HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

22 June 2011

TARCEVA 25 mg, film-coated tablet
B/30 (CIP code: 369 232-3)

TARCEVA 100 mg, film-coated tablet
B/30 (CIP code: 369 234-6)

TARCEVA 150 mg, film-coated tablet
B/30 (CIP code: 369 235-2)

Applicant: ROCHE S.A.S.

Erlotinib (tyrosine kinase inhibitor)
ATC code: L01XE03

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

Date of Marketing Authorisation (Centralised Procedure): 19 September 2005 (non-small cell lung cancer), and amendments to Marketing Authorisations of 24 January 2007 (pancreatic cancer) and 27 April 2010 (extension of the indication to be assessed).

Reason for request:
Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication “maintenance treatment of non-small cell cancer”.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

erlotinib

1.2. Indication

"Non-small cell lung cancer (NSCLC):
Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy.
Tarceva is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.
When prescribing Tarceva, factors associated with prolonged survival should be taken into account.
No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR)-IHC negative tumours (see section 5.1 of the SPC).

Pancreatic cancer:
Tarceva, in combination with gemcitabine, is indicated for the treatment of patients with metastatic pancreatic cancer.
When prescribing Tarceva, factors associated with prolonged survival should be taken into account (see SPC).
No survival advantage could be shown for patients with locally advanced disease."

1.3. Dosage

"Non-small cell lung cancer:
The recommended daily dose of Tarceva is 150 mg taken at least one hour before or two hours after the ingestion of food.
When dose adjustment is necessary, the dose should be reduced in 50 mg steps"

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XE	Tyrosine kinase inhibitor
L01XE03	Erlotinib

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines:
None

2.3. Medicines with a similar therapeutic aim

For maintenance treatment:

- ALIMTA (pemetrexed)

“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.”

- AVASTIN (bevacizumab)

“is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Avastin as a single agent until disease progression.”

Other medicinal products used for the treatment of non-small cell lung cancer:

- IRESSA (gefitinib)
- GEMZAR (gemcitabine)
- NAVELBINE (vinorelbine)
- TAXOTERE (docetaxel)
- TAXOL (paclitaxel) and its generics
- ELDISINE (vindesine)
- ENDOXAN (cyclophosphamide)
- HOLOXAN (ifosfamide)
- CISPLATYL (cisplatin) and its generics
- PARAPLATIN (carboplatin) and its generics [indicated only as second-line treatment]

3 ANALYSIS OF AVAILABLE DATA

The submitted dossier includes a phase III study (B018192, SATURN), the results of which are analysed below.

3.1. Efficacy

Study B018192[1]

Phase III, multicentre, randomised, double-blind, comparing TARCEVA with placebo as maintenance treatment of patients with locally advanced or metastatic (Stage IIIb/IV) non-small cell lung cancer (NSCLC) who have completed four cycles of platinum-based chemotherapy in the absence of unacceptable toxicity and/or progression disease..
Patients were randomised 1:1 to receive TARCEVA 150 mg or placebo orally once daily until disease progression.

The inclusion criteria were:

➢ Selection phase
- Histologically documented, advanced (Stage IIIB) or metastatic (Stage IV) cancer.
- Tumour tissue samples within three weeks of the patient starting chemotherapy.
- measurable disease according to the RECIST criteria.
- previous adjuvant or neo-adjuvant treatment permitted if completed ≥ 6 months before start of the chemotherapy phase.
- ECOG PS performance status equal to 0 or 1.

➢ Evaluation phase
- Completion of 4 cycles of a standard platinum-based chemotherapy without progression (complete, partial response or stable disease). A maximum interval of 21 days between end of the last chemotherapy cycle and randomisation was allowed.
- ECOG PS of 0 – 1.
- Life expectancy of at least 12 weeks
- granulocyte count ≥ 1,500/mm^3; Platelet count ≥ 100,000/mm^3; Haemoglobin level ≥ 9 g/dl
- AST/SGOT and ALT/SGPT < 2.5 times the upper normal limit in the absence of liver metastases and up to five times the upper normal limit in case of liver metastases.

Study objectives:
The two primary efficacy endpoints of the study were:
- progression-free survival in all patients regardless of their tumour's EGFR protein expression status (EGFR IHC+ and EGFR IHC-),
- progression-free survival in patients whose tumours had EGFR protein overexpression determined by immunohistochemistry (EGFR IHC+).
Progression-free survival was defined as the time from the date of randomisation to the first date disease progression was recorded or the date of all-cause death whichever occurred first.

Secondary endpoints were:
- overall survival, defined as the time from the randomisation date to the date of all-cause death. The overall survival analysis was performed for all patients, for patients with EGFR

[1] Cappuzzo F, Ciuleanu T, Stelmakh *et al*. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicenter, randomised, placebo-controlled phase 3 study. Lancet Oncology 2010; 11: 521-29.

protein expression positive tumours and for those with EGFR protein expression negative tumours.
- progression-free survival for patients with EGFR protein expression negative tumours,
- time to disease progression, defined as the time from the randomisation date to the first date disease progression was recorded,
- the response rate determined according to the RECIST criteria,
- quality of life (QoL) measured according to three criteria:
    - time to symptom progression
    - time to deterioration in trial outcome index
    - time to deterioration of quality of life

Statistical analysis
The statistical analysis referred to in the protocol planned:
- a log-rank test to compare the two treatment arms,
- a Kaplan-Meier analysis method to measure progression-free survival (PFS) and overall survival,
- calculation of a hazard ratio (HR), with a 95% confidence interval.

The alpha level of 5%lwas split between the two co-primary endpoints: 3% for the PFS in the whole study population, and 2% for estimating PFS in the EGFR IHC+ patient population.

Results:

Of the 1949 patients screened in the selection phase, 889 patients with locally-advanced or metastatic NSCLC with non-progressive disease (complete or partial tumour response or stable disease) following four cycles of platinum-based doublet were randomised as follows:
- 438 patients in the TARCEVA group,
- and 451 patients in the placebo group.

The efficacy analysis was performed on 884 patients and the median follow-up period was 11.4 months in the TARCEVA group and 11.5 months in the placebo group.
The median age of patients was 60 years. All the patients were in a generally good condition (the ECOG score was 0 in a third of the patients and 1 in the others).
Around 40% of the patients had a squamous cell tumour, around 40% an adenocarcinoma and in 18% of the cases the histology was unknown.

The median progression-free survival was 12.3 weeks in the TARCEVA group versus 11.1 weeks in the placebo group, i.e. an absolute gain of 1.2 weeks in favour of TARCEVA (HR = 0.71, 95% CI: [0.62; 0.82]).
EGFR IHC+ population:
In the group of patients with EGFR protein expression immunohistochemistry -positive tumour (EGFR IHC+) (n = 621), the median progression-free survival was 12.3 weeks in the TARCEVA group versus 11.1 weeks in the placebo group, i.e. an absolute gain of 1.2 weeks (HR = 0.69, 95% CI [0.58; 0.82]).

Secondary endpoints:

- overall survival

The median overall survival was 12 months in the TARCEVA group versus 11 months in the placebo group, i.e. an absolute difference of 1 month in favour of the TARCEVA group (HR = 0.81, 95% CI [0.70; 0.95]).
An analysis of overall survival in patients with EGFR tumour protein expression positive tumour (EGFR IHC+; n = 621) showed similar results to those observed for the total population. The median overall survival in this group was 12.8 months in the TARCEVA group versus 11 months in the placebo group (HR = 0.77, 95% CI [0.64; 0.93]).

Similarly, the hazard ratio for overall survival was 0.77 (95% CI [0.61; 0.97]) in patients with EGFR protein expression negative tumour.

- progression-free survival in the EGFR IHC- population
In patients whose tumour EGFR protein expression was negative (EGFR IHC-; n = 388), the progression hazard ratio was 0.78 (95% CI [0.63; 0.96]).

- time to progression
The median time to progression was 12.3 weeks in the TARCEVA group versus 11.3 weeks in the placebo group (HR = 0.70 (95% CI [0.61; 0.82]).

- response rate and disease control
The best response rate, corresponding to patients with complete response or partial response after randomisation, was 11.9% in the TARCEVA group versus 5.4% in the placebo group (p = 0.0006).
The proportion of partial response was 11% in the TARCEVA group versus 4.7% in the placebo group. The disease stabilisation rate was similar between the two groups: 48.6% in the TARCEVA group versus 45.4% in the placebo group.
The disease control rate (defined as the percentage of patients with complete, partial or stable response) was 60.6% in the TARCEVA group versus 50.8% in the placebo group.

- quality of life
In the quality of life analyses, 438 patients in the TARCEVA group and 451 patients in the placebo group were included.
- the median time to symptom deterioration was similar between the two treatment groups: 18.3 weeks in the TARCEVA group versus 17.6 weeks in the placebo group (HR = 0.91; 95% CI [0.74; 1.12]);
- the time to deterioration in the clinical index was 18.1 weeks in the TARCEVA group versus 18.9 weeks in the placebo group (HR = 1.06; 95% CI [0.87; 1.31]);
- the time to deterioration of quality of life was also similar: a median of 12.6 weeks in the TARCEVA group versus 12.3 weeks in the placebo group (HR = 0.96; 95% CI [0.79; 1.16]).

The efficacy data from the sub-group of patients with a stable disease (population accepted by the MA, n = 487) stem from an exploratory analysis carried out *post hoc* which suggest the following results:
- a median progression-free survival of 12.1 weeks in the TARCEVA group versus 11.3 weeks in the placebo group, i.e. an absolute difference of 1.2 weeks in favour of TARCEVA.
- a median overall survival of 11.9 months in the TARCEVA group versus 9.6 months in the placebo group, i.e. an absolute difference of 2.3 months in favour of TARCEVA.
- no difference between the two groups according to the results of the quality of life assessment.

3.2. Adverse effects

In the overall study population, treatment discontinuations due to adverse effects were reported in 4.4% of the patients in the TARCEVA group versus 1.1% of the patients in the placebo group. In the group of stable patients, 15 patients (6%) in the TARCEVA group experienced an adverse event leading to withdrawal from the study versus five patients (2.1%) in the placebo group.
Severe adverse events (Grade ≥ 3) were recorded in 24.7% of patients in the TARCEVA group versus 12.1% of patients in the placebo group. The difference between the two groups was mainly due to the frequency of diarrhoea and skin rash.
Likewise in the overall population, the most frequently observed adverse events in the population of stable patients receiving TARCEVA were:
- rash: 61.2% in the TARCEVA group versus 9.9% in the placebo group (60.3% versus 9.4% of the overall population),

- diarrhoea: 21.2% in the TARCEVA group versus 4.7% in the placebo group (20.3% versus 4.5% of the overall population).

3.3. Conclusion

In a phase III, multicentre, randomised, double-blind study comparing TARCEVA with placebo as a maintenance treatment of patients with locally advanced or metastatic (Stage IIIb/IV) non-small cell lung cancer (NSCLC) following four cycles of platinum-based chemotherapy who had not experienced unacceptable intolerance at the end of treatment and/or disease progression.
Patients whose tumours showed a complete or partial response or whose disease was stable after four chemotherapy cycles were randomised 1:1 to receive TARCEVA 150 mg or placebo orally once daily until disease progression.
orally once daily until disease progression
In the ITT population, the median progression-free survival (primary endpoint) was 12.3 weeks in the TARCEVA group versus 11.1 weeks in the placebo group, i.e. an absolute gain of 1.2 weeks in favour of TARCEVA (HR = 0.71, 95% CI: [0.62; 0.82]).
In the population of patients with immunohistochemistry positive EGFR tumour protein expression (EGFR IHC+) (n = 621), the median progression-free survival in this sub-group was 12.3 weeks in the TARCEVA group versus 11.1 weeks in the placebo group, i.e. an absolute gain of 1.2 weeks (HR = 0.69, 95% CI [0.58; 0.82]). Similar results were observed in cases of tumours in which EGFR is not expressed (EGFR IHC-)
The median overall survival was 12 months in the TARCEVA group versus 11 months in the placebo group, i.e. a net difference of 1 month in favour of the TARCEVA group (HR = 0.81, 95% CI [0.70; 0.95]).
No difference in quality of life between the two groups was shown.

In all, ITT analysis revealed a marginal gain in terms of progression-free survival (1.2 weeks) and of overall survival (1 month) without any improvement in quality of life and with an increase in severe adverse events (Grade ≥ 3) – in particular gastrointestinal (diarrhoea) and cutaneous (skin rash) – which were recorded in 24.7% of the patients in the TARCEVA group versus 12.1% of the patients in the placebo group.
The efficacy data from the sub-group of patients with a stable disease (population accepted by the MA, n = 487) stem from an exploratory analysis carried out post hoc and suggest the following results:

- a median progression-free survival of 12.1 weeks in the TARCEVA group versus 11.3 weeks in the placebo group, i.e. a net difference of 1.2 weeks in favour of TARCEVA.
- a median overall survival of 11.9 months in the TARCEVA group versus 9,6 months in the placebo group, i.e. a net difference of 2.3 months in favour of TARCEVA.
- no difference between the two groups as regards the results of the quality of life assessment.

The Committee stresses the following points:

- in cases of non-squamous tumours, current guidelines for the management of advanced-stage NSCLC[2] point to the necessity of selecting patients according to histological type and EGFR mutation status before considering a first-line treatment. The use of tyrosine kinase inhibitors (TKI) can only be envisaged if there is EGFR mutation. The patients included in the study had a range of pathologies: around 40% of the patients had a squamous cell tumour, around 40% an adenocarcinoma and in 18% of the cases the histology was unknown.
- patients with EGFR-activating mutations, and therefore candidates for treatment with TKI (including TARCEVA), accounted for only 5.5% (49/889) of the patients included.
- the efficacy data from the sub-group of patients with a stable disease (population accepted by the MA, n = 487) stem from a *post hoc* exploratory analysis.

This does not make it possible to single out those patients that are likely to benefit from this proprietary medicinal product.

All in all, taking into account all the points made above, the Committee considers that it is not possible to quantify the effect of TARCEVA and its place in the maintenance treatment of non-small cell lung cancer.

[2] Recommandations professionnelles Cancer du poumon non à petites cellules. Collection Recommandations & référentiels [Professional guidelines – Non-small cell lung cancer. Guidelines and standards collection], INCa, Boulogne-Billancourt, September 2010

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Non-small cell lung cancer (NSCLC) is a life-threatening condition;
These proprietary medicinal products are intended as a curative therapy.
The efficacy/tolerance ratio is low.

Public health benefit:

Non-small cell lung cancer represents a moderate public health burden.

Given the severity of its prognosis, improving its management constitutes a public health need.

In light of the results of the study – which included patients whose tumours expressed the epidermal growth factor receptor (EGFR) or did not – it is not expected that TARCEVA will have any impact in terms of reducing morbidity and mortality in comparison with placebo, given the marginal impact it had on progression-free survival in the clinical study, without any demonstrable improvement in quality of life. Besides, the real life possibility of there being a negative impact on the quality of life cannot be ruled out, especially given the high risk of onset of severe adverse events, especially gastrointestinal and cutaneous adverse events in the treated population.

Consequently, it is not expected that there will be any public health benefit for TARCEVA in this indication.

This medicinal product is a first-line therapy;
Alternative medicinal products exist;

Given the failure to provide any demonstration in line with the guidelines for the management of NSCLC (cf. the Conclusion section), the Committee considers that it is not possible to quantify the effect of TARCEVA and its place in the maintenance treatment of non-small cell lung cancer.
At this stage, the actual benefit is insufficient to justify its reimbursement by National health Insurance.

4.2. Improvement in actual benefit (IAB)

Not applicable.

4.3. Transparency Committee recommendations

The transparency Committee recommends that TARCEVA not be included on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use and various public services.