HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 October 2010

ARZERRA 100 mg, concentrate for solution for infusion
B/3 (CIP code: 577 117-9)
B/10 (CIP code: 577 118-5)

Applicant: GLAXOSMITHKLINE

Ofatumumab
ATC code: L01XC10

List I

Orphan medicinal product (7/11/2008)

Medicinal product for hospital use only. Prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicinal product requiring special monitoring during treatment.

Date of "conditional" (centralised European) Marketing Authorisation: 19/04/2010

A "conditional" Marketing Authorisation has been granted for this medicinal product.

This means that additional proof is expected for this product. The European Medicines Agency (EMA) will re-evaluate any new information about this medicinal product every year and, if necessary, this SPC will be updated.

Reason for request: Inclusion on the list of medicines approved for hospital use.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Ofatumumab

1.2. Background
Ofatumumab is a human monoclonal antibody which binds to the CD20 antigen.

1.3. Indication
"ARZERRA is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab."

1.4. Dosage
"ARZERRA should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available.

Premedication
Patients should be premedicated 30 minutes to 2 hours prior to ARZERRA infusion according to the following dosing schedule:

Infusion number (dose)	Intravenous corticosteroid dose	Analgesic dose	Antihistamine dose
1 (300 mg)	Equivalent to 100 mg prednisolone	Equivalent to 1000 mg paracetamol	Equivalent to 10 mg cetirizine
2 (2000 mg)	Equivalent to 100 mg prednisolone	Equivalent to 1000 mg paracetamol	Equivalent to 10 mg cetirizine
3-8 (2000 mg)	Equivalent to 0-100 mg prednisolone [a)]	Equivalent to 1000 mg paracetamol	Equivalent to 10 mg cetirizine
9 (2000 mg)	Equivalent to 100 mg prednisolone	Equivalent to 1000 mg paracetamol	Equivalent to 10 mg cetirizine
10-12 (2000 mg)	Equivalent to 50-100 mg prednisolone [b)]	Equivalent to 1000 mg paracetamol	Equivalent to 10 mg cetirizine
[a)] If the second infusion is completed without a severe adverse drug reaction, the dose may be reduced at the discretion of the physician. [b)] If the ninth infusion is completed without a severe adverse drug reaction, the dose may be reduced at the discretion of the physician.			

Dosage
The recommended dose is 300 mg of ofatumumab for the first infusion and 2000 mg of ofatumumab for all subsequent infusions. The infusion schedule is 8 consecutive weekly infusions, followed 4-5 weeks later by 4 consecutive monthly (i.e. every 4 weeks) infusions.

First and second infusions
The initial rate of the first and second infusion of ARZERRA should be 12 ml/hour. During the infusion, the rate should be doubled every 30 minutes to a maximum of 200 ml/hour (see SPC).

Subsequent infusions
If the second infusion has been completed without severe infusion-related adverse drug reactions (ADRs), the remaining infusions can start at a rate of 25 ml/hour and should be doubled every 30 minutes up to a maximum of 400 ml/hour (see SPC)."

"Paediatric population
ARZERRA is not recommended for use in children under 18 years old due to insufficient data on safety and/or efficacy.

Elderly
No substantial differences were seen in tolerance and efficacy related to age. Based on available safety and efficacy data in the elderly, no dose adjustment is required (see SPC).

Renal impairment
No formal studies of ARZERRA in patients with renal impairment have been performed. No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance >30 ml/min) (see SPC).

Hepatic impairment
No formal studies of ARZERRA in patients with hepatic impairment have been performed. However, patients with hepatic impairment are unlikely to require dose modification (see SPC).

Method of administration
ARZERRA is for intravenous infusion and must be diluted prior to administration (see SPC)."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2009)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XC	Monoclonal antibodies
L01XC10	Ofatumumab

2.2. Medicines in the same therapeutic category

Comparator medicinal productsnes
No monoclonal antibody is indicated for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab.

2.3. Medicines with a similar therapeutic aim

Other treatments indicated for chronic lymphocytic leukaemia:
- CHLORAMINOPHENE (chlorambucil)
- FLUDARA (fludarabine)
- LEVACT (bendamustine)
- MABCAMPATH (alemtuzumab), indicated when combination chemotherapy which includes fludarabine is not appropriate
- MABTHERA (rituximab) indicated particularly in combination with chemotherapy for the treatment of patients with chronic lymphocytic leukaemia who have relapsed or are refractory.

The data available on efficacy and tolerance are limited in patients previously treated with monoclonal antibodies including MABTHERA, or in patients who are refractory to an earlier treatment with MABTHERA combined with chemotherapy.
This extension of indication obtained on 21/08/2009 has not so far been the subject of an application for reimbursement.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CVP (cyclophosphamide, vincristine, prednisone) combination chemotherapies, etc.

3. ANALYSIS OF AVAILABLE DATA

The dossier submitted contains 2 studies, a phase I/II study with dose escalation (Hx-CD20-402) and a non-comparative phase II study (Hx-CD20-406).
Only the non-comparative phase II study (Hx-CD20-406)[1] is analysed below.

3.1. Efficacy

Non-comparative phase II study for which the main objective was to evaluate the efficacy of ARZERRA in patients with chronic lymphocytic leukaemia with failure or intolerance of fludarabine and alemtuzumab treatment.

Inclusion criteria:
- patients with CLL requiring treatment,
- refractory to fludarabine (after a minimum of 2 cycles),
- refractory to alemtuzumab (after a minimum of 12 administrations) or ineligible for/intolerant of alemtuzumab (because of bulky lymphadenopathy, > 5 cm),

A patient was regarded as refractory to prior treatment if he/she did not show a partial response or if the disease progressed during treatment or within 6 months after the last administration of fludarabine or alemtuzumab.
- patients 18 or more years old,
- Eastern Cooperative Oncology Group (ECOG) performance score 0-2,
- life expectancy of at least 6 months.

Treatment:
Patients were to receive, after premedication, 12 i.v. infusions of ofatumumab:
- one weekly infusion of ofatumumab for 8 weeks in a dose of 300 mg for the first infusion and 2000 mg for the following ones;
- followed, 4 to 5 weeks later, by a monthly infusion for 4 months in a dose of 2000 mg.

Primary endpoint: percentage overall response (complete + partial response) over a period of 24 weeks evaluated by an independent committee (cf. appendix).

Secondary endpoints including:
- progression-free survival, defined as the time between randomisation and progression or death,
- overall survival, defined as the time between randomisation and death,
- duration of the response, defined as the time between the initial response and the progression of the disease or death,
- time before use of an alternative treatment, defined as the time between randomisation and use of a new treatment for CLL other than ofatumumab.

Results:

The 154 patients who received ofatumumab included 3 subgroups of patients:

- the patients refractory to treatment with fludarabine and alemtuzumab (corresponding to the MA population) (n = 59)
- the patients refractory to fludarabine and ineligible for/intolerant of treatment with alemtuzumab because of bulky lymphadenopathy (n = 79),
- the “others”, corresponding to patients ineligible for/intolerant of treatment with fludarabine and/or alemtuzumab (n = 16).

[1] Wierda WG, Kipps TJ, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. Journal of Clinical Oncology 2010; 28(10):1749-1755.

The median age of the patients was 63 years old with 10% of patients over 75 years old. 34% of patients were in Binet stage B and 58% in stage C.
Among the 151 patients whose cytogenetic data were available on inclusion, chromosome aberrations were detected in 118 patients: deletion of 17p (33 patients), deletion of 11q (50 patients), trisomy 12q (16 patients) and of 13q deletion (19 patients).
Patients had received a median of 5 earlier treatments, mainly alkylating agents (94% of patients), monoclonal antibodies (60%) including rituximab as monotherapy or in combination therapy (57%), purine analogues in combination therapy (81%) and single-agent chemotherapy (68%). In particular, 18% of patients had been treated with the combination fludarabine-rituximab and 29% with fludarabine-cyclophosphamide-rituximab.

The efficacy data presented are the result of an initial interim analysis provided for in the protocol.

Results for the primary endpoint (cf. Table 1):
In the overall study population, the percentage overall response rate was 52%.
In the subgroup of 59 patients refractory to fludarabine and alemtuzumab (corresponding to the MA population), the percentage overall response rate was 58% (34/59), with 0% complete response.

Table 1: Main efficacy results of the study Hx-CD20-406 as a function of the patient subgroups

	Total population n = 154	Patients refractory to treatment with fludarabine and alemtuzumab, (corresponding to the AM population) n = 59	Patients refractory to fludarabine and ineligible for/ intolerant of treatment with alemtuzumab because of bulky lymphadenopathy, n = 79	"Other" patients n = 16
Percentage overall response rate (primary endpoint) [95% CI]	52% (80/154) [41-62]	58% (34/59) [40-74]	47% (37/79) [32-62]	56% (9/16) [24-85x]
Percentage: - complete response - partial response - stable response - progression - response could not be evaluated	1% (1/154) 52% (79/154) 36% (55/154) 7% (11/154) 5% (8/154)	0 58% (34/59) 31% (18/59) 3% (2/59) 8% (5/59)	1% (1/79) 46% (36/79) 41% (32/79) 10% (8/79) 3% (2/79)	0 56% (9/16) 31% (5/16) 6% (1/16) 6% (1/16)
Median progression-free survival [95% CI]	6 months [5.5-7.1]	5.7 months [4.5-8]	5.9 months [4.9-6.4]	8.9 months [3.5-11.8]
Median overall survival [95% CI]	17.1 months [11.1-20.2]	13.7 months [9.4-not assessable]	15.4 months [10.2-20.2]	not assessable

Results for secondary endpoints (cf. Table 1):

In the overall study population:
- the median progression-free survival time was 6 months and the median overall survival time 17.1 months;
- the median duration of the response was 6 months;
- another treatment for CLL was prescribed for 57% of the patients. The median time before this alternative treatment was used was 8.7 months.

In the subgroup of patients refractory to fludarabine and alemtuzumab (corresponding to the MA population):
- the median progression-free survival time was 5.7 months and the median overall survival time 13.7 months;
- the median duration of the response was 7.1 months;
- another treatment for CLL was prescribed for 31 patients (53%). The median time before this alternative treatment was used was 9 months.

Subgroup analyses: in the population specified in the MA (n = 59), multiple efficacy analyses were made, particularly in patients previously treated with rituximab (n = 35) and in those with chromosomal abnormalities: deletions of 17p (n = 17) and 11q (n = 24). No conclusions can be drawn from these analyses which were exploratory.

Monoclonal antibodies are usually used in combination with chemotherapy for the management of CLL. Efficacy data for ofatumumab in combination with chemotherapy are not available.

Other data:
The company quotes in its dossier a retrospective study[2] used to describe the results of different backup treatments (intensive chemotherapies, fludarabine in combination, monoclonal antibodies, single-agent chemotherapy) in 99 patients, 58 of whom were refractory to fludarabine and alemtuzumab and 41 were refractory to fludarabine (patients treated between 1998 and 2006).
The comparison of ofatumumab with these historical data does not allow an unbiased evaluation to be made of the size of the effect. Consequently, it cannot be taken into account by the Committee.

The company has undertaken to carry out:
- a phase IV observational study to obtain additional efficacy and tolerance results for ofatumumab in patients with CLL,
- an open randomised study to evaluate the efficacy and tolerance of ofatumumab versus a treatment of the investigator's choice in patients with CLL refractory to fludarabine with substantial lymphadenopathy (i.e. in a population different to the one currently specified in the MA)[3].

3.2. Adverse effects

The tolerance data are taken from study Hx-CD20-406.

In the overall study population:
Discontinuation of treatment on account of adverse events, whatever the grade, was reported in 14% of patients.
The adverse events which commonly led to discontinuation of treatment were infections (7%), mainly pneumonia and sepsis, including septic shock.
The severe adverse events reported in 53% of patients (82/154) were most commonly:
- bacterial, viral and fungal infections (33%): 18% of patients developed grade 3 and 5% developed grade 4 severe infection. Fatal infections occurred in 10% of patients.
- a total of 40 of the 154 patients (26%) had an infection which necessitated hospitalisation and antibiotic therapy.

[2] Tam CS, O'Brien S, et al. The natural history of fludarabine-refractory chronic lymphocytic leukemia patients who fail alemtuzumab or have bulky lymphadenopathy. *Leuk Lymphoma.* 2007;48:1931-1939.
[3] EPAR ARZERRA, page 61/63, January 2010

- haematological toxicity (12%) such as neutropenia (6%): one patient had neutropenia grade 3 and 8 neutropenia grade 4. Febrile neutropenia was reported in 2 patients (1%).
- general disorders and infusion-related reactions (10%).

In the subgroup of patients refractory to fludarabine and alemtuzumab (corresponding to the MA population):
Discontinuation of treatment for adverse events, regardless of grade, was reported in 20% of patients.
Adverse events which commonly led to discontinuation of treatment were infections (12%), mainly pneumonia and sepsis including septic shock.
The severe adverse events reported in 54% of patients (32/59) were most commonly:
- infections (37%): 17% of patients developed grade 3 and 7% grade 4 severe infections. Fatal infections occurred in 17% of patients.
- a total of 19 of the 59 patients (32%) developed an infection which necessitated hospitalisation and antibiotic therapy.
- haematological toxicity (10%) such as neutropenia (5%): 1 patient developed grade 3 and 2 developed grade 4 neutropenia. No febrile neutropenia was reported.
- general disorders and infusion-related reactions (8%).

3.3. Conclusion

The efficacy and tolerance data for ARZERRA are limited. They are from a non-comparative phase II study which included patients with chronic lymphocytic leukaemia with failure or intolerance to fludarabine and alemtuzumab. These patients had received a median of 5 earlier treatments.
The available results are from an interim analysis of a subgroup of 59 patients refractory to fludarabine and alemtuzumab (corresponding to the MA population) among the 154 included.
The percentage overall response rate over a period of 24 weeks (primary endpoint) was 52% in the overall study population and 58% with a 0% complete response rate in the subgroup specified in the MA.
In the overall study population, the median progression-free survival time was 6 months and the median overall survival was 17.1 months.
In the subgroup refractory to fludarabine and alemtuzumab, the median progression-free survival time was 5.7 months and the median overall survival was 13.7 months.

In the subgroup refractory to fludarabine and alemtuzumab, discontinuation of treatment on for adverse events, regardless of grade, was reported in 20% of patients. Adverse events which commonly led to discontinuation of treatment were infections (12%), mainly the lower respiratory tract infections (pneumonia) and sepsis. The commonest severe adverse events reported in 54% of the patients (32/59) were infections (37%), haematological toxicity (10%) general disorders and infusion-related reactions (8%).

In total, given the current state of the data, the effect size is difficult to assess because of the methodology used, an interim analysis of a subgroup of patients in a non-comparative study and historical comparison with the results of a retrospective study.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic lymphocytic leukaemia (Binet stages B and C) is characterised by the proliferation and accumulation of a malignant clone of mature B line lymphocytes in the bone marrow, blood and lymphoid organs and is life-threatening;

This medicinal product is intended as curative therapy;

In view of the data (efficacy hard to assess in view of the methods used and the non-zero toxicity), the efficacy/adverse effect ratio is low;

Public health benefit:

Chronic lymphocytic leukaemia (CLL) is a moderate public health burden.

Improving its therapeutic management is a public health need falling within the scope of the fight against cancer.

The quality of the data available is not sufficient to allow an evaluation of the impact in terms of mortality of the medicinal product ARZERRA.

ARZERRA could help to meet the public health need identified in patients refractory to treatment with fludarabine and with alemtuzumab.

Overall, the public health benefit of ARZERRA cannot be evaluated in this indication.

At this stage of the disease, there is no alternative drug treatment that has been validated in patients refractory to fludarabine and alemtuzumab. This medicinal product constitutes a salvage treatment.

In view of the limited clinical data obtained from an interim analysis of a subgroup of patients in a non-comparative phase II study and given the absence of any alternative treatment validated in extensively pretreated patients who are refractory to fludarabine and alemtuzumab, the Committee attributes to ARZERRA a moderate actual benefit, on a provisional basis, pending additional data.

4.2. Improvement in actual benefit

In view of the limited clinical data based on:

- efficacy results taken from a subgroup (n = 59) of a non-comparative phase II study,
- a historical comparison with the results of a retrospective study,

it is not possible to assess the therapeutic contribution of this medicinal product.

Consequently, the transparency Committee believes that the medicinal product ARZERRA does not provide any improvement in actual benefit (IAB V) in the management of chronic lymphocytic leukaemia in patients refractory to fludarabine and alemtuzumab, on a provisional basis, pending additional data.

4.3. Therapeutic use

The decision to treat the patient (or to wait) depends on the patient's general condition (age and comorbidities), the stage of the disease and the presence of poor prognostic markers (peripheral lymphocyte doubling time less than 12 months, raised β2-microglobulin, p53 mutation, etc.). Most cases of the disease, i.e. stages A (Binet) or 0, I, II (Rai), are asymptomatic and do not require specific treatment.

When treatment of CLL is undertaken, it primarily is with:

- an alkylating agent: chlorambucil, whether or not combined with corticosteroids, cyclophosphamide
- a purine analogue, particularly fludarabine phosphate (alone or in combination), which can be used as first- or second-line treatment. A recent study showed that treatment with fludarabine alone did not provide any additional benefit in overall survival compared to chlorambucil monotherapy in subjects over 65 years of age[4].

[4] Eichhorst BF, et al; German CLL Study Group (GCLLSG). First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009; 114(16): 3382-91.

- combinations of the COP or CVP type (cyclophosphamide, vincristine, prednisone); CHOP (cyclophosphamide, Adriamycin, vincristine, prednisone)
- a monoclonal antibody (rituximab).

Autologous stem cell transplants may be offered to young subjects who have achieved complete remission.
In patients with few comorbidities, the reference first-line treatment is the combination rituximab + fludarabine + cyclophosphamide (R-FC)[5,6]. In the event of a first late relapse, the initial treatment can be used again. Alemtuzumab is used in cases of refractory disease or early progression, particularly in cases with 17p deletion. For later relapses, other treatments such as bendamustine are used. Preliminary data, not validated by the MA for bendamustine, suggest that bendamustine in combination with rituximab is effective[7]. For a limited number of patients in whom all treatment options have failed, ofatumumab constitutes an option for patients who are refractory to fludarabine and alemtuzumab. Efficacy data for ofatumumab in combination with chemotherapy are not available.

ARZERRA is a salvage treatment for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab.

4.4. Target population

The target population for ARZERRA is patients with CLL, Binet stage B or C who are refractory to fludarabine and alemtuzumab.

In 2005, the incidence of CLL[8] in France was estimated to be 3224 cases. According to the EPAR[9], the estimated prevalence of CLL is 3.5/10,000 i.e. 17,500 adults in France.
Stage B and C account for almost 45% of cases[10] i.e. 7880 patients.
Since no accurate epidemiological data are available on the proportion of patients who are refractory to fludarabine and alemtuzumab, this is estimated to be 1% of the prevalent population (expert opinion).

On this basis, the target population for ARZERRA is estimated to be about 80 patients a year.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

4.5.1 Packaging

The 100 mg vial packaging is not appropriate for the prescription requirements.
The recommended dose according to the SPC is 300 mg ofatumumab for the first infusion and 2000 mg ofatumumab for all subsequent infusions.
The 100 mg vial packaging therefore necessitates the use of 3 vials for the first administration and 20 vials for subsequent administrations.
The company has made a commitment to the EMA to develop a new more appropriate packaging (June 2011).

[5] Eichhorst B, Hallek M, Dreyling M: Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 21 (5): v162-v164, 2010
[6] French Society of Haematology, reference 2009
[7] Fisher, ASH 2009, summary 205; Fisher, ASH 2008, summary 330
[8] Presentation of the most recent data on cancer incidence and mortality in France and the trends over the past 25 years (1980-2005) - Press conference held on 21 February 2008. INVS/Hôpitaux de Lyon/FRANCIM/INCA
[9] EMA, ARZERRA EPAR, 20/01/2010
[10] Binet J.L et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981; 48:198-206.

APPENDIX: Response criteria according to NCIWG 1996 (Cheson et al, 1996)

Parameter	Complete Remission	Partial Remission	Progressive Disease
Lymphocytes	<4.0 x 10^9/L	≥50% reduction from baseline	≥50% increase to at least 5.0 x 10^9/L
Lymphadenopathy	Absence by physical exam	≥50% reduction (physical examination)	≥50% increase for at least 2 weeks or new palpable node ≥1cm
Organomegaly	Normal size spleen and liver by physical exam	≥50% reduction if abnormal at baseline	≥50% increase
Constitutional Symptoms	None	Not defined	Not defined
Neutrophils	≥1.5 x 10^9/L	≥1.5 x 10^9/L or 50% improvement from baseline	Not defined
Platelets	>100 x 10^9/L	>100 x 10^9/L or 50% improvement from baseline	Not defined
Hemoglobin	>11.0 g/dL (untransfused)	>11.0 g/dL or 50% improvement from baseline (untransfused)	Not defined
Bone Marrow	Normocellular for age, <30% lymphocytes, no B-lymphoid nodules.	If done, ≥30% lymphocytes and/or B-lymphoid nodules	Not defined
Response Definition	**All above to be met for at least 2 months. If persistent nodules in bone marrow = nPR**	**Meets criteria for first 3 for at least 2 months, and at least 1 other of above to be met**	**At least 1 of above to be met, or transformation to more aggressive histology**