representing a 61% reduction in the relative risk of progression or death (RR = 0.39 [95% CI: 45-72%]).

In the MabThera® group, 18 patients (11%) had died by the time of analysis, compared with 36 patients (22%) in the untreated group (p = 0.0039).

The estimated overall 3-year survival rate was 89.2% in the MabThera® group and 78.4% in the untreated group (RR = 0.44 [95% CI: 22-75%]; p = 0.0039).

The median overall survival period had not been reached in either group by the analysis date.

Subgroup analysis showed that MabThera® maintenance therapy prolonged the median progression-free survival of patients irrespective of the induction chemotherapy used: CHOP (37.5 months vs. 11.6 months, p < 0.0001) or R-CHOP (51.9 months vs. 22.1 months, p = 0.0071). The same was true for the quality of the response to the induction therapy: complete response (52.8 months vs. 14.3 months in the untreated group, p = 0.0008) or partial response (37.8 months vs. 14.3 months in the untreated group, p = 0.0001).

[1] Follicular Lymphoma International Prognostic Index, including 5 prognostic factors (age > 60 years; Ann Arbor stage III-IV; number of nodal areas affected ≥ 5; haemoglobin > 12 g/dl; LDH > normal).

### 3.2. Adverse effects

The adverse effects observed in this study were those already known for each of the protocols used, particularly in patients receiving MabThera® (fever, pain, skin rashes, urticaria, muscle cramps, etc.).

During maintenance therapy, the frequency of grade 3-4 neutropenia was higher in the MabThera® group (10% vs. 4% in the untreated group), as was the incidence of grade 3-4 infections (11% vs. 3% in the untreated group).

### 3.3. Conclusion

In a phase III open-label study, 465 patients with relapsed or refractory follicular lymphoma were randomised in a first stage to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or a combination of MabThera® plus CHOP (R-CHOP). In a second stage, 334 patients that had a complete or partial remission after the induction therapy were randomised to either MabThera® maintenance therapy or no therapy.

After the induction therapy (median follow-up of 31 months), the R-CHOP group was observed to have almost 14 months longer median progression-free survival than the CHOP group (33.2 months against 19.4 months), corresponding to a 38% reduction in the risk of progression or death (p = 0.0001).

During maintenance therapy, median progression-free survival (primary endpoint) was longer in the MabThera® group (42.2 months) than in the untreated group (14.3 months) (p < 0.0001). There was a 61% reduction in the relative risk of progression or death (RR = 0.39 [95% CI: 45-72%]).

The median overall survival period (corresponding to 50% of patients alive) had not been reached in either group by the analysis date.

The estimated overall 3-year survival rate was 89.2% in the MabThera® group and 78.4% in the untreated group (RR = 0.44 [95% CI: 22-75%]; p = 0.0039).

During maintenance therapy, the principal adverse reactions associated with MabThera® were haematological effects (10% of grade 3-4 neutropenia against 4% in the untreated group) and infections (11% of grade 3-4 infections against 3% in the untreated group).

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Non-Hodgkin's follicular lymphoma is a slowly progressing disease with a median survival of 8 to 10 years, and is therefore life-threatening.

The efficacy/adverse effects ratio is high.
This is a second-line or later curative treatment.

There is no alternative medicinal product validated for maintenance treatment (the non-medicinal alternative being a haematopoietic stem cell transplant).

Public health benefit:

The public health burden of follicular lymphoma in the population of patients requiring MabThera® maintenance therapy is low, in view of the small number of patients concerned.

Improving the management of this disease is a public health priority (Cancer Plan) that is only partly covered by existing therapies.

The available data show that MabThera® has a major effect on progression-free survival and overall 3-year survival. At this stage in the disease, when the median survival is estimated to be 6 to 8 years, the effect of MabThera® in terms of overall survival beyond this median has yet to be demonstrated.

At a population level, the expected impact on morbidity-mortality is low, given the small size of the population concerned.

Consequently, MabThera® is expected to have a certain public health benefit in this indication. This benefit may be quantified as low.

The actual benefit of MabThera® in the context of maintenance treatment for non-Hodgkin's follicular lymphoma is substantial.

### 4.2. Improvement in actual benefit

In maintenance treatment for relapsed or refractory follicular lymphoma, MabThera® provides a major IAB (IAB I) in terms of efficacy compared with the current treatment strategy.

### 4.3. Therapeutic use

Follicular lymphomas often progress slowly and may be compatible with a normal lifestyle even without treatment for several months or years. The median survival today is approximately 8 to 10 years.

Complete eradication cannot be expected with any treatment, even intensifications with autologous transplants.

Treatment should be started on the basis of signs of clinical disease progression (inflammatory syndrome, or impact on general health evaluated by the WHO performance status score) and the presence of an appreciable tumour mass. Treatment should then comprise chemotherapy adjusted according to age and tumour size.

While the standard CHOP combination, the primary treatment for lymphomas, is still used (sometimes at reduced doses in the elderly) because of its rapid efficacy, other treatments are more often prescribed in view of their better efficacy/toxicity balance, such as the CVP combination (in which doxorubicin, the most toxic drug in CHOP, has been removed), rituximab in combination with CVP, or combinations including fludarabine.

Once post-chemotherapy remission has been achieved, the patient is usually monitored until a relapse triggers a further course of therapy. The cytotoxic agent may then be changed and may again induce remission; successive relapses, however, increase resistance to treatment.

MabThera® is the first medicinal product to have validated the benefit of maintenance therapy following remission in the context of the treatment of relapsed or refractory follicular lymphomas.

### 4.4. Target population

The incidence of non-Hodgkin's lymphoma in 2000 was 9,900 cases[2].

Follicular lymphoma accounts for 20 to 30% of non-Hodgkin's lymphomas in Europe[3]. Almost 80% of these patients are in stages III-IV[4].

The patients eligible for MabThera® maintenance therapy must be induction therapy responders. In the EORTC 20981 study, the overall response rate in the induction stage was approximately 80%.

The target population for MabThera® in this indication extension is estimated at 1,200 to 1,900 cases per year.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the new indication and at the posology in the Marketing Authorisation.

[2] Trends in cancer incidence and mortality in France from 1978 to 2000 (INVS 2003)
[3] Solal Celigny P et al. 'Lymphomes folliculaires'. In: Solal Celigny P et al. Lymphomes 3rd ed., Frison-Roche, Paris 1997:171-203
[4] Horning SJ. Follicular lymphoma: have we made any progress? Ann Oncol. 2000; 11 Suppl 1:23-7