HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 March 2006

Tarceva 25 mg, film-coated tablet, (369 232-3)
Tarceva 100mg, film-coated tablet, (369 234-6)
Tarceva 150 mg, film-coated tablet, (369 235-2)
B/ 30

Applicant: Roche

erlotinib

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

Date of Marketing Authorisation: 19 September 2005

Reason for application: Inclusion on the list of drugs reimbursed by National Insurance and approved for use in hospitals

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

erlotinib

1.2. Background

Erlotinib selectively and reversibly inhibits Human Epidermal Receptor 1 (HER1) tyrosine kinase (TK) activity (HER1 is also called EGFR, Epidermal Growth Factor Receptor). Inhibition by erlotinib of intracellular phosphorylation of EGFR results in cell stasis and/or death.

1.3. Indication

Tarceva is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen.
When Tarcevais prescribed, factors associated with prolonged survival should be taken into account.
No survival benefitl or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumors (see SPC section 5.1).

1.4. Dosage

Tarceva treatment should be supervised by a physician experienced in the use of anticancer therapies.

The recommended daily dose of Tarceva is 150 mg taken at least one hour before or two hours after the injestion of food.

When dose adjustment is necessary, it does should be reduced in 50 mg steps (see SPC section 4.4).

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see SPC section 4.5).

Hepatic impairment: Erlotinib is eliminated by hepatic metabolism and biliary excretion. The safety and efficacy of erlotinib have not been studied in patients with hepatic impairment. Therefore caution should be exercised when administering Tarceva to patients hepatic impairment. Use of Tarceva in patients with severe hepatic impairment is not recommended (see SPC section 5.2).

Renal impairment: The safety and efficacy of erlotinib have not been studied in patients with renal impairment (serum creatinine concentration>1.5 times the upper normal limit). Based on pharmacokinetic data, no dose adjustments appear necessary in patients with mild or moderate renal impairment (see SPC section 5.2). Use of Tarceva in patients with severe renal impairment is not recommended.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L Antineoplastic and immunomodulating agents
01 Antineoplastic agents
X Other antineoplastic agents
34 Erlotinib

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

Cisplatin (Cisplatyl)
Carboplatin (Paraplatin)
Cyclophosphamide (Endoxan)
Docetaxel (Taxotere)
Doxorubicin (Adriblastine)
Etoposide (Vepeside)
Gemcitabine (Gemzar)
Ifosfamide (Holoxan)
Pemetrexed (Alimta)
Paclitaxel (Taxol)
Vindesine (Eldisine)
Vinorelbine (Navelbine)

3 ANALYSIS OF AVAILABLE DATA

The dossier contained:
- two phase I dose-ranging studies in subjects with advanced-stage solid tumours (studies 248-004 and 248-005)
- one supporting phase II study, no. A248-1007
- one phase III pivotal trial (BR.21 trial) in subjects with NSCLC previously treated with first- or second-line chemotherapy.

3.1. Efficacy

Trial A248-1007:
Non-comparative phase II study assessing the efficacy and safety of erlotinib in 57 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) (stage IIIB-IV) with relapse after at least one course of platinum chemotherapy; all patients were EGFR+.
Tarceva was given orally every day at a dose of 150 mg. Treatment was given continuously for at least 8 weeks and not exceeding 52 weeks, or until disease progression or onset of toxicity.

Primary endpoint: objective response rate[1]

Secondary endpoints:
- level of disease stabilisation
- duration of response, defined as the time from the first assessment of complete/partial response to disease progression or death among patients who had achieved a complete/partial response
- Progression-free survival, defined as the time from the first drug administrationto the first observation of disease progression, or administration of another antitumour therapy. Patients without disease progression at time of database lock were censored on the date of the last tumour assessment
- overall survival, defined as the time from inclusion until death from any cause
- safety

Results:

Global objective response rate (primary endpoint) was 12.3% (CI = 95%: 5.1%–23.7%).
Disease stabilisation was recorded in 22 patients (38.6%). Response rate was identical irrespective of type or number of previous courses of prior chemotherapy (1, 2 or more).
Median duration of response (complete or partial) was 19.7 weeks [11.7–80.3 weeks].
Median progression-free survival was 9 weeks (CI =95%: 8.0–15.3), one-year progression-free survival was 10.5% (CI = 95%: 4.0–21.5%).
Median overall survival was 8.4 months (CI= 95%: 4.8-13.9 months) and survival rate at 1 year was 40.4% (CI= 95%: 27.6-54.2%).

[1] Objective response rate is defined as the sum of complete and partial responses

Trial BR 21

Published randomised (2:1) double-blind placebo-controlled phase III trial (BR 21)[2] in 731 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and who had already received one or two lines of chemotherapy.

Primary endpoint: overall survival

Secondary endpoints:
- overall response rate[3]
- duration of response, defined as the time from the first assessment of complete/partial response to disease progression or death among patients who had achieved a complete/partial response
- Progression-free survival (defined as thetime from randomization to the first observation of disease progression or death due to any cause)
- Assessment of time to deterioration of the following three symptoms: cough, dyspnoea and pain
- safety

Results:

About two-thirds of the patients in the trial were male and approximately one-third had a baseline ECOG performance status of 2 and 9% had a baseline ECOG performance status of 3.
A prior platinum containing regimen had been given to 93% of patients in the Tarceva group and to 92% of patients in the placebo group. Approximately half the patients had received first-line therapy.

Median overall survival was 6.67 months in the Tarceva group (CI 95%: 5.52-–7.79 months) compared with 4.70 months in the placebo group (CI 95%: 4.11-–6.28 months) (p=0.002). Hazard ratio for death in the Tarceva group compared to the placebo group was 0.73 (CI 95%: 0.60–0.87).
12-month survival rate was 31.2% in the Tarceva group and 21.5% in the placebo group.
Effect on overall survival was similar in patients who had previously received only one line of chemotherapy compared with more than one.
Median progression-free survival was 9.7 weeks in the Tarceva group compared with 8 weeks in the placebo group.
Global response rate was 8.9% in the Tarceva group.
Median duration of disease stabilisation was 24.9 weeks under Tarceva and 21.1 weeks under placebo.
In the 45% patients with known EGFR expression status[4], the hazard ratio was 0.68 (CI 0.49–0.94) for patients with EGFR-positive tumours (n=127) and 0.93 (CI 0.63–1.36) for patients with EGFR-negative tumours (n=111). In the remaining 55% of patients with unknown EGFR expression status, the hazard ratio was 0.77 (CI 0.61–0.98).

Time to deterioration of the three symptoms (cough, dyspnoea and pain) was significantly longer in patients treated with Tarceva: time to deterioration of cough was increased by 2.9 months (3.7 for the placebo arm versus 6.6 months for the Tarceva arm; p=0.041), time to deterioration of dyspnoea was increased by 2 months (2.8 months for the placebo arm versus 4.8 months for the Tarceva arm; p=0.031) and time to deterioration of pain was

2 Shepherd FA et al. Erlotinib in previously treated non–small-cell lung cancer N Engl J Med 2005;353:123-32.
[3] sum of complete and partial responses
[4] defined by IHC using EGFR PharmaDx kit and defining EGFR-negative as less than 10% tumour cells staining

increased by approximately 1 month (1.9 months for the placebo arm versus 2.8 months for the Tarceva arm; p=0.04).

The Committee notes that apart from the fact that patients included in this trial had to have already received at least one or two lines of chemotherapy, it was not stated whether their disease was progressing (after failure) or was stabilised (and therefore in the maintenance phase). In fact, median progression-free survival was 8.0 weeks and median duration of stabilisation was 21.1 weeks under placebo. This long period of disease stabilisation without treatment could suggest that a certain number of patients had been randomised not at the time of disease progression under the first or second line of chemotherapy, but while the disease was still in a period of stabilisation.

3.2. Undesirable effects

The most commonly reported undesirable effects in the comparative study were diarrhoea and a skin rash.
The dose was reduced because of undesirable effects in 19% of patients in the Tarceva group compared with 2% in the placebo group. Treatment was withdrawn from 5% of patients in the Tarceva group.

3.3. Conclusion

In a comparative phase III trial against placebo in 731 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one chemotherapy regimen, Tarceva improved median survival (primary endpoint) by 2 months in comparison with placebo (6.67 months under Tarceva compared with 4.70 months under placebo; p=0.002). Median progression-free survival was 9.7 weeks under Tarceva compared with 8 weeks under placebo.
No survival benefit was demonstrated in patients treated with Tarceva whose tumour EGFR expression was negative.
The Committee note that patients included in this trial had to have already received at least one or two lines of chemotherapy, but it was not stated whether these patients had all failed their previous treatment or whether treatment with Tarceva had been given as maintenance therapy after chemotherapy.
The main side-effects observed in the comparative trial were digestive (diarrhoea) and cutaneous.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Lung cancer is a life-threatening disease;
Tarceva is intended as curative therapy;

Anticipated Public Health Impact (currently being validated):

The public health burden of locally advanced or metastatic non-small cell lung cancer, particularly in patients who have failed at least one chemotherapy regimen, is substantial.

As second-line therapy, the therapeutic requirement is only partly covered by the reference drugs in current practice (docetaxel and pemetrexed) as patients fail rapidly and have a life expectancy of less than one year. As third-line therapy, the therapeutic requirement is not covered as there are no effective treatments in this situation, and Tarceva is likely to partly satisfy this requirement.

In view of the available data and as there are no data on direct comparison with docetaxel or pemetrexed, it is not possible to estimate the additional anticipated impact on mortality and morbidity of Tarceva used as second-line therapy. However, it is anticipated that Tarceva used as third-line therapy would have a minor impact on mortality and morbidity.

Consequently, in the current state of knowledge and in view of the minor foreseeable impact on mortality and morbidity of Tarceva as third-line therapy, a public health benefit is anticipated for this medicinal product. This benefit is minor.

The efficacy/undesirable effects ratio is high.
This medicinal product is a second-line or third-line medicine0.
Alternative drug therapies are available.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit:

Tarceva contributes a minor improvement in actual benefit (level IV) as third-line treatment for non-small cell lung cancer as part of normal management.

In view of the absence of data from direct comparison with accepted second-line comparator drugs (docetaxel, pemetrexed) in the treatment of non-small cell lung cancer, Tarceva does not provide any improvement in actual benefit (level V) as a second-line therapy.

4.3. Therapeutic use

At the locally advanced or metastatic stage of non-small cell lung cancer, systemic chemotherapy is indicated.
The 2003 ASCO guidelines and the FNCLCC[5] SOR[6] Committee recommendations on chemotherapy for inoperable stage III and IV non-small cell lung cancer agree in recommending a chemotherapy regimen combining two agents, one of which should be a platinum drug, in patients with performance status ≤ 2. As second-line therapy, the recommended treatment is docetaxel chemotherapy for patients who have progressed after receiving platinum chemotherapy. It should be noted that since that time docetaxel has obtained a Marketing Authorisation as first-line therapy in combination with cisplatin in patients who have not previously received chemotherapy in this indication. Pemetrexed is also used as second-line therapy in patients who have progressed after first-line platinum chemotherapy.
There have been no direct comparisons between Tarceva and the second-line drugs (docetaxel and pemetrexed). However, the degree of effect on global survival in this study seems to be similar to that reported in a study comparing docetaxel with palliative care (7.0 compared with 4.6 months; p=0.047) as second-line therapy[7]. Its role in this situation has yet to be determined.
Tarceva clearly has a place in third-line therapy, a situation in which the efficacy of chemotherapy has not been established.

4.4. Target population

The target population for Tarceva consists of patients with locally advanced or metastatic NSCLC who have received at least one previous line of chemotherapy (second-line and more).
In 2000, incidence of lung cancer in France was estimated to be 27 743 patients (*Commission d'orientation sur le cancer* report, 2003).
Non-small cell lung cancer (NSCLC) accounts for nearly 80%–85% of cases, i.e. 22 194–23 582 patients. Locally advanced or metastatic stages are IIIB and IV.

Stages IIIB and IV are thought to account for nearly 63% of cases of NSCLC (KBP- study 2000 Rev Mal Respir, 2002, 19, 727-734).
The first-line therapy failure rate is about 70%[8] according to data from the Taxotere clinical trial (used in combination with cisplatin).

On the basis of these data, the target population of Tarceva would be 9800–10 500 cases a year.

4.5. Transparency Committee recommendations

The Committee recommends inclusion on the list of medicines reimbursed by National Insurance and/or on the list of medicines approved for use by hospitals and various public services.

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[5] FNCLCC: Federation of French Cancer Centres
[6] SOR: Standards, Options and Recommendations
[7] Shepherd FA et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy JCO 2000;18:2095-2103

[8] Transparency Committee Opinion on docetaxel (Taxotere), 21 July 2004

4.5.1. Packaging:
Appropriate for prescription conditions

4.5.2. Reimbursement rate: 100%