HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

4 November 2009

IRESSA 250 mg film-coated tablets
Pack of 30 (CIP: 395 950-7)

Applicant: ASTRAZENECA

gefitinib

List I
Medicine for hospital prescription only. To be prescribed only by oncologists, haematologists, or doctors competent in oncology.
Medicinal product requiring special surveillance during treatment.

Date of MA (European centralised procedure): June 24, 2009

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
gefitinib

1.2. Background
Gefitinib is a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. It is active against tumours with activating mutations of EGFR tyrosine kinase.

1.3. Indication

“IRESSA is indicated for adults in the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK”.

1.4. Dosage

“Treatment with IRESSA must be initiated and monitored by a physician experienced in the use of cancer treatments.
The recommended dosage of IRESSA is one 250 mg tablet per day. Patients forgetting to take a dose should take it as soon as they remember. If the next dose is due in less than 12 hours, patients must not take the forgotten dose. Patients must not take a double dose (two doses at once) if they forget a dose”.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L	Antineoplastic and immunomodulatory agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XE	Tyrosine kinase inhibitors
L01XE02	gefitinib

2.2. Medicines in the same therapeutic category

Comparator medicines

In second and third-line treatment, TARCEVA (erlotinib), whose indication is the following:
"treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) refractory to at least one prior chemotherapy regimen.
When prescribing Tarceva, factors associated with prolonged survival should be taken into account.
The treatment has not demonstrated any benefit in terms of survival or other clinically significant effects in patients with EGFR-negative tumours".

2.3. Medicines with a similar therapeutic aim

- ALIMTA (pemetrexed)
- GEMZAR (gemcitabine)
- NAVELBINE (vinorelbine)
- TAXOTERE (docetaxel)
- TAXOL (paclitaxel) and its generics
- ADRIBLASTIN (doxorubicin) and its generics
- ELSIDINE (vindesine)
- ENDOXAN (cyclophosphamide)
- HOLOXAN (ifosfamide)
- AVASTIN (bevacizumab)
- CISPLATYL (cisplatin) and its generics
- PARAPLATIN (carboplatin) and its generics [indicated only in second-line treatment]

3. ANALYSIS OF AVAILABLE DATA

The application includes three phase III clinical studies:
- IPASS study in first-line treatment of non-small cell lung cancer (NSCLC)
- ISEL and INTEREST studies in patients with previously treated NSCLC.

3.1. Efficacy

A/ First-line treatment

IPASS open-label, randomised study, conducted in Asia, comparing IRESSA to the carboplatin/paclitaxel combination in patients with locally advanced or metastatic NSCLC (stage IIIb or IV) with adenocarcinoma-type histology, previously untreated.

Inclusion criteria included:
- former light smokers (stopped ≥ 15 years and fewer than 10 pack years) or non-smokers
- performance status 0 to 2
- life expectancy ≥ 12 weeks

Patients were randomised into two groups to receive:
- either IRESSA, one 250 mg tablet daily until progression
- or paclitaxel (200 mg/m²) + carboplatin AUC[1] 5 or 6, every 21 days with no more than 6 treatment cycles.

Method:
The primary study analysis was a non-inferiority analysis on progression-free survival.
The statistical analysis was based on the following assumption: non-inferiority was established if the upper 95% confidence interval limit of the relative risk of progression-free survival was below 1.2.
Once non-inferiority was established, a superiority test was foreseen with an upper 95% confidence interval limit not exceeding 1.0 for the HR.

Primary endpoint: progression-free survival defined as the time between randomisation and tumour progression or death regardless of cause.

Secondary endpoints:
- overall survival
- objective tumor response (sum of complete and partial responses according to RECIST criteria)
- quality of life evaluated by Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) and Trial Outcome Index (TOI) scales
- disease-related symptoms evaluated using the Lung Cancer sub-scale (LCS)

Results:
The ITT analysis concerned 1,217 patients and the PP analysis 1,196 patients.
The majority of patients were women (79.3%) and the median age was 57 years. Most patients were non-smokers (93.7%). Approximately one third of patients were stage IIIB and two-thirds (69%) were stage IV.

[1] Due to its specific toxicity on platelet lineage, Calvert defined an area under the curve to be achieved in order to avoid excessive toxicity. In this case the patient is treated with an area under the curve (AUC) intention, expressed in mg/ml x minutes.

Table 1: Progression-free survival of patients in the two trial groups (ITT and PP)

	ITT		PP	
	IRESSA N=609	Carboplatin plus paclitaxel N=608	IRESSA N=597	Carboplatin plus paclitaxel N=580
Median progression-free survival (months)	**5.7**	**5.8**	**NP**	**NP**
Disease progression Number (%)	453 (74.4)	497 (81.7)	446 (74.7)	489 (84.3)
Hazard Ratio (HR) 95% CI p	0.741 [0.651 – 0.845] <0.0001		0.743 [0.652 – 0.848] <0.0001	

NP: not provided in application

The primary efficacy analysis was based on the ITT population.
In the ITT population, the median progression-free survival (primary endpoint) was 5.7 months in the IRESSA group and 5.8 months in the carboplatin+paclitaxel group.
The hazard ratio (HR) was 0.741 with an upper 95% confidence interval limit of 0.845, which was therefore lower than the limit of 1.2 foreseen in the protocol.
Similar results were observed in the PP population: HR = 0.743 with an upper 95% confidence interval limit of 0.848.
As the upper 95% confidence interval limit was below both the non-inferiority and superiority thresholds, IRESSA demonstrated an absolute gain of 0.1 month in terms of median progression-free survival compared to the comparator.
The objective tumor response rates were 43% in the IRESSA group and 32% in the carboplatin+paclitaxel group (p=0.0001).
Median overall survival did not differ between the two groups (18.6 months in the IRESSA group and 17.3 months in the comparator group).
An improvement in the quality of life was demonstrated for the IRESSA group in two of the three scales used (FACT-L and TOI).

A subgroup analysis according to EGFR status involved 437 (36%) of the study patients: 261 with an EGFR mutation and 176 without.
In patients with an EGFR mutation, a gain of 3.2 months in absolute values in progression-free survival was observed in the IRESSA subgroup compared to the comparator group (9.5 months versus 6.3 months; HR = 0.48, 95%CI: 0.36-0.64, p <0.0001).
In patients without EGFR mutation, progression-free survival was lower than in the comparator group, with 1.5 months for IRESSA and 5.5 months for carboplatin+paclitaxel (HR = 2.85, 95%CI[2.05-3.98], p <0.0001).
Tumors response rates were 71.2% in the EGFR mutation subgroup and 47.3% in the comparator subgroup (p=0.0001). In the EGFR mutation-free subgroup, tumor response rates were 1.1% with IRESSA and 23.5% with carboplatin+paclitaxel (p=0.0013).
No difference was observed in the median overall survival of the two subgroups.

B/Previously treated

INTEREST Study

Open-label, randomised study comparing IRESSA to docetaxel in patients with locally advanced or metastatic NSCLC refractory to first or second-line treatment.

Inclusion criteria included:
- progression or relapse after first or second-line chemotherapy including at least one platinum salt-based.
- performance status 0 to 2
- eligible for chemotherapy with docetaxel

Patients were randomised into two groups to receive:
- either IRESSA, one 250 mg tablet daily until progression
- or docetaxel (75 mg/m^2) IV infusion for one hour every 21 days until progression or unacceptable toxicity.

Methods:
The main objective was to compare IRESSA to docetaxel in terms of overall survival.
The protocol foresaw two primary co-analyses:
- to demonstrate the non-inferiority of IRESSA compared to docetaxel in the PP population and if the latter was established, to perform a superiority test in the ITT population.
- to test the superiority of IRESSA in the subgroup of patents with EGFR gene amplification (FISH+).
The non-inferiority was established if the upper limit of the 96% confidence interval of the relative risk was below 1.154.

Primary endpoint: overall survival defined as the time between randomisation and death regardless of cause.

Secondary endpoints:
- progression-free survival
- objective response (sum of complete and partial responses according to RECIST criteria)
- quality of life evaluated by FACT-L and TOI scales
- disease-related symptoms evaluated using LCS
- safety

Results:
A total of 1,466 patients were randomised.
The median age was 61 in the IRESSA group and 60 in the docetaxel group.
Around two-thirds of the patients were men. Almost 84% of the patients were refractory to first-line treatment.
In the PP population (n=1433), median overall survival time were 7.6 months in the IRESSA group and 8.0 months in the docetaxel group (HR = 1.020, [0.905 – 1.150]; p=0.7332).
The upper 96% confidence interval limit was 1,150, therefore lower than the 1.154 foreseen in the protocol. IRESSA therefore demonstrated its non-inferiority compared to docetaxel. However, the objective of superiority compared to docetaxel was not achieved.

The subgroup analysis of patients with a tumour with EGFR mutation concerned 44 (3%) of the 1,466 patients included. No difference was observed in overall survival in the two groups (HR = 0.832 [0.414 – 1.670]; p= 0.6043).
Progression-free survival was 7.0 months, compared to 4.1 months (HR = 0.16 [0.05-0.49]; p=0.0012) and the objective response rates were 42.1% versus 21.1% (p=0.0361).

ISEL study

Randomised, double-blind placebo-controlled study on patients with locally advanced or metastatic non-small cell lung cancer refractory to first or second-line chemotherapy.

Inclusion criteria included:
- progression or relapse after first or second-line chemotherapy of which at least one platinum-salt based.
- performance status 0 to 3
- patients refractory or intolerant to last chemotherapy

Randomisation was conducted according to a ratio of 2:1:
- IRESSA, one 250 mg tablet daily, plus optimal symptomatic treatment, until progression
- placebo plus optimal symptomatic treatment.

Primary endpoint: overall survival defined as the time between randomisation and death regardless of cause.

Secondary endpoints:
- time until treatment fails
- objective response (sum of complete and partial responses according to RECIST criteria);
- quality of life evaluated by FACT-L scale
- disease-related symptoms evaluated using LCS
- safety

Results:
A total of 1,692 patients were randomised.
The median age was 62 in the IRESSA group and 61 in the placebo group.
Around two-thirds of the patients were men. 48.7% of patients were refractory to first-line chemotherapy and 50% to second-line chemotherapy.
Around two-thirds of patients had a performance status of 0 to 1. 80% of cases were at a metastatic stage.
The study's primary objective was not achieved: overall survival did not differ between the two groups (5.6 months in the IRESSA group compared to 5.1 months in the placebo group p=0.087).
The subgroup analysis of patients with a tumour with EGFR mutation concerned 26 (1.5%) of the 1,692 patients included and does not enable any conclusions to be drawn.

3.2. Adverse effects

In the data from phase III studies IPASS, INTEREST and ISEL combined (2,462 patients treated with IRESSA), the most common adverse events, occurring in over 20% of patients, were diarrhoea and skin reactions (rash, acne, dryness of the skin and itching). Around 8% of patients had a grade 3 or 4 adverse event. 3% of patients discontinued treatment due to adverse events.
Interstitial lung diseases occurred in 1.3% of cases. These were often severe (CTC grades 3-4) and fatal.

3.3. Conclusion

In first-line treatment of non-small cell lung cancer, IRESSA was evaluated in a randomised study (IPASS) compared to carboplatin+paclitaxel chemotherapy in patients selected as follows: mainly women, of Asian origin, non-smokers with an adenocarcinoma-type histology.
In the general population, IRESSA demonstrated an absolute gain of 0.1 month (5.8 vs. 5.7 months) in terms of median progression-free survival (primary endpoint) compared to the comparator.
Median overall survival did not differ between the two groups (18.6 months in the IRESSA group and 17.3 months in the comparator group). The overall survival results are not mature (number of events not reached). The quality of life analysis results showed an improvement in the IRESSA group in two of the three scales used (FACT-L and TOI).
A subgroup analysis according to EGFR status involved 36% of the study patients.
In patients with an EGFR mutation, an absolute gain of 3.2 months in progression-free survival was observed for IRESSA compared to the comparator group (9.5 months versus 6.3 months; HR = 0.48, 95%CI: 0.36-0.64, p <0.0001). However, in patients without any EGFR mutation, progression-free survival was lower with IRESSA than in the comparator group (1.5 months for IRESSA and 5.5 months for carboplatin+paclitaxel; HR = 2.85, 95%CI: 2.05-3.98, p <0.0001).

In second-line treatment of the NSCLC, the vast majority of which without any EGFR mutation, IRESSA was evaluated in one randomised study (INTEREST) compared to docetaxel. Non-inferiority was established. However, the objective of superiority compared to docetaxel was not achieved.
The subgroup analysis of patients with a tumour with EGFR mutation concerned 44 of the 1,466 patients included (3%). No difference was observed in overall survival in the two groups.

In second or third-line treatment of the NSCLC, the vast majority of which without any EGFR mutation, IRESSA was evaluated in one randomised placebo-controlled study (ISEL). The study's primary objective was not achieved: overall survival did not differ between the two groups (5.6 months in the IRESSA group and 5.1 months in the placebo group, p=0.087).
The subgroup analysis of patients with a tumour with EGFR mutation concerned 26 of the 1,692 patients included (1.5%) and does not enable any conclusion to be drawn.

The most common adverse events reported with IRESSA, occurring in over 20% of patients, were diarrhoea and skin reactions (rash, acne, dryness of the skin and itching).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Non-small cell lung cancer (NSCLC) is a life-threatening condition;
This product is intended to provide curative treatment;
The efficacy/adverse effects ratio is high;
It is a first, second or third-line treatment;
There are alternative medicines available.

Public health benefit:

In France, lung cancer is the leading cause of cancer mortality in men and the third most common cause in women and is a major public health burden. The burden of locally advanced or metastatic non-small cell lung cancer (NSCLC) (80 to 85% of lung cancers) is high. The burden of the population likely to benefit from IRESSA (patients having a tumour with activating EGFR mutation) can be considered moderate due to the prevalence of activating EGFR mutations, estimated as 16.5% of NSCLC patients in France.

The improvement in the management of cancer patients and their quality of life constitutes a public health need falling within the scope of public health priorities (Public Health Act 2004, Cancer plan, Plan on improvement in quality of life of patients with chronic diseases).

Given the data available from the IPASS clinical study (absolute gain of 3.2 months in progression-free survival and significant improvement in quality of life and disease-related symptoms from subgroup analysis), a moderate impact in terms of morbidity and mortality and quality of life is expected for patients with an activating EGFR mutation given IRESSA in first-line treatment. However, the results from the IPASS study on overall survival will be necessary once follow-up time is sufficient.

Given the more limited data available for second and third-line treatment of patients with an activating EGFR mutation, it is not possible to assume that IRESSA will have any impact on morbidity and mortality and quality of life.

Furthermore, it is not certain whether the trial results can be transposed to clinical practice given the profile of patients included (the majority were of Asian phenotype) and the uncertainty as to whether, prior to prescription, tests for the activating EGFR mutation, to identify potential responders, were actually carried out.

In addition, like oral chemotherapy, IRESSA may have an effect on the way the healthcare system is organised (hospitalisations avoided, management transferred to consultations).

IRESSA is therefore likely to meet an identified public health need.

Consequently, IRESSA is expected to benefit public health in this first-line indication. This benefit is low.

The Committee stresses that in both MA indication subpopulations (2nd and 3rd line), the number of patients with a tumour with an EGFR mutation is very low in the submitted studies. Nonetheless, it grants IRESSA a substantial actual benefit for patients with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK.

4.2. Improvement in actual benefit

In first-line treatment of locally advanced or metastatic NSCLC with activating mutation of EGFR-TK, IRESSA provides a minor IAB (level IV) compared to carboplatin + paclitaxel.

In 2nd or 3rd line treatment of locally advanced or metastatic NSCLC, the data available is limited: fewer than 5% of the patients included in both studies submitted had a tumour with EGFR mutation. Hence, the committee feels that IRESSA does not improve actual clinical benefit (level V) as far as usual management is concerned.

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 the advanced stage of the disease (approximately 30% at a locally advanced stage and 40% at the metastatic stage) and the early stage only concerns 25 to 30% of patients.

Standard first-line treatment in advance-stage patients is dual therapy containing a platinum salt (gemcitabine, vinorelbine, docetaxel, paclitaxel or pemetrexed solely in the non-squamous type combined with cisplatin or carboplatin). The survival rates reported for most of these treatments were 33% for 1 year and 11% for 2 years[2].

Combined therapy compared to single cisplatin therapy appears to increase overall survival and time to treatment failure by approximately 2 months[3][4]. An anti-angiogenic treatment may be added to chemotherapy for the non-squamous form. However its use appears to be limited to patients who do not have a tumour in contact with the large vessels of the chest or brain metastases.

Erlotinib has an MA in the treatment of tumours with EGFR mutation. It is only used after second-line therapy.

Given the data available, IRESSA is a new first-line treatment method for patients with NSCLC where the tumour has an activating EGFR mutation. Its relevance has not been established for patients with an EGFR mutation-free tumour, for which platinum salt-based chemotherapy is the standard treatment. In the absence of comparative data, its relevance compared to erlotinib, particularly in third-line treatment, remains to be seen.

4.4. Target population

The target population of IRESSA is patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR.

The data used to calculate the size of this population is as follows:

The incidence of lung cancer in France was last estimated in 2005 by the Health Monitoring Institute (InVS) and the Francim network, who noted 30,650 new cases per year (InVS, 2008).

80 and 85% of these were non-small cell cancers (KBP French lung cancer cohort followed up in 2000)[5], i.e. 25,440 new cases per year.

At initial diagnosis of the disease, it may be estimated that:

- 65% (16,536 patients) are at inoperable stages IIIB and IV,

[2] 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.

[3] 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.

[4] 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;18:122-130.

[5] F. Blanchon F, Grivaux M, Collon T, Zureik M, Barbieux H, Benichou-Flurin M, et al. Epidémiologie du cancer bronchique primitif pris en charge dans les centres hospitaliers généraux français. Etude KBP-2000-CPHG du Collège des Pneumologues des Hôpitaux Généraux (CPHG). Rev Mal Respir 2002; 19:727-34.

- 35% (8,904 patients) have localised cancer and are eligible for initial management by surgery or radiotherapy. However, 2 out of every 5 patients (3,560 patients) will relapse and will be eligible for systemic treatment.

Hence, 20,000 patients are potentially eligible for first-line treatment for stage IIIB and IV lung cancer.

The activating mutation of EGFR is found in 16.5% of cases[6].

Hence, the target population of IRESSA in first-line treatment can be estimated as 3,300 patients per year.

According to the docetaxel clinical trial data, the failure rate in first-line treatment is around 70%[7] (used in combination with cisplatin) and is in line with the failure rate seen in the IPASS study (response rate observed in 32% of patients on carboplatin+paclitaxel). There is no precise data on the percentage of patients refractory to second-line chemotherapy who may be treated again with chemotherapy. If we consider that all patients refractory to first-line treatment will be eligible for second-line treatment, this number of patients can be estimated as 2,300 per year.

Overall, the target population for IRESSA in the MA's indication can be estimated as 5,600 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 the indication and at the dosage in the MA.

The Transparency Committee wishes to receive practical data on how the activating EGFR mutation is sought (access to platforms, time to obtain results with regard to start of treatment) and on how these conditions change over time.

In addition, the Transparency Committee would like a study to be conducted of patients treated with IRESSA in France to document in a real-life treatment situation:

- the characteristics of patients being treated: age, gender, race, stage of disease, line of treatment and prior treatments, history of smoking, treatment initiation conditions (presence of activating EGFR mutation);
- the characteristics of the prescribers (speciality, type of institute, etc.);
- the impact of the treatment on the health of the population concerned in terms of morbidity and mortality (clinical benefit, safety, etc.) and quality of life.

The study duration must be justified by an independent scientific committee.

If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, cannot answer all the questions raised by the Transparency Committee, a specific study must be conducted.

4.5.1. Packaging

Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 100%

[6] Blons H, Côté JF, Le Corre D, Riquet M, Fabre-Guilevin E, Laurent-Puig P, Danel C. Epidermal growth factor receptor mutation in lung cancer are linked to bronchioloalveolar differentiation. Am J Surg Pathol. 2006;30:1309-15.

[7] Opinion of the Transparency Committee on docetaxel (TAXOTERE) of July 21, 2004.