HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

OPINION

26 November 2008

ALIMTA 100 mg, powder for concentrate for solution for infusion (CIP 383 080-2) Pack of 1
ALIMTA 500 mg, powder for concentrate for solution for infusion (CIP 565 825-3) Pack of 1

Applicant: LILLY FRANCE

pemetrexed

ATC code: L01BA04

List I

Medicine for hospital prescription only. Can only be prescribed by oncologists or haematologists, or physicians competent in oncology. Medicinal product requiring specific monitoring during treatment.

Date of Marketing Authorisation 20 September, 2004 - Variations: 31 October 2007 - 8 April 2008 (centralised procedure)

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the extension of indication for first line treatment of non-small cell lung cancer
and
change in the wording of the indication for second-line treatment which is now restricted to patients with non-small cell lung cancer "other than predominantly squamous cell histology".

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-naive 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.

Reminder: the previous wording for second-line treatment was as follows: "Alimta is indicated as monotherapy in the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy."

1.3. Dosage

"ALIMTA in combination with cisplatin: The recommended dose of ALIMTA is 500mg/m^2 of body surface area administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75mg/m^2 of body surface area infused over 2 hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin (see also cisplatin Summary of Product Characteristics for specific dosing advice).

ALIMTA as single agent: in patients treated for non-small cell lung cancer after prior chemotherapy, the recommended dose of ALIMTA is 500mg/m^2 of body surface area 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 (2008)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01B	Antimetabolites
L01BA	Folic acid analogue
L01BA04	Pemetrexed

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

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

3. ANALYSIS OF AVAILABLE DATA

The file submitted by the company was examined in two parts:

- An extension of indication as first-line treatment of non-small cell lung cancer other than predominantly squamous cell histology
- A change in the wording of the indication for second line treatment in non-small cell lung cancer other than predominantly squamous cell histology (indication already included on the list of medicines approved for use in hospitals).

3.1. Efficacy

A/ Extension of indication as first-line treatment of non-small cell lung cancer other than predominantly squamous cell histology

This extension of indication is based on data from the pivotal study H3E-MC-JMDB the results of which are analysed below.

Study H3E-MC-JMDB[1]

A randomised, open-label phase III study comparing Alimta plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with locally advanced or metastatic (stage IIIb or IV) NSCLC.

Design:
The primary study analysis was a non-inferiority analysis of overall survival.
The statistical analysis was based on the following assumption: non-inferiority is established if the upper limit of the 95% confidence interval of the relative risk is below 1.176.

Patients were randomly assigned to two groups to receive every 3 weeks, with a maximum of 6 treatment cycles:
- either Alimta (500 mg/m²) + cisplatin (75 mg/m²); 21-day cycle (D1)
- or gemcitabine (1250 mg/m²) + cisplatin (75 mg/m²); 21-day cycle (D1 and D8)

Primary efficacy endpoint: overall survival defined as the time between random randomisation and death from any cause.

Secondary endpoints:
- Progression-free survival: Time from the date of randomisation to the date of first observed disease progression (clinical or objective) or death from any cause;
- Time to disease progression i.e. time from the date of randomisation to the date of first observed disease progression (clinical or radiological);
- Treatment response duration, i.e. the time between the first documented objective response and the date of first observed disease progression or date of death from any cause;
- Time to treatment failure i.e. the time between the date of randomisation and the date of the following events: death, withdrawal from study, progression (clinical or radiological) or discontinuation of treatment;
- Objective response rate;
- Safety.

[1] Scagliotti G V et al**.** Phase III study comparing cisplatin plus gemcitabine With cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non–small-cell lung cancer. JCO Early Release, published online ahead of print May 27 2008. Journal of Clinical Oncology, 10.1200/JCO.2007.15.0375

Results:

The ITT analysis concerned 1,725 patients and the PP analysis 1,666 patients.
The median age was 61 years.
Most patients were men (70.1%). All the patients had a good general health status (performance status from 0 to 1).
Approximately one quarter of patients was at stage IIIb and three quarters at stage IV.
Adenocarcinoma was the most frequently observed histological type in the two groups (50.6% in the Alimta group and 47.6% in the Gemzar group). Squamous cell carcinoma was detected in nearly 30% of tumour specimens.

Table 1: Overall survival of patients in the two trial arms (ITT and PP)

	ITT		PP	
	Alimta cisplatin N=862	Gemzar cisplatin N=863	Alimta cisplatin N=838	Gemzar cisplatin N=828
Median overall survival (months) 95% CI	10.28 [9.82; 11.24]	10.28 [9.56; 10.91]	10.38 [9.82; 11.30]	10.45 [9.72; 11.14]
Probability of survival (%) at:				
6 months	73.05	72.61	73.79	73.72
12 months	43.48	41.94	43.84	42.52
18 months	26.16	24.56	26.52	24.88
24 months	18.94	13.98	19.20	14.20
Unadjusted Hazard Ratio (HR) 95% CI p (non-inferiority)	0.93 [0.83-1.04] <0.0001		0.93 [0.84-1.04] <0.0001	
Adjusted Hazard Ratio * (HR) 95% CI p (non-inferiority)	0.94 [0.84-1.05] <0.0001		0.94 [0.84-1.05] <0.0001	

Adjusted HR and p values were calculated using a Cox model, taking into account the treatment and 4 cofactors: ECOG PS, gender, disease stage and diagnostic test (histology or cytology).

The primary efficacy analysis was based on the ITT population.
For the ITT population, the median overall survival was 10.28 months in the Alimta - cisplatin group and 10.28 months in the gemzar – cisplatin group.
The hazard ratio (HR) was 0.93 with an upper limit of the 95% confidence interval of 1.04 which was therefore lower than the limit of 1.176 planned in the protocol.
Similar results were observed in the PP population: HR = 0.93 with an upper limit of the 95% confidence interval of 1.04.

The progression-free survival and overall response rate were similar in the two groups: the median progression-free survival was 4.8 months with Alimta - cisplatin vs 5.1 months with gemcitabine - cisplatin (RR 1.04; 95% CI 0.94 - 1.15), and the overall response rate was 30.6% (95% CI 27.3 - 33.9) with Alimta - cisplatin vs 28.2% (95% CI 25.0 - 31.4). The duration of response was 4.5 months in the Alimta - cisplatin group vs 5.1 months in the gemcitabine - cisplatin group.

A subgroup analysis of overall survival, planned in the protocol, was performed. The following factors were taken into account: disease stage, performance status, gender, disease stage and basis for diagnosis (cytology or histology), smoking history, age, ethnic origin and squamous cell histology or not.
The effect of Alimta - cisplatin treatment was similar to that of gemcitabine-cisplatin in all patients' subgroups except in the histology-ic subgroups.
In the subgroup of patients with squamous cell carcinoma, the non-inferiority of Alimta - cisplatin was not demonstrated because the upper limit of the 95% CI of the HR was superior to the non-inferiority margin of 1.176. Since squamous cell carcinoma patients represented one third of the patients in the two groups (453/1725), the efficacy results did not validate the use of the Alimta - cisplatin combination in this population. The non-inferiority of Alimta - cisplatin was demonstrated in the subgroup of patients with non-squamous cell carcinoma (adenocarcinoma or large cell carcinoma).

Table 2: Survival results by histology subgroups

Histology subgroups	Median overall survival (months)				Adjusted relative risk (95% CI)	Superiority p value
	Alimta+cisplatin		Gemcitabine+cisplatin			
Adenocarcinoma (n=847)	12.6 (10.7 - 13.6)	n=436	10.9 (10.2 - 11.9)	n=411	0.84 (0.71-0.99)	0.033
Large cells (n=153)	10.4 (8.6 - 14.1)	n=76	6.7 (5.5 - 9.0)	n=77	0.67 (0.84-0.96)	0.027
Others (n=252)	8.6 (6.8 – 10.2)	n=106	9.2 (8.1 – 10.6)	n=146	1.08 (0.81-1.45)	0.586
Squamous cells (n=473)	9.4 (8.4 – 10.2)	n=244	10.8 (9.5-12.1)	n=229	1.23 (1.00-1.51)	0.050

The Committee underlines that the protocol of this non-inferiority study does not allow conversion into a superiority analysis all the more as this was a subgroup analysis (histological type). These results may therefore only be considered as an indication.

In comparison with the gemcitabine-cisplatin group, patients treated by Alimta-cisplatin required fewer red blood cell transfusions (16.1% versus 27.3%, p<0.001) and platelet transfusions (1.8% versus 4.5%, p=0.002). Patients also required less administration of erythropoietin (10.4% versus 18.1%, p<0.001), G-CSF/GM-CSF (3.1% versus 6.1%, p=0.004), and iron preparations (4.3% versus 7.0%, p=0.021).

3.2. Adverse events

In the study, the number of treatment discontinuations for serious adverse effects considered to be related to the treatment was 1.8% in the Alimta-cisplatin group and 2.8% in the gemcitabine-cisplatin group.
Grades 3-4 neutropenia were observed in 15.1% of cases with Alimta-cisplatin and 26.7% with gemcitabine-cisplatin. Grades 3-4 thrombocytopenia were observed in 4.1% of cases with Alimta - cisplatin and 12.7% with gemcitabine - cisplatin.
The incidence of increased creatinine of all grades was of 10.1% in the Alimta - cisplatin group and 6.9% in the gemcitabine - cisplatin group. The incidence of acute renal insufficiency was of 0.6% in the Alimta - cisplatin group and 0% in the gemcitabine - cisplatin group.
Nine (1.1%) treatment-related deaths were listed for the Alimta - cisplatin group and 6 (0.7%) for the gemcitabine - cisplatin group.
There was no difference in the safety profile of Alimta plus cisplatin between histology subgroups.

3.3. Conclusion

In a comparative study (pivotal study H3E-MC-JMDB) in 1,725 chemonaive patients with locally advanced or metastatic non-small cell lung cancer, the primary analysis confirmed the non-inferiority of Alimta combined with cisplatin compared to gemcitabine combined with cisplatin.
Subgroup analysis showed that Alimta - cisplatin and gemcitabine - cisplatin had similar effects in patient subgroups (disease stage, patient performance status, gender, disease stage and basis for diagnosis (cytology or histopathology), smoking history, age, ethnic origin and squamous or non-squamous histology) except for the subgroup of patients with squamous cell tumours.
In the subgroup of patients with squamous cell carcinoma, the non-inferiority of Alimta - cisplatin compared to gemcitabine - cisplatin was not demonstrated. Since patients with squamous cell carcinoma represented one third of patients in the two groups (453/1,725), the efficacy results did not validate the use of the Alimta - cisplatin combination in this population. The non-inferiority of Alimta - cisplatin was demonstrated in the subgroup of patients with an adenocarcinoma or large cell carcinoma.
The safety profile was different between the two treatments with in particular more frequent haematological adverse effects in the gemcitabine group and more frequent renal adverse effects in the Alimta group.

B/ Change in the wording of the already listed indication (second-line treatment of non-small cell lung cancer)

The initial wording of the indication for pemetrexed (Alimta) was: “Alimta is indicated as monotherapy in the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.” This indication was based on the results of the pivotal study H3E-MC-JMEI evaluated by the French Transparency Committee in March 2005.
Recent publications have reported the reduced efficacy of Alimta in the case of hyper-expression of thymidate synthetase (Sigmond, 2003; Giovannetti 2005). This hyper-expression is more frequent in squamous cell tumours. In light of these data, a retrospective analysis of study H3E-MC-JMEI was performed integrating the histological type of the tumour (squamous or non-squamous histology).

1/ Summary of study H3E-MC-JMEI data:

Randomised, open-label, non-inferiority study comparing Alimta (500 mg/m^2 every 3 weeks) with docetaxel (75 mg/m^2 every 3 weeks) in patients with inoperable, locally advanced or metastatic (Stage IIIb or IV) non-small cell lung cancer after prior first-line chemotherapy. All the patients in the Alimta group received vitamin supplements.
This was a study of overall survival, and the upper limit of the Hazard Ratio had to be lower than 1.11 from a Cox model with treatment as single independent variable. Secondary endpoints were time to progression, progression-free survival, objective response rate, duration of response, time to treatment failure, quality of life and toxicity.
An analysis by Rothmann's method based on historical data was decided during the study, in which a HR<1.21 would represent an efficacy equal to at least 50% of that observed with docetaxel during the historical comparison with supportive care.

Efficacy results:
According to the preplanned analysis criteria (fixed margins), the results do not demonstrate the non-inferiority of Alimta compared to docetaxel: the upper limit of the Hazard Ratio was 1.20 which was therefore above the protocol-fixed non-inferiority margin.
Analysis with the Rothmann method suggests that the quantitative effect of Alimta is between 52% and 157% of that of docetaxel.

Safety results:
In comparison with docetaxel, grade III and IV haematological adverse effects were less common in the Alimta group with in particular fewer cases of neutropenia (5.3% and 40.2%) and febrile neutropenia (1.9% and 12.7%). The frequency of other grade III and IV adverse effects was similar in the two groups, except for the rise in hepatic transaminases and more frequent thrombocytopenia in the Alimta group and more frequent diarrhoea and alopecia in the docetaxel group. The most frequent adverse effects (> 10%) of Alimta monotherapy were haematological and gastrointestinal effects, fatigue, skin rash and desquamation.

2/ Results of the post-hoc analysis:

The objective of this retrospective analysis was to test for an interaction between the efficacy of Alimta and tumour histology (squamous or non-squamous) and if such an interaction exists, analyse the effect of chemotherapies on overall survival and progression-free survival by histological type.
The analysis confirmed the existence of a significant interaction between tumour histology (squamous versus non-squamous) and the treatment effect. The results suggested:
- in the group of patients with predominantly non-squamous cell histology tumour, a higher efficacy of pemetrexed (Alimta) compared to docetaxel (Taxotere) in terms of overall survival and progression-free survival;
- in the group of patients with squamous cell histology tumour, a higher efficacy of docetaxel (Taxotere) compared to Alimta in terms of overall survival and progression-free survival;
- A similar efficacy of docetaxel (Taxotere) regardless of the histological type of the tumour.

In light of these data on the different tumour histological types, the wording of the indication for Alimta as second-line treatment was modified by restricting it to patients with non-squamous non-small cell lung cancer.
The committee took this opportunity to underline the importance of performing this targeted analysis in patients with non-squamous cell carcinoma.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Non-small cell lung cancer (NSCLC) is a life-threatening disorder;
These proprietary products are intended as curative treatment;
Their efficacy/adverse effects ratio is high;
They are used as first- and second-line therapy;
There are alternative drugs available.

Public health benefit

In terms of public health, the burden of locally advanced or metastatic non-small cell lung cancer (NSCLC), in particular in the patients concerned by the MA indication (namely, cancer of other than predominantly squamous cell histology), is high. This cancer has a relatively high incidence and a high morbidity and mortality.

The improved management of lung cancer is a public health need established in the scope of identified priorities (GTNDO[2] for the management of cancer). Although treatments currently exist, there is a large therapeutic public health need in this disease as patients rapidly fail treatment.

However, currently available data are insufficient and it is impossible to conclude that ALIMTA may have an additional impact on NSCLC-related morbidity and mortality compared to existing therapies. Moreover, there are no available data that allows the assessment of the impact of this proprietary medicine might have on quality of life.

ALIMTA should not therefore address an identified public health need.

Consequently, ALIMTA is not expected to provide a public health benefit in the treatment of advanced or metastatic non-squamous NSCLC.

The actual benefit of Alimta is substantial.

4.2. Improvement in actual benefit

In the treatment of non-small cell lung cancer of other than predominantly squamous cell histology,

- As first-line treatment and in combination with cisplatin, Alimta provides no improvement in actual benefit (IAB V) compared to gemcitabine (GEMZAR).
- As second-line treatment and as monotherapy, Alimta provides no improvement in actual benefit (IAB V) compared to docetaxel (TAXOTERE).

4.3. Therapeutic use

Surgery is the treatment of choice for the early stages of NSCLC. However, a high proportion of patients are diagnosed at an advanced stage of the disease (approximately 30% at a locally advanced stage and 40% at the metastatic stage) and the early stage accounts for only 25 to 30% of patients.

Standard first-line treatment of patients with advanced disease consists in bitherapy containing a platinum salt (cisplatin or carboplatin) combined with gemcitabine, vinorelbine, docetaxel or paclitaxel. The 1-year survival rate reported with these treatments was from 31% to 46% depending on the study[3]. Bitherapy containing a platinum salt compared to cisplatin monotherapy seems to increase overall survival and time to treatment failure by

[2] National Technical Group for Defining Public Health Objectives (DGS-2003)

[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.

approximately 2 months[4,5]. An anti-angiogenic treatment may be combined with chemotherapy for the non-squamous form. However its use seems to be limited to patients who do not have a tumour in contact with the large vessels of the chest or do not have brain metastases.
Pemetrexed (Alimta) combined with a platinum salt as first-line treatment represents a new alternative treatment for NSCLC with non-squamous histology.

4.4. Target Population

The target population of Alimta is represented by patients with locally advanced or metastatic non-small cell lung cancer of other than predominantly squamous cell histology for whom 1st or 2nd line chemotherapy is indicated.
The following information was used to calculate the size of this population:
The last estimation of the incidence of lung cancer in France was made in 2005 by the Health Monitoring Institute and the Francim network, who noted 30,650 new cases per year (InVS, 2008).
Among those, between 80 and 85% are non-small cell cancers (KBP French lung cancer cohort follow up in 2000) (Blanchon, 2002), 25,440 new cases per year.

At initial diagnosis of the disease, it may be estimated that:
- 65% (16,536 patients) are at the inoperable stages IIIb and IV,
- 35% (8,904 patients) patients have locally-advanced cancer and are eligible for initial management by surgery or radiotherapy. However the disease will relapse in 2 out of 5 of these patients (3,560 patients) who will be eligible for systemic treatment.

Hence, 20,000 patients are potentially eligible for first-line treatment for stage IIIb and IV lung cancer.
More that half (53%) of NSCLC have a predominantly non-squamous cell histology,
The number of patients with locally advanced or metastatic non-small cell lung cancer with a predominantly non-squamous cell histology in whom 1st or 2nd line chemotherapy is indicated may be estimated to be 10,600 per year.

Updating of the target population for second-line treatment:
Approximately 60% (expert opinion) of patients who have received first-line treatment (10,600 patients),will relapse and become eligible for second-line chemotherapy for locally advanced or metastatic disease i.e. 6,400 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in this extension of indication.

[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;16:2459-2465

[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. Journal of Clinical Oncology, Vol 18. Issue 1 (January), 2000: 122