HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

5 May 2010

ALIMTA 100 mg, powder for concentrate for solution for infusion
Pack of 1 (CIP: 383 080-2)

ALIMTA 500 mg, powder for concentrate for solution for infusion
Pack of 1 (CIP: 565 825-3)

Applicant: LILLY FRANCE

pemetrexed
ATC code: L01BA04

List I
Medicine for hospital prescription only. Prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation (centralised procedure): 20 September 2004 - Amendments: 31 October 2007 – 8 April 2008 – 2 July 2009

Reason for request: Inclusion on the list of medicines approved for hospital use in the extension of indication “as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
pemetrexed

1.2. Indications
"Malignant pleural mesothelioma

ALIMTA in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

ALIMTA in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

ALIMTA is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

ALIMTA is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel."

1.3. Dosage

"ALIMTA as single agent: in patients treated for non-small cell lung cancer after prior chemotherapy, the recommended dose of ALIMTA is 500 mg/m2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01B	Antimetabolites
L01BA	Folic acid analogues
L01BA04	pemetrexed

2.2. Medicines in the same therapeutic category

Comparator medicines
None

2.3. Medicines with a similar therapeutic aim

- GEMZAR (gemcitabine)
- NAVELBINE (vinorelbine)
- TAXOTERE (docetaxel)
- TAXOL (paclitaxel) and its generics
- ADRIBLASTINE (doxorubicin) and its generics
- ELSIDINE (vindesine)
- ENDOXAN (cyclophosphamide)
- HOLOXAN (ifosfamide)
- AVASTIN (bevacizumab)
- CISPLATYL (cisplatin) and its generics
- PARAPLATIN (carboplatin) and its generics [indicated as second-line therapy only]
- TARCEVA (erlotinib) [indicated as second-line therapy only]

3. ANALYSIS OF AVAILABLE DATA

The dossier submitted comprises a pivotal study, H3E-MC-JMEN, the results of which are analysed below.

3.1. Efficacy

Study H3E-MC-JMEN

Phase III randomised double-blind study comparing ALIMTA with placebo in maintenance treatment of patients with locally advanced or metastatic (stage IIIb or IV) non-small cell lung cancer (NSCLC) who had previously received 4 cycles of platinum-based chemotherapy and who did not show progression of the disease.

The patients were assigned at random to two groups that were to receive the following every 3 weeks until progression:
- either Alimta (500 mg/m²) on day 1 of each 21-day cycle + optimal symptomatic treatment
- or placebo (0.9% sodium chloride) + optimal symptomatic treatment

Optimal symptomatic treatment could include, among other things, analgesics, transfusions, pleural tap and/or nutritional support, and also palliative radiotherapy.

Primary endpoint: progression-free survival, defined as the interval between the date of randomisation and the date of observation of (objective) progression or death irrespective of cause.

Note: The main aim of the study was initially to compare overall survival in the 2 treatment groups with a sample size of 660 patients. On 21 February 2007 – during the inclusion period (4 March 2005 to 17 August 2007) – the protocol was amended such that progression-free survival was designated as the primary endpoint and overall survival as the secondary endpoint.

Secondary endpoints:
- overall survival, defined as the interval between randomisation and death irrespective of cause;
- time to progression of the disease, i.e. the interval between the date of randomisation and the date of first observation of disease progression (radiological);
- percentage objective (partial and complete) response rate
- time to worsening of symptoms, i.e. the interval between the date of randomisation and the date of worsening for each of the 9 items on the lung cancer symptom scale. Symptom worsening was defined as an increase of 15 mm on the 100 mm visual analogue scale.
- tolerance.

Inclusion criteria included:
- age $\geq$ 18 years,
- histological or cytological diagnosis of NSCLC of stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or stage IV (metastatic) prior to any therapy;
- prevous induction chemotherapy consisting of one of the following doublets: gemcitabine plus carboplatin or cisplatin, paclitaxel plus cisplatin or carboplatin, docetaxel plus cisplatin or carboplatin;

- documented proof of a tumour response: complete, partial, or disease stable. The tumour response had to have been evaluated between cycle 4 of induction and the date of randomisation.

Results:

The ITT analysis covered 663 patients.
Their median age was 60 years. The majority of the patients were men (72.9%). The general status of all the patients was good (performance index level of 0 to 1).
Nearly a fifth (19%) of the patients was at stage IIIB and 80% were at stage IV. Adenocarcinoma was the commonest histological type found in the two groups (50.3% in the ALIMTA group and 47.7% in the placebo group). Squamous-cell carcinoma was found in 27.5% of the tumour samples.
The induction chemotherapy was a doublet combining a platinum salt with gemcitabine in 58.1% of cases, with paclitaxel in 35.9% of cases, and with docetaxel in 5.9% of cases.

The median progression-free survival (primary endpoint) was 4.27 months in the ALIMTA group versus 2.60 months in the placebo group, i.e. an absolute gain of 1.67 months (HR = 0.50, 95% CI 0.42-0.61, $p < 0.00001$).
Median overall survival was 13.37 months in the ALIMTA group versus 10.58 months in the placebo group, i.e. an absolute gain of 2.79 months (HR = 0.79, 95% CI 0.65-0.95, $p < 0.012$).
The 1-year survival rate was estimated at 55% in the ALIMTA group and 43% in the placebo group.
The percentage objective response rate was 6.8% in the ALIMTA group versus 1.8% in the placebo group, $p = 0.005$.

A subgroup analysis according to histological type (squamous-cell n = 181 and non-squamous-cell n =482) was undertaken. In the subgroup of patients with a non-squamous-cell-type tumour (MA population), the median progression-free survival was 4.5 months with ALIMTA versus 2.6 months with placebo, i.e. an absolute gain of 1.9 months (HR = 0.44, 95% CI 0.36-0.55, $p < 0.00001$). Median overall survival was 15.47 months with ALIMTA versus 10.28 months with placebo, i.e. an absolute gain of 5.19 months (HR = 0.70, 95% CI 0.56-0.88, $p = 0.002$).
The 1-year survival rate was estimated at 60% in the ALIMTA group and 42% in the placebo group. The percentage objective response rate was 7.4% in the ALIMTA group versus 1.9% in the placebo group, $p = 0.018$.

In the subgroup of patients with a squamous-cell-type tumour, ALIMTA did not demonstrate efficacy in comparison with placebo.

LCSS questionnaire data were collected from about half the patients (48.1% of the patients in the ALIMTA group and 54.5% of the patients in the placebo group). They showed an increase in the time to worsening for two items (pain and haemoptysis) out of the nine evaluated on the LCSS, in favour of the ALIMTA group. Similar results were observed in the subgroup of patients with a non-squamous-cell-type tumour.

Salvage chemotherapy was initiated in 51% of the patients in the ALIMTA group and 67% of the patients in the placebo group.

3.2. Adverse effects

In the study, interruption of treatment on account of adverse events occurred in 7.9% of the ALIMTA group as opposed to 2.3% of the placebo group. Of the events that were possibly connected with the treatment, 2.3% were linked to a decrease in renal function in the ALIMTA group.

No patients in the placebo group showed a serious adverse event, as opposed to 5% (n = 22) in the ALIMTA group. The reported events were mainly haematological (anaemia, febrile neutropenia, and thrombocytopenia) and infectious (pneumonia, erysipelas, urosepsis, and oral candidiasis) in nature.

3.3. Conclusion

A phase III randomised double-blind study compared ALIMTA with placebo in maintenance treatment of patients with locally advanced (stage IIIb) or metastatic (stage IV) non-small cell lung cancer who had previously received 4 cycles of platinum-based chemotherapy and who did not show progression of the disease.
The median progression-free survival (primary endpoint) was 4.27 months in the ALIMTA group versus 2.60 months in the placebo group, i.e. an absolute gain of 1.67 months (HR = 0.50, 95% CI 0.42-0.61, $p < 0.00001$).
Median overall survival was 13.37 months in the ALIMTA group versus 10.58 months in the placebo group, i.e. an absolute gain of 2.79 months (HR = 0.79, 95% CI 0.65-0.95, $p < 0.012$). The percentage objective response rate was 6.8% in the ALIMTA group versus 1.8% in the placebo group, $p = 0.005$.
A subgroup analysis according to histological type (squamous-cell and non-squamous-cell) was undertaken. In the subgroup of patients with a non-squamous-cell-type tumour (MA population), the median progression-free survival was 4.5 months with ALIMTA versus 2.6 months with placebo, i.e. an absolute gain of 1.9 months (HR = 0.44, 95% CI 0.36-0.55, $p < 0.00001$). Median overall survival was 15.47 months with ALIMTA versus 10.28 months with placebo, i.e. an absolute gain of 5.19 months (HR = 0.70, 95% CI 0.56-0.88, $p = 0.002$).
In the subgroup of patients with a squamous-cell-type tumour, ALIMTA did not demonstrate efficacy in comparison with placebo.

The tolerance profile of ALIMTA was mainly marked by renal and haematological (anaemia and febrile neutropenia) toxicity.

The Committee stresses that the protocol of this study does not permit to give an answer to the question of the benefit of introducing ALIMTA immediately versus delayed therapy in cases of progression in patients who have responded to first-line therapy.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Non-small cell lung cancer (NSCLC) is a life-threatening disease;
These proprietary products are intended for curative treatment;
The efficacy/adverse effects ratio is high;
Public health benefit:

In public-health terms, the burden of locally advanced or metastatic non-small cell lung cancer (NSCLC), in particular in patients who come under the MA indication (namely, cancer other than predominantly squamous cell histology, in patients who have responded or are stable after 1st line platinum-based chemotherapy) is moderate. This is because this cancer, which is relatively frequent, is responsible for considerable morbidity/mortality.

Improving the management of lung cancer is a public-health need that constitutes an established priority (Public Health Law 2004[1], Cancer Plan , GTNDO[2]). Despite the existence of the current treatment possibilities, there is a considerable public-health need in respect of this disease, in that patients rapidly fail.

On the basis of the available clinical data (improvement of progression-free survival and overall survival in a trial of ALIMTA in maintenance treatment versus placebo-usual treatment strategy), it is expected that the proprietary product ALIMTA will have a small additional impact on NSCLC-related morbidity/mortality in comparison with existing therapies.

The extent to which these results can be carried over into the real-life treatment situation is acceptable.

Thus the proprietary product ALIMTA as maintenance treatment should be able to help meet the identified public-health need.

Consequently, a public-health benefit is expected for the proprietary product ALIMTA in maintenance treatment of advanced or metastatic non-squamous NSCLC. This benefit is slight.

It is a first-line treatment;
There are treatment alternatives;

The actual benefit of ALIMTA is substantial.

4.2. Improvement in actual benefit (IAB)

ALIMTA, as maintenance therapy, brings a minor IAB (level IV) in the MA indication.

4.3. Therapeutic use

Surgery is the treatment of choice for early stages of NSCLC. However, a large proportion of patients are diagnosed at an advanced stage of the disease (about 30% at the locally advanced stage and 40% at the metastatic stage), and the early stage accounts for only about 25 to 30%.
The standard first-line treatment for patients with advanced-stage disease consists in bitherapy based on a platinum salt (cisplatin or carboplatin) in combination with gemcitabine or vinorelbine or docetaxel or paclitaxel or pemetrexed only in the non-squamous type. The

[1] Loi de santé publique [Public Health Law] 2004 – No. 2004-806 of 9 August 2004: objective: malignant tumours [rapport_DREES_indicateurs - July 2005]
[2] *Groupe Technique National de Définition des Objectifs [National technical group for the setting of public-health objectives] (DGS [Ministry of Health]-2003)

1-year survival rate reported for these treatments was 31% to 46% depending on the study[3]. Bitherapy based on a platinum salt seems to increase overall survival and the time to treatment failure by about 2 months in comparison with cisplatin monotherapy[4,5]. Antiangiogenic therapy can be combined with chemotherapy in the non-squamous form. However, its use seems to be limited to patients who do not have a tumour situated in contact with the major thoracic vessels and who do not have cerebral metastases.
After remission, obtained generally after 4 to 6 cycles of first-line chemotherapy, patients enter a "treatment break" phase, only going on to receive second-line therapy if the disease progresses. In this strategy, less than 50% of patients given first-line therapy and relapsing after the "treatment break" are then eligible for another line of treatment[6].
Maintenance monotherapy with bevacizumab can be offered in patients who have received bevacizumab in combination with induction chemotherapy.
ALIMTA monotherapy for maintenance therapy of locally advanced or metastatic non-squamous NSCLC immediately after platinum-based chemotherapy is a new method of treatment; it can only be offered for patients who have not previously received first-line ALIMTA.
In the absence of direct comparisons, the place of ALIMTA remains to be clarified in the following cases:

- as immediate treatment after induction chemotherapy versus delayed treatment
- as maintenance treatment in comparison with AVASTIN.

4.4. Target population

The target population for ALIMTA is patients with stage IIIb and IV non-squamous non-small cell lung cancer who have previously received 4 cycles of platinum-based chemotherapy (without ALIMTA) and do not show progression of the disease.

In the projections for the year 2009 made by the Institut de Veille Sanitaire [French Insitute for Public Health Surveillance], the incidence of lung cancer in France is put at 34,500 new cancer cases per year[7].
80 to 85% of these are non-small cell lung cancer (NSCLC) cases, which, based on a figure of 83% (KBP French lung-cancer cohort followed up in 2000)[8], is 28,640 new cases per year.
On initial diagnosis of the disease, it is estimated that:

- 63% (18,050 patients) are non-operable stage IIIb and IV cases,
- 35% (10,590 patients) are patients with advanced localised cancer eligible for initial treatment with surgery or radiotherapy, but that 40% of these will relapse (4230 patients) and be eligible for systemic therapy.

Thus, 22,280 patients are potentially eligible for first-line treatment for stage IIIb and IV NSCLC.
Approximately 60%, or 13,400, of the NSCLC cases in France are histologically of the non-squamous type.
It is estimated that about half, or 6700, of these patients (expert opinion) would not be treated with ALIMTA as first-line therapy.

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[3] Suresh Ramalingam and Chandra P. Belani. Systemic Chemotherapy for Advanced Non-Small Cell Lung Cancer: Recent Advances and Future Directions. The Oncologist 2008;13(suppl 1):5–13

[4] Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: A Southwest Oncology Group study. J Clin Oncol 1998;16:2459-65

[5] Sandler A. B, Nemunaitis J, Denham C, et al. Phase III Trial of Gemcitabine Plus Cisplatin Versus Cisplatin Alone in Patients With Locally Advanced or Metastatic Non–Small-Cell Lung Cancer. J Clin Oncol 2000;18:122-30

[6] Hensing et al. Factors associated with the likelihood of receiving second line therapy for advanced non-small cell lung cancer. Lung Cancer 2005;47:253-59

[7] http://www.invs.sante.fr/applications/cancers/projections2009/rapport_projections_nationales_cancer_2009.pdf

[8] Blanchon F, Grivaux M, Collon T, Zureik M, Barbieux H, Bénichou-Flurin M, Breton JL, Coëtmeur D, Delclaux B, Asselain B, Piquet J. Epidémiologie du cancer bronchique primitif pris en charge dans les centres hospitaliers généraux français. *Rev Mal Respir* 2002;19:727-34

A tumour response or stabilisation is observed in 40% and 60%[9,10,11] of patients after first-line therapy, which is 2680 to 4020 patients eligible for maintenance therapy with ALIMTA.
The target population for ALIMTA in this indication extension is thus estimated at 2700 to 4000 patients 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 this extension of indication.

[9] Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-98
[10] Brodowicz T et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006;52:155-63
[11] Fidias et al, Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009; 27:591-8.