HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

1 October 2008

MABTHERA 100 mg, concentrate for dilution for infusion
Pack of 2 (CIP: 560 600-3)

MABTHERA 500 mg, concentrate for dilution for infusion
Pack of 1 (CIP: 560 602-6)

Applicant: ROCHE

Rituximab

List I
Medicine for hospital prescription only. To be prescribed only by oncologists or haematologists, or doctors competent in oncology, specialists in rheumatology or internal medicine. Medicinal product requiring specific monitoring during treatment.
The first dose must be given in the hospital.

Date of Marketing Authorisation (centralised European) and its variations: 2 June 1998 - 21 March 2002 - 2 August 2004 - 6 July 2006 - 18/01/2008

Reason for request: Inclusion on the list of medicinal products approved for use by hospitals in the extension of indication “for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy”.
This wording for the indication has extended the use of MabThera to combination with all chemotherapy instead of CVP chemotherapy.

Reminder of previous indication of 2 August 2004: “MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with "CVP" chemotherapy”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Rituximab

1.2. Background

Rituximab is a genetically engineered chimeric mouse/human monoclonal anti-CD20 antibody.

1.3. Indications

"Non-Hodgkin's lymphoma

MabThera monotherapy 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 for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

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

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

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 anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies."

1.4. Dosage

"The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients with follicular NHL is: 375 mg/m2 body surface area per cycle, for up to 8 cycles.

MabThera should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2008 Classification

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

2.2. Medicines in the same therapeutic category

Comparator drug
None

2.3. Medicines with a similar therapeutic aim

As monotherapy:
- CHLORAMINOPHENE (chlorambucil)
- ENDOXAN (cyclophosphamide)
- FLUDARA (fludarabine)
- ZEVALIN (ibritumomab tiuxetan)

Cytotoxic combinations in particular the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone), the CHVP regimen alone (cyclophosphamide, doxorubicin, etoposide, prednisolone) or in combination with interferon alfa and the CVP combination (cyclophosphamide, vincristine, prednisolone).

3. ANALYSIS OF AVAILABLE DATA

Since August 2004, MabThera is indicated "for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy". This indication was based on the results of the pivotal study M39021 evaluated by the French Transparency Committee on 8 June 2005.

On 18 January 2008, this indication, discussed in this dossier, was extended to combination with any type of chemotherapy: "treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy".

The current laboratory dossier is based on 53 months of follow-up data (instead of 30 months) of pivotal study M39021 and on the results of three other randomised phase III studies (studies FL-2000. GLSG'00 and OSHO-39) using MabThera in combination with chemotherapy other than CVP i.e. the CHOP, MCP, and CHVP + interferon-alpha regimens.

The dossier also describes a published meta-analysis[1] of seven randomised studies (including a total of 1943 patients) which compared chemotherapy plus MabThera with the same chemotherapy without MabThera in indolent lymphomas (low grade or slow growing)[2], with overall survival as primary endpoint. Five of the studies concerned patients with follicular lymphoma, including three as first-line treatment (previously reported studies M39021. GLSG'00 and OSHO-39) and two studies on relapsing patients (outside the indication evaluated here). This meta-analysis therefore provides little additional information about first-line treatment of patients.

3.1. Efficacy

1/ Summary of the pivotal study data

A phase III, randomised, open-label comparison of the efficacy and safety of chemotherapy combining MabThera with the CVP protocol (R-CVP) with CVP alone, in 322 patients with previously untreated stage III or IV follicular lymphoma.

Treatments studied (every 3 weeks for 8 cycles):
- CVP: (cyclophosphamide 750 mg/m^2 on day 1; vincristine 1.4 mg/m^2 on day 1; prednisolone 40 mg/m^2 on days 1-5).
- R-CVP: rituximab 375 mg/m^2 administered on day 1 of the CVP cycle.

Primary efficacy endpoint: time to treatment failure defined as the time between randomisation and one of the following events: progression or tumour relapse, death from whatever cause, institution of another antitumor treatment or no response after 4 cycles of treatment.

Secondary endpoints: objective response rate (complete responses, unconfirmed complete responses[3] and partial responses) according to the criteria of Cheson et al., response duration, overall survival, time to institution of new anti-tumour treatment or death, disease-free survival (for patients with a complete response), time to progression, safety.

[1] Schulz H. et al. Immunochemotherapy with rituximab and overall survival in patients With indolent or mantle cell lymphoma: A systematic review and meta-analysis. J Natl Cancer Inst 2007;99(9):706-14
[2] Follicular lymphomas represent a subgroup of indolent lymphomas
[3] Normal physical examination, no enlarged lymph nodes, disappearance of lymphatic mass or reduction in its volume by more than 75%, normal or undetermined bone marrow status

Results:

Efficacy was analysed for 321 patients (162 R-CVP, 159 CVP).

At 18 months, the R-CVP combination was more effective than CVP alone for time to treatment failure (25.9 months vs 6.7 months, p<0.0001) and on the risk of occurrence of an event leading to treatment failure which was reduced by 67% (95% CI: 56%-76%).
At 30 months, a significant difference was maintained for time to treatment failure and certain secondary endpoints (objective response rate, response duration, time to institution of a new antitumor treatment or death, disease-free survival).
No conclusion could be made about overall survival (current median survival from 8 to 10 years) because of the limited follow-up duration of 30 months.

2/ Updating of the pivotal study data

The analysis of the efficacy data of pivotal study M39021 is available with a median patient follow-up of 53 months (4.4 years). These results confirm that MabThera combined with CVP chemotherapy increased the time to treatment failure (primary endpoint) compared to CVP chemotherapy alone (27 months versus 6.6 months, p<0.0001). They also show a significant difference between the two groups for the 53-month survival rate (secondary endpoint): 80.9% in the MabThera + CVP regimen group versus 71.1% in the CVP alone group (HR=0.60; 95% CI = [0.38-0.96]; p= 0.029).

3/ Efficacy data for MabThera combined with chemotherapy regimens other than CVP

- **Study GLSG'00**

A phase III, randomised, open-label comparison of the efficacy and safety of chemotherapy combining MabThera with the CHOP regimen (R-CHOP) with CHOP alone, in 428 patients with previously untreated stage III or IV follicular lymphoma.

The primary endpoint was the time to treatment failure defined as above.
Secondary endpoints were the response rate, response duration and overall survival.

Study treatments:
- CHOP regimen:
  cyclophosphamide: 750 mg/m² IV day 1
  doxorubicin: 50 mg /m² IV day 1
  vincristine: 1.4 mg/m² (not exceeding 2mg/²) IV day1
  prednisone: 100 mg/m²/day, days 1-5
  One cycle every 21 days with a maximum of 6-8 cycles
- MabThera 375 mg/m^2 combined with the CHOP regimen (R-CHOP) administered on D1 of each cycle

Results:

The median age was 54 years in the R-CHOP group and 57 years in the CHOP group.
After a median follow-up of 18 months, the median time to treatment failure was not reached in the R-CHOP group and was 31.2 months in the CHOP group.
The overall response rate was 96% in the R-CHOP group vs 90% in the CHOP group (p=0.011). The median response duration was not reached in the two groups.
The estimation of overall survival rate at 2 years was 95% in the R-CHOP group vs 90% in the CHOP group (p=0.016).

Study OSHO-39

A phase III, randomised, open-label comparison of the efficacy and safety of chemotherapy combining MabThera with the MCP regimen (R-MCP) with MCP alone, in patients with previously untreated stage III or IV follicular lymphoma, lymphoplasmocytic lymphoma or mantle cell lymphoma.

Study treatments:
- MCP regimen:

mitoxantrone: 8 mg/m², IV days 1 and 2
chlorambucil 3 mg/m² per os t.i.d., day 1 to 5
prednisolone 25 mg/m²/day, days 1 to 5
One cycle every 28 days with a maximum of 8 cycles

- MabThera 375 mg/m² combined with the MCP regimen (R-MCP) administered on D2 of each cycle.

The primary endpoint was the response rate (complete and partial).
Secondary endpoints were progression-free survival, overall survival, event-free survival, response duration and time to change of treatment.

The statistical hypothesis and main analysis only concerned follicular lymphoma and only these results are reported (N=201).

Results:

The median age was 60 years in the R-MCP group and 57 years in the MCP group. A total of 201 patients were enrolled in the study.
The median study follow-up was 47 months.
The overall response rate (primary endpoint) was 92% in the R-MCP group vs 75% in the MCP group (p=0.0009). The median response duration was not reached in the R-MCP group and was 35 months in the MCP group.
The median progression-free survival was not reached in the R-MCP group and was 28.8 months in the MCP group.
Median event-free survival was not reached in the R-MCP group and was 28.8 months in the MCP group.
The median time to a change in treatment was not reached in the R-MCP group and was 29.4 months in the MCP group.
The estimation of overall survival rate at 4 years was 87% in the R-MCP group vs 74% in the MCP group (p=0.0096).

Study FL-2000

This was a phase III, randomised, open-label comparison of the efficacy and safety of MabThera combined with the CHVP-interferon regimen (R-CHPV- IFN) versus CHVP-interferon alone, in 358 patients with previously untreated stage II to IV follicular lymphoma.

Study treatments:
- CHVP-interferon regimen:

cyclophosphamide: 600 mg/m² IV day 1
doxorubicin: 25 mg/m² IV day 1
etoposide: 100 mg/m² IV day 1
prednisone: 40 mg/m²/day, days 1-5

One cycle every 28 days (for the first 6 cycles, then every 56 days for the following 6 cycles).
Interferon-α2b: 4.5 MIU (3 MIU in patients aged 70 years or more), 3 times weekly, SC, for 18 months

- MabThera 375 mg/m² combined with the CHVP-interferon regimen (R-CHVP-INF) administered on days D1 and D8 of cycles 3 and 4 and D1 of cycles 5 and 6 of chemotherapy. Only 6 cycles every 28 days with MabThera.

The primary endpoint was the event-free survival defined as in the previous studies, by time to treatment failure.

Secondary endpoints were progression-free survival, overall survival, event-free survival, response duration and time to change of treatment.

Results:

The median age of the study patients was 60 years. The median study follow-up was 42 months.
The median event-free survival (primary endpoint) was not reached in the R-CHVP-interferon group and was 36 months in the CHVP-interferon group.
The overall response rate was 94% in the R-CHVP-interferon group vs 85% in the CHVP-interferon group.
The estimation of overall survival rate at 3.5 years was 91% in the R-CHVP-interferon group vs 84% in the CHVP-interferon group (p=0.029).

3.2. Adverse effects

Safety data were obtained from two of the published studies (GLSG'00 and OSHO-39) and in pivotal study M39021 (data not provided in study FL-2000).
The most frequent adverse events in patients receiving rituximab were hypersensitivity reactions and other infusion-related reactions (rash, rigors, (flu-like symptoms etc.) and leukopenia/neutropenia.
Only 2 treatment discontinuations due to an acute infusion-related reaction were reported in study GLSG'00 and one grade-3 reaction was reported in study OSHO-39. In the pivotal study, 9% of patients in the rituximab group had an acute grade 3 or 4 reaction. The other events that were more frequent (all grades together) in the groups containing rituximab with a difference in incidence > 2% were infections, fever, cardiac arrhythmias, neurological disorders and bone pain.

In study GLSG'00. a higher incidence of cardiac events (arrhythmia and heart failure) was observed in the MabThera group, compared with the control group (3% versus 1%). This difference was not found in the other studies.

3.3. Conclusion

Roche submitted additional 53-month (4.4 years) follow-up data concerning the pivotal study M39021 in first line treatment of follicular lymphoma. This study was examined on 8 June 2005 by the Committee after a median follow-up of 30 months.
These results obtained with a longer follow-up confirm than MabThera combined with CVP chemotherapy increased the time to treatment failure (primary endpoint) compared to CVP chemotherapy alone (27 months versus 6.6 months, $p<0.0001$); they also showed a difference between the two groups for overall survival (secondary endpoint) (80.9% versus 71.1%, $p= 0.029$) at 53 months.

The dossier also comprised three randomised studies that made it possible to extend the use of MabThera to chemotherapy combinations other than the CVP regimen.
An improvement was observed in each of the three studies in the efficacy endpoints and in particular the response rate, progression-free survival and overall survival estimated after 2, 3 or 4 years depending on the study. The median follow-up in these studies was from 18 to 47 months.

The most frequent adverse events in patients receiving rituximab were hypersensitivity reactions and other infusion-related reactions (rash, rigors, flu-like symptoms etc.) and leukocytopenia/neutropenia.

Overall, these data confirm the value of adding MabThera to chemotherapy for first-line treatment of follicular lymphoma. As the length of follow-up in the studies provided was limited (4.4 years) in comparison with median survival which is now 8 - 10 years, no definite conclusions may be made about overall survival.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Follicular non-Hodgkin's lymphoma is a slowly progressing, life-threatening disorder with a median survival of 8 to 10 years;
The efficacy/safety ratio is high;
MabThera is intended for first-line curative treatment;
There are alternative drugs and a non-pharmacological treatment comprising haematopoietic stem cell transplantation;

Public health benefit:

Follicular lymphoma is a serious and life-threatening disorder that progresses slowly. It constitutes a moderate public health burden. The patients concerned by the indication represent a low public health burden because of their small numbers.

The need for the improved management of follicular lymphoma comes within the scope of an identified public health priority (GTNDO[4]).

This review of new clinical trial data shows that the addition of MABTHERA to chemotherapies may be expected to have a moderate impact on the morbidity and mortality associated with follicular lymphoma.

Consequently, the proprietary product MABTHERA is expected to have a public health benefit. This benefit is small on the population health outcome.

The actual benefit is substantial.

4.2. Improvement in actual benefit

In the treatment of previously untreated stage III-IV follicular lymphoma, MabThera in combination with chemotherapy provides a major improvement in actual benefit (level I) in terms of efficacy compared to chemotherapy alone.

4.3. Therapeutic use

Follicular lymphoma often progresses slowly and may be compatible with a normal life even without treatment for several months or years. The median survival is now approximately 8 to 10 years.
However it cannot be cured by any treatment including autograft-supported dose-intensification chemotherapy.
The criteria leading to institution of treatment are signs of clinical progression (inflammatory syndrome, repercussion on general status evaluated by the WHO performance status score) and the existence of a large tumour mass. Treatment then comprises chemotherapy adapted to the patient's age and the size of the tumour mass.
Although the conventional CHOP combination, primary therapy for lymphomas, is still used (sometimes at lower doses in elderly subjects), because of its rapid efficacy, other treatments with a higher efficacy/toxicity ratio such as the CVP combination (in which doxrubicin, the most toxic drug, is removed from CHOP) or combinations using fludarabine are more often prescribed.

[4] National Technical Group for Definition of Public Health Goals

Finally, during recent years, the addition of interferon-alpha has improved response rates and relapse-free survival of follicular NHL in combination with a CHVP-type chemotherapy (similar to CHOP, but with reduced doses) and even the overall survival (although this result was not confirmed by other studies), but this treatment is often poorly tolerated, and certain patients must stop it prematurely.
Chemotherapy alone is no longer the reference strategy today.
The combination of MabThera with standard first-line chemotherapy represents the first-line treatment of choice[5].
Once remission has been induced by chemotherapy, the patient is monitored until a new relapse occurs justifying resumption of treatment. A change of cytotoxic drug may then be tried and this may again induce a remission, though the resistance to treatment increases with the number of relapses.

4.4. Target Population

In 2005, the incidence of non-Hodgkin's lymphoma was estimated to be 10,000 cases per year[6].
Follicular lymphoma accounts for 20 to 30% of non-Hodgkin's lymphoma in Europe[7]. In nearly 80% of cases, the diagnosis is made at stage III-IV[8].

The target population of MABTHERA in the treatment of patients with previously untreated stage III-IV follicular lymphoma is 1,600 to 2,400 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicinal products approved for use in hospital in this extension of indication.

[5] ESMO; Newly diagnosed follicular lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol 2007; 18 (Suppl. 2): i63-i64.
[6] InVS, HCL, Francim, INCa: Présentation des dernières données d'incidence et de mortalité par cancer en France et des tendances des 25 dernières années (1980-2005) – Press Conference of 21 February 2008
[7] Solal Celigny P et al. "Follicular lymphomas". In: Solal Celigny P et al. "Lymphomas" 3rd, Frison-Roche, Paris 1997:171-203
[8] Horning SJ. Follicular lymphoma: have we made any progress ? Ann Oncol. 2000;11 Suppl 1:23-7