HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

17 September 2008

MABCAMPATH 30mg/ml, concentrate for dilution for infusion
Pack of 3 vials (CIP: 565 837.1)

Applicant: BAYER SANTE – Division Bayer Schering Pharma

Alemtuzumab

List I

Medicinal product with restricted prescription:
Hospital prescription.
To be prescribed only by oncologists or haematologists, or doctors competent in oncology.
Medicinal product requiring specific monitoring during treatment.
The first dose must be given in the hospital.

ATC Code: L01XC04

Date of MA and its variations: 6 July 2001 (centralised procedure)
19 December 2007: extension of indication (centralised procedure)

Proprietary medicine included on the list of medicines approved for use by hospitals

Reason for request: change in the wording of the indication to encompass use in first-line treatment of B-cell chronic lymphocytic leukaemia.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Alemtuzumab*
*humanised IgG1 kappa monoclonal antibody.

1.2. Indication

Previous wording:
“MabCampath is indicated in the treatment of chronic lymphoid leukaemia (LLC) in patients exposed to alkylating agents and who did not show a complete or partial response to fludarabine phosphate or in whom this type of treatment only produced a short remission (less than 6 months)”.

Extension of indication (new wording)
“MabCampath is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) for whom fludarabine combination chemotherapy is not appropriate."

1.3. Dosage

“MabCampath should only be administered under the supervision of a physician experienced in the use of cancer therapy.
MabCampath solution must be prepared according to the instructions provided. All doses should be administered by intravenous infusion over approximately 2 hours.
Patients should be premedicated with oral or intravenous steroids, an appropriate antihistamine and analgesic, 30-60 minutes prior to each MabCampath infusion during dose escalation and as clinically indicated thereafter.
Antibiotics and antivirals should be administered routinely to all patients throughout and following treatment.
During the first week of treatment, MabCampath should be administered in escalating doses: 3 mg on day 1, 10 mg on day 2 and 30 mg on day 3 (assuming that each dose is well tolerated). Thereafter, the recommended dose is 30 mg daily administered 3 times weekly on alternate days up to a maximum of 12 weeks.
In most patients, dose escalation to 30 mg can be accomplished in 3-7 days. However, if acute moderate to severe adverse reactions occur due to cytokine release (hypotension, rigors, fever, shortness of breath, chills, transient skin rashes and bronchospasm) at the 3 mg or 10 mg dose levels, then those doses should be repeated daily until they are well tolerated before further dose escalation is attempted.
Median duration of treatment was 11.7 weeks for first line patients and 8.0 weeks for previously treated patients.
MabCampath should be discontinued and the patient monitored once all laboratory and clinical criteria for a complete response are met.
If a patient improves (i.e. achieves a partial response or disease stabilization) and then reaches a plateau without any further improvement for 4 weeks or more, then MabCampath should be discontinued and the patient monitored. Treatment should be discontinued if there is evidence of disease progression.
In the event of serious infection or severe haematological toxicity, MabCampath should be interrupted until the event resolves. It is recommended that MabCampath should be interrupted in patients whose platelet count falls to < 25.000/µl or whose absolute neutrophil count (ANC) drops to < 250/µl. MabCampath may be reinstituted after the infection or toxicity has resolved. MabCampath should be permanently discontinued if autoimmune anaemia or autoimmune thrombocytopenia appears. The following table summarises the recommended procedure following the occurrence of haematological toxicity while on therapy:

Haematological toxic effect (platelets < 25 000/µl and/or ANC < 250/µl)	Reinstitution of MabCampath
First occurrence	After resolution, resume at 30 mg*
Second occurrence	After resolution, resume at 10 mg*
Third occurrence	Permanently discontinue treatment
In case of a decrease of ANC and/or platelet count ≤ 50% from baseline value in patients starting treatment with a baseline ANC ≤ 500/µl and/or baseline platelet count of ≤ 25.000/µl	Withhold treatment with MabCampath. When ANC and/or platelet count returns to baseline values, resume treatment with MabCampath*.

*If treatment was withheld for more than 7 days, MabCampath must be reinstituted by dose escalation.

There are no dose modifications recommended for severe lymphopenia given the mechanism of action of MabCampath.

Children and adolescents (below 17 years of age):
No studies have been conducted (see section 4.4). MabCampath is not recommended for use in the paediatric age group.

Elderly (over 65 years of age):
Recommendations are as stated above for adults. Patients should be monitored carefully.

Renal or hepatic impairment:
No study has been conducted in this patient population.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2008 Classification

L01XC04

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic drugs
L01XC	Monoclonal antibodies
L01XC04	Alemtuzumab

2.2. Medicines in the same therapeutic category

No other monoclonal antibody is indicated in the treatment of B-cell chronic lymphocytic leukaemia.

2.3. Medicines with a similar therapeutic aim

Antineoplastic medicinal products indicated in the treatment of B-CLL that may be prescribed as first-line treatment. According to the guidelines of the European Society for Medical Oncology 2008[1] these treatments are:

- FLUDARA (fludarabine), as monotherapy or in combination with ENDOXAN (cyclophosphamide)
- CHLORAMINOPHENE (chlorambucil)

1 Eichhorst B, Hallek M, Dreyling M: Chronic lymphocytic leukemia: ESMO clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology, 19. may 2008

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The laboratory submitted a phase III study (CAM307), comparing the efficacy of alemtuzumab (MabCampath) with that of chlorambucil (Chloraminophene) in first-line treatment of chronic lymphocytic leukaemia (CLL). This study was demanded by the CHMP when marketing approval was granted for MabCampath in 2001.

3.1.1 Method

- Study design: open-label, randomised study,
- Primary efficacy endpoint: progression-free survival, defined as the time between randomisation and first documented disease progression or death from whatever cause. A blinded review of the response was made by an Independent Response Review Panel: (IRPP),
- Secondary endpoints
    - Overall survival, defined as the time from randomisation to death from whatever cause.
    - Complete response rate and overall response rate (complete response + partial response) evaluated according to criteria defined by the National Cancer Institute Working Group (NICWG – 1996)[2],
    - Response duration (evaluated by the expert panel from the date of the best response to treatment),
    - Time to treatment failure, defined as the time from the date of randomisation to the date of disease progression or death from whatever cause, or premature trial discontinuation because of adverse effects.
    - Time to use of an alternative treatment,
- Statistical methods
    - The difference between treatments for progression-free survival was evaluated by the log-rank test, stratified for Rai stage (I-II or III-IV). Analyses were performed on an intention-to-treat basis.
    - The calculated sample size required to demonstrate a difference of 50% between treatments for progression-free survival, with a power of 80% and an α risk of 5%, was 142 per group.

[2] **Complete response**: no detectable disease [on clinical examination or CT-scan: no lymphadenopathy and hepatomegaly or splenomegaly; no B symptoms; normal CBC (platelets > 100 x 10^9/L; polymorphonuclear leukocytes > 1.5 x 10^9 /l; Hb > 11.0 g/dl (not transfused)]
Partial response: reduction of 50% or more in the lymphocyte count compared to screening visit; reduction of 50% or more in lymphadenopathy and size of liver and spleen (if hepatomegaly or splenomegaly at screening); and at least one of the following parameters (platelets > 10 x 10^9 /l or 50% improvement compared to screening; polymorphonuclear leukocytes > 1.5 x 10^9 /l or 50% improvement compared to screening; Hb > 11.0 g/dl (not transfused) or 50% improvement compared to screening)
Disease progression: an increase of at least 50% in the combined size of at least two enlarged lymph nodes or detection of new enlarged lymph nodes; increase of 50% or more in the size of the liver or spleen or detection of hepatomegaly or splenomegaly during the clinical examination; increase of 50% or more in circulating lymphocyte count to at least 5 x10^9 /L; transformation of the disease (Richter's syndrome or prolymphocytic leukaemia with more than 55% of prolymphocytes).

- Inclusion criteria
  - Previously untreated patients, with stage I to IV CLL according to the Rai[3] staging system, in progression and requiring treatment,
  - Histologically confirmed diagnosis of B-cell CLL with CD5, CD19 or CD23 markers.
- Treatment
  - Alemtuzumab was administered by the IV route. The starting dose was 3 mg and this was increased to 10 mg then 30 mg according to the tolerability of treatment. It was then continued at a dosage of 30 mg, 3 times weekly. The total duration of treatment was 12 weeks including the dose-escalation period. Treatment was stopped if no signs of CLL were detected in blood and bone marrow tests by flow cytometry, if there was no improvement after 4 to 8 weeks of treatment or if treatment was interrupted for more than 4 weeks for intolerance.

    Concomitant treatments: patients received premedication by diphenhydramine and paracetamol, at least before the first injection and before each dose escalation. If the prevention of side effects was insufficient, meperidine or hydrocortisone IV could be used. Patients also had to receive anti-infective prophylaxis: trimethoprim/sulfametoxazole and famciclovir during treatment and for at least 2 months after the last dose.
  - Chlorambucil was administered orally, at the dose of 40mg/m² body surface area, once every 28 days. Treatment was repeated for a maximum of 12 cycles. Treatment was stopped in the case of complete remission or if a response reached a plateau (stability for 2 months)
  - In the 2 groups, treatment had to be stopped in the case of disease progression or unacceptable toxicity.
- Patient follow-up

  Patients had to be followed up each month until the occurrence of disease progression, a change in CLL treatment or for 18 months following the administration of the first dose of treatment. Follow-up was performed every 3 months if there was no progression at 18 months (until progression or the need for a change in CLL treatment) and for the patients whose disease progressed during the study. All randomised patients had to receive long-term follow-up to evaluate survival.
- Study schedule:
  - Inclusions: December 2001 to July 2004
  - Last dose of treatment administrated: May 2005
  - Stop of data collection: June 2006

[3] **Stage 0:** isolated blood and marrow lymphocytosis; **stage I:** high lymphocyte count + enlarged lymph nodes; **stage II:** high lymphocyte count + splenomegaly and/or hepatomegaly; **stage III**: high lymphocyte count + anaemia; **stage IV:** high lymphocyte count + thrombocytopoenia. Rai et al, Blood 1975. 46:219-34

3.1.2 Results

- Baseline patient characteristics

Table 1: Baseline characteristics

	Alemtuzumab (n=149)	**Chlorambucil (n=148)**
Gender		
Male	106 (71.1%)	107 (72.3%)
Female	43 (28.9%)	41 (27.7%)
Age-group		
< 65	96 (64.4%)	96 (64.9%)
≥ 65	53 (35.6%)	52 (35.1%)
Age (years)		
Mean (standard deviation) [range]	59.8 (9.92) [35. 86]	59.2 (10.70) [36. 83]
Rai Stage (expert panel)		
0	4 (2.7%)	1 (0.7%)
I	50 (33.6%)	54 (36.5%)
II	43 (28.9%)	42 (28.4%)
III	24 (16.1%)	25 (16.9%)
IV	26 (17.4%)	24 (16.2%)
Missing	2 (1.3%)	2 (1.4%)

- Primary efficacy endpoint: progression-free survival (ITT analysis)

Fifteen patients were censored on D1, including 9 patients evaluated at stage 0 or with a diagnosis of B-cell CLL that was not confirmed by the expert panel.
Overall 193 disease progressions or deaths were recorded, including 2 in stage 0 patients with a diagnosis of B-cell CLL that was not confirmed by the expert panel. The analysis of progression-free survival was based on the evaluation of eligibility made by the expert panel (Rai stage and diagnosis of B-CLL) and was therefore performed on 191 identified events in stage I-IV patients.

Table 2: Progression-free survival

	Alemtuzumab (n=149)	**Chlorambucil (n=148)**
Number of events (progression or death)	82	109
Median* progression-free survival in months (95% CI) [range]	14.6 (12.3; 21.7) [0.6; 25.1]	11.7 (9.9; 13.2) [0.3; 27.9]
% of censored data	45	26.4
Statistical significance†	p = 0.0002‡; p = 0.0001§	
Hazard Ratio (95% CI) ||	0.58 (0.435; 0.775) ‡; 0.58 (0.431; 0.768) §	

*: Kaplan-Meier method; CI: confidence Interval; †: treatments were compared using the log-rank test and the missing stages were taken into account; ‡: Non-stratified; §: Stratified on Rai stage: ||: hazard ratio calculated with the Cox model stratified or not according to the Rai stage; missing stages (table 1) were taken into account;

- Secondary endpoints (ITT analyses)

  - Overall survival

No significant difference was observed between groups for overall survival; 24 deaths were observed in each group with 83.9% of censored data with MabCampath and 83.8% with chlorambucil.

- Complete response rate and overall response rate (complete response + partial response evaluated by the expert panel) (table 3)

Table 3: Response rate

Response	Alemtuzumab (n=149)	Chlorambucil (n=148)
Complete* n (%) (95% CI)	36 (24.2%) (17.5%, 31.8%)	3 (2.0%) (0.4%; 5.8%)
Partial n † (%)	88 (59.1%)	79 (53.4%)
Overall n (%)‡ (95% CI)	124 (83.2%) (76.2%, 88.8%)	82 (55.4%) (47.0%; 63.6%)

*p<0.0001 exact Fisher test; †: NS; ‡ p<0.0001,Chi ^{2} test

The complete response and overall response rates were significantly higher in the group treated with alemtuzumab.

- Overall response duration (complete response + partial response evaluated by the expert panel) (table 4)

Table 4: Overall response

	Alemtuzumab (n=149)	Chlorambucil (n=148)
Number of overall responses n	124	82
Median duration*, in months (95% CI) [range]	16.2 (11.5; 23.0) [0.7; 23.7]	12.7 (10.2; 14.3) [3.7; 48.9]
% of censored data†	46.0	34.1

*: Kaplan-Meier method; †: data for 7 patients whose Rai I-IV stage was not confirmed by the expert panel (2 complete responses and 5 partial responses) were censored on D1

No statistically significant difference was observed between the two groups.

- Time to treatment failure (table 5)

Table 5: Treatment failure

	Alemtuzumab (n=149)	Chlorambucil (n=148)
Number of treatment failures	96	115
Median duration*, in months (95% CI) [range]	9.8 (7.8; 13.4) [0.3; 22.3]	11.3 (9.3; 12.9) [0.2; 27.9]
% of censored data	35.6	22.3
Hazard Ratio (95% CI)†	0.82 (0.625; 1.079) ‡; 0.82 (0.624; 1.077) §	

*: Kaplan-Meier method; †: Hazard Ratio calculated with the Cox model, including missing stage data; ‡: Non-stratified; §: stratified on Rai stage.

No statistically significant difference was observed between the two groups.

- Time to alternative therapy

Table 6: Time to alternative therapy,

	Alemtuzumab (n=149)	Chlorambucil (n=148)
Alternative therapy n (%)	59 (39.6%)	86 (58.1%)
Median time* † (95% CI) [range] months	23.3 (20.7; 31.0) [0.6; 31.0]	14.7 (12.6; 16.8) [0.4; 29.9]
Statistical significance	p=0.002 †; p=0.001‡	
% of censored data§	56.4	37.2
Hazard Ratio (95% CI) ||	0.55 (0.398; 0.753; 0.54 (0.391; 0.742)	

*: Kaplan-Meier method; †: treatments were compared with the log-rank test, non stratified; ‡, stratified on Rai stage; §: data for 9 patients whose Rai I-IV stage was not confirmed by the expert panel on D1; ||: Hazard Ratio calculated with the Cox model, including missing stage.

The median time to alternative therapy was statistically longer in the group treated with alemtuzumab.

Overall:
This study showed a significant difference in favour of alemtuzumab for the primary endpoint: median progression-free survival (14.6 months versus 11.7 months).
For the secondary endpoints, a significant difference in favour of alemtuzumab was observed for the complete response rates (36% versus 3%), global response (83.2% versus 55.4%) and median time to alternative therapy (23.3 months versus 14.7 months). The study did not show a significant difference between groups for overall survival, total response duration (complete response +partial response) and time to treatment failure.

3.2. Safety

3.2.1 Exposure

The safety analysis concerned patients who received one of the study treatments at least once i.e. 147 in each group.

- In the group treated by alemtuzumab, the distribution of administered doses was as follows:

Table 7: Alemtuzumab, doses administered:

Doses administered	Number of patients (%)
Patients not reaching the 30 mg dosage	4/147 (2.7%)
Patients who received 1 to 9 doses of 30 mg	14/147 (9.5%)
10 to 20 doses	24/147 (16.3%)
21 -30 doses	30/147 (20.4%)
>30 doses	75/147 (51%)

The median cumulative dose was 956 mg and the median treatment duration was 11.7 weeks.

- In the group treated by chlorambucil, the distribution of administered cycles was as follows:

Table 8: Chlorambucil, cycles administered,

Number of cycles	Number of patients (%)
1	5/147 (3.4%)
2	13/147 (8.8%)
3	20/147 (13.6%)
4	10/147 (6.8%)
5	12/147 (8.2%)
6	5/147 (3.4%)
7	12/147 (8.2%)
8	9/147 (6.1%)
10	10/147 (6.8%)
11	8/147 (5.4%)
12	43/147 (29.3%)

The median cumulative dose was 515 mg and the median number of cycles administered was 7.

3.2.2 Adverse effects

- All adverse events had to be collected during treatment and for one month after treatment. Unresolved serious adverse events, infections and treatment-related adverse effects also had to be collected for 6 months after the end of treatment.

- The most frequent adverse effects considered to be related to treatment (table 9) were, in the group treated by alemtuzumab: fever, viraemia or CMV infection, chills, urticaria, hypotension and rashes; in the group treated with chlorambucil: nausea and vomiting.

Excepting cytomegalovirus infections, the rate of infections was similar in the 2 groups (45.6% in the alemtuzumab group and 50.3% in the chlorambucil group). However, it should be pointed out that viraemia may have been detected more frequently in the alemtuzumab-treated group as the PCR test for CMV planned in the protocol, was performed weekly with alemtuzumab and monthly with chlorambucil.

Some adverse effects with alemtuzumab were related to the infusions: fever, chills, urticaria, hypotension, nausea, skin rashes, dyspnoea, vomiting, diarrhoea and bronchospasm. These adverse effects were more frequent after the first doses.

Table 9: Adverse effects, with an frequency > 5%, noted during the study

	Alemtuzumab (n=147)	**Chlorambucil (n=147)**
MedDRA preferred terms	**n (%)**	**n (%)**
Fever	94 (63.9%)	5 (3.4%)
Cytomegalovirus viraemia	79 (53.7%)	10 (6.8%)
Chill	74 (50.3%)	-
Urticaria	22 (15.0%)	1 (0.7%)
Hypotension	21 (14.3%)	-
Nausea	19 (12.9%)	51 (34.7%)
Cytomegalovirus infection	19 (12.9%)	-
Rash/eruption	18 (12.2%)	1 (0.7%)
Neutropenia	13 (8.8%)	2 (1.4%)
Hypertension	12 (8.2%)	-
Tachycardia	12 (8.2%)	-
Vomiting	10 (6.8%)	27 (18.4%)
Headaches	11 (7.5%)	5 (3.4%)
Dyspnoea	10 (6.8%)	-
Fatigue	9 (6.1%)	7 (4.8%)
Thrombocytopenia	8 (5.4%)	7 (4.8%)

- Haematological toxicity was noted in the 2 treatment groups. The frequency of neutropenia was higher in the alemtuzumab-treated group. The frequency of thrombocytopenia and anaemia was similar in the 2 groups (table 10).

Table 10: Adverse effects, with grade > 3 and frequency ≥ 3 %, noted during the study

	Alemtuzumab (n=147)	**Chlorambucil (n=147)**
MedDRA preferred terms	**n (%)**	**n (%)**
Fever	12 (8.2%)	-
Neutropenia	11 (7.5%)	2 (1.4%)
Thrombocytopenia	8 (5.4%)	6 (4.1%)
Cytomegalovirus infection	6 (4.1%)	-
Cytomegalovirus viraemia	6 (4.1%)	-
Chill	5 (3.4%)	
Anaemia	3 (2%)	5 (3.4%)

- Serious adverse events were more frequent in the alemtuzumab-treated group (table 11). For the serious adverse effects, only CMV viraemia and infections were more frequent in the group treated with alemtuzumab (table 12).

Table 11: Serious adverse effects, with a frequency ≥ 3%, noted during the study*

	Alemtuzumab (n=147)	**Chlorambucil (n=147)**
MedDRA preferred terms	**n (%)**	**n (%)**
Cytomegalovirus viraemia	16 (10.9%)	-
Pneumonia	10 (6.8%)	5 (3.4%)
Cytomegalovirus infection	8 (5.4%)	-
Fever	8 (5.4%)	2 (1.4%)

*These events were grade 1 to 3

Table 12: Serious adverse effects, with a frequency ≥ 3%, noted during the study*

	Alemtuzumab (n=147)	**Chlorambucil (n=147)**
MedDRA preferred terms	**n (%)**	**n (%)**
Cytomegalovirus viraemia	16 (10.9%)	-
Cytomegalovirus infection	8 (5.4%)	-

*These events were grade 1 to 3

- Treatment was stopped because of the occurrence of an adverse event in 33 patients in the alemtuzumab group and 17 in the chlorambucil group.

- Forty-eight deaths were recorded during the study: 24 in the alemtuzumab-treated group and 24 in the chlorambucil-treated group. A single death in the chlorambucil-treated group was considered by the investigator to be related to treatment.

3.2.3 Safety of alemtuzumab in previously treated patients

- The marketing authorisation of MabCampath distinguishes between undesirable effects observed in first-line patients (see above) and those observed in previously treated patients such as:

- Very common grade 3 or 4 infections
- Common severe bleeding

- Moreover, alemtuzumab was the object of an “letter to prescribers” from AFSSAPS in February 2008 reporting 6 deaths of infectious origin occurring during a clinical study carried out in B-CLL patients treated by alemtuzumab for consolidation after obtaining a remission with fludarabine and rituximab combination chemotherapy. This letter specified that this was an off-label treatment, that should not therefore be used outside a clinical study.

Overall:
In patients receiving first-line treatment, adverse effects were globally more frequent in the alemtuzumab-treated group. Treatment was stopped because of the occurrence of an adverse event in 33 patients in the alemtuzumab group and 17 in the chlorambucil group. The number of deaths was the same in the 2 groups.

In addition, the MA of MabCampath mentions adverse effects noted in previously treated patients: very common grade 3 or 4 infections and common severe bleeding.

3.3. Conclusion

- A phase III study (CAM307), compared the efficacy of alemtuzumab (MabCampath) with that of chlorambucil (Chloraminophène) during first-line treatment of chronic lymphocytic leukaemia (CLL). This study was demanded by the CHMP when marketing authorisation was granted to MabCampath in 2001.
This was an open-label, randomised study. The primary endpoint was progression-free survival (time from date of randomisation to date of first documented disease progression or death from whatever cause. This study showed a significant difference in favour of alemtuzumab (14.6 months versus 11.7 months) for this endpoint.
For the secondary endpoints, there was a significant difference in favour of alemtuzumab for the complete response rates (36% versus 3%),overall response (complete response + partial response) (83.2% versus 55.4%) and median time to alternative therapy (23.3 months versus 14.7 months). For the other secondary endpoints, the study did not show any difference between the groups: overall response duration, time to treatment failure and overall survival (the EPAR of MabCampath specifies that the demonstration of a benefit in terms of overall survival is not demanded for CLL as no treatment or treatment combination has yet been shown to provide such as benefit in this indication).
Overall, adverse effects were more frequent in the alemtuzumab-treated group with, in particular, infusion-related adverse effects especially during the first doses: fever, chills, urticaria, hypotension, skin rashes, and dyspnoea. Other more frequent adverse effects in the alemtuzumab-treated group were cytomegalovirus infections and viraemia, neutropenia, hypertension and tachycardia. Two serious adverse reactions were more frequent in the alemtuzumab group: cytomegalovirus infections and viraemia.
Adverse effects that were more frequent in the chlorambucil-treated group were nausea and vomiting.
Treatment was stopped because of the occurrence of an adverse event in 33 patients in the alemtuzumab group and 17 in the chlorambucil group.
The number of deaths was the same in the 2 groups.

The MA of MabCampath also mentions adverse effects observed in previously treated patients: very common grade 3 or 4 infections and common severe bleeding.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

- Seriousness of the disease
  Chronic lymphocytic leukaemia is life-threatening; the median survival ranges from 1.5 years to more than 10 years depending on the stage at diagnosis. This disease mainly affects subjects aged over 55 years[4].
- This proprietary medicine is intended to provide curative treatment.
- The efficacy/safety ratio is high.
- Public health benefit: chronic lymphocytic leukaemia (LLC) represents a moderate public health burden.
  Improvement in its management is a public health need lying within the scope of the fight against cancer.

4 Eichhorst B, Hallek M, Dreyling M: Chronic lymphocytic leukemia: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology, 19. may 2008

The available data suggest that alemtuzumab will not have an impact on mortality. Theoretically it should improve morbidity, though a population health outcome improvement is unlikely in real life taking into account the small number of patients concerned, the incidence of adverse effects and the lack of quality-of-life data.
Consequently, MabCampath is not expected to benefit public health.

- Therapeutic use: This proprietary product is intended for first or second-line therapy.
- There are alternative therapies.
- The actual benefit of this proprietary drug is substantial.

4.2. Improvement in actual benefit

Taking into account:

- The size of the observed effect,
- The fact that it is difficult to interpret the effect of treatment because of differences between the two groups for the percentage of censored data and owing to the fact that the study did not specifically include patients for whom fludarabine combination chemotherapy is appropriate,

MABCAMPATH provides a minor improvement in actual benefit (IAB IV) for first-line management of B-cell chronic lymphocytic leukaemia in cases where fludarabine combination chemotherapy is inappropriate.

Reminder:
The Transparency Committee opinion of 9 January 2002 granted MabCampath a high IAB (II) as salvage medication (3rd line chemotherapy after first-line therapy with chlorambucil and fludarabine as 2nd line): “for these patients at a therapeutic dead end (advanced stages of the disease and failure or early relapse after 1st and 2nd-line treatments), the improvement in actual benefit is considered to be substantial”

4.3. Therapeutic use

4.3.1 Therapeutic use[5]

- Symptom-free Binet stages A and B and Rai stages 0, I and II require regular monitoring every 3 months without treatment. Patients with active disease defined by rapid progression (lymphocyte count doubling time less than 6 months), require the same treatment as patients with advanced stage CLL.
- First-line chemotherapy:
  It concerns the advanced stages: Binet stages A and B with symptoms, Binet stage C; Rai stages II with symptoms, Rai stages III-IV.
  Possible treatments are purine analogues (fludarabine) and chlorambucil. Fludarabine is indicated as monotherapy, it is also used in combination with cyclophosphamide. Randomised studies have not currently shown any benefit in terms of overall survival for any of these alternative treatments.
  In patients in good general health, the international guidelines[5] recommend the fludarabine and cyclophosphamide combination as first-line treatment.
  In patients with comorbidities (renal failure in particular), chlorambucil or a reduced dose of fludararabine may be given as monotherapy.

5 Eichhorst B, Hallek M, Dreyling M: Chronic lymphocytic leukemia: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology, 19 May 2008

- Second-line chemotherapy:
  If relapse or progression occurs during the year following treatment or in the absence of response to first-line treatment, the following alternative treatments are possible depending on the nature of the first chemotherapy:
    - Fludarabine or fludarabine-cyclophosphamide (FC) after chlorambucil
    - Fludarabine in combination (FC) ± a monoclonal antibody in resistant patients or patients relapsing after fludarabine.
    - Monoclonal antibody (alemtuzumab) in particular for patients refractory to chemotherapy.
    - Allograft.

4.3.2 Therapeutic use

MabCampath is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is not appropriate.
Such combination chemotherapy is used for first or second-line treatment depending on the case according to ESMO 2008 guidelines.

It should to be noted that the characteristics of patients "for whom fludarabine combination chemotherapy is not appropriate" are not defined in the company's application dossier.

4.4. Target population for first-line treatment

The target population of MabCampath for first-line treatment comprises patients with CLL (Binet stages B and C) for whom fludarabine combination chemotherapy is not appropriate.
According to INVS[6], the estimated number of new cases of CLL was 3224 in 2005. The incidence is increasing very slightly at a rate of 0.6% per year in men and 1.2% in women.
Stages B and C account for approximately 45% of cases[7] i.e. approximately 1450.
As each patient generally receives first-line treatment for less than one year, the number of treated patients will be close to the incident cases.
Cases in which fludarabine combination chemotherapy is not appropriate are mainly chromosome 17 abnormalities, immunoresponsive cancer or severe comorbidities, representing a population of from 400 to 450 patients per year (expert opinion).
According to the literature, chromosome 17 abnormalities are present in 3% to 27% patients depending on the stage of the disease and the existence of resistance to conventional treatment[8]; they are present in 3 to 8% patients receiving first-line treatment (expert opinion); in the study presented by the company (CAM 307), a deletion of chromosome 17 was found in 21 patients out of 297, i.e. 7% of included patients.
The proportion of patients with a cancer diagnosed at the same time as CLL is from 3% to 13.9% depending on the study[9].[10] [11]

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6 INVS – Changes in cancer incidence and mortality in France from 1980 to 2005 - chronic lymphocytic leukaemia - 30 January 2008
7 JL Binet *et al.* A new prognosis classification of chronic lymphocytic leukemia derived from a multivariate analysis. Cancer 1981 Jul 1;48(1):198-206
8 Moreno C, Montserrat E: new prognosis markers in chronic lymphocytic leukemia; Blood review, 2008. 22. 211-219
9 Lauvin R, Le Breton-Kashi Y, Jego P, Grosbois B, Lblay R: Primary malignant tumors (lymphomas excluded) in patients with chronic lymphocytic leukemia. A series of 22 cases from a retrospective sudy of 248 patients. Ann Med Interne (Paris) 1996;.147 (6):389-92
10 Hadnagy C, Marinca E, Macavei I, Sass G. The simultaneous occurrence of chronic lymphatic leukemia with malignant tumors and the lymphatic reaction caused by malignant growths). Folia Haematol Int Mag Klin Morphol Blutforsh, 1986; 113(5):633-7
11 Thurmes P, Call T, Slager S, Zent C, Jenkins G, Schwager S, Bowen D, Kay N, Shanafelt T; Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leuk Lymphoma, 2008; 49 (1): 49-56

The proportion of patients presenting at least one severe comorbidity (including a cancer of whatever type) is estimated to be 46%[6].
It is not possible to evaluate how these different populations overlap.
On this basis, the target population of MabCampath for first-line treatment would be from 400 to 650 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends maintaining inclusion on the list of medicines reimbursed by National Insurance in the marketing authorisation with the new wording of the indication.