TRANSPARENCY COMMITTEE

OPINION

6 June 2012

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 inhibitors)
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 (European centralised procedure): 19 September 2005 (non-small cell lung cancer), and amendments to Marketing Authorisation of 24 January 2007 (pancreatic cancer), 27 April 2010 (maintenance treatment) - 24 August 2011 (extension of indication to be evaluated)

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication “first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations”.

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 for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations.
TARCEVA is also indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum-based first-line 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) 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

“Patients with Non-Small Cell Lung Cancer:
EGFR mutation testing should be performed prior to initiation of TARCEVA therapy in chemo-naïve patients with advanced or metastatic NSCLC.
The recommended daily dose of TARCEVA is 150 mg taken at least one hour before or two hours after the ingestion of food.”
2.1. ATC 2011 Classification

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

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines:
- IRESSA (gefitinib)
  “AB: substantial
  IAB: In the first-line treatment of locally advanced or metastatic NSCLC and in the
  presence of an EGFR-TK activating mutation, IRESSA provides a minor IAB (level IV)
  compared to carboplatin plus paclitaxel.”, TC Opinion of 4 November 2009

2.3. Medicines with a similar therapeutic aim

- ALIMTA (pemetrexed)
- AVASTIN (bevacizumab)
- GEMZAR (gemcitabine)
- NAVELBINE (vinorelbine)
- TAXOTERE (docetaxel)
- TAXOL (paclitaxel) and its generics
- ELDISINE (vindesine)
- ENDOXAN (cyclophosphamide)
- HOLOXAN (ifosfamide),
- CISPLATYL (cisplatin) and its generics
- PARAPLATINE (carboplatin) and its generics (which has a MA for second-line use)
The dossier submitted includes one phase III study (ML20650, EURTAC), the results of which are analysed below.

3.1. Efficacy

Study ML20650
Open-label randomised study comparing TARCEVA with platinum-based chemotherapy in treatment-naïve patients with locally advanced or metastatic (stage IIIb or IV) non-small cell lung cancer (NSCLC) whose tumour has an EGFR mutation (deletion of exon 19 or mutation of exon 21).

Study Treatments:

- TARCEVA 150 mg per day; the treatment was continued until disease progression or the appearance of toxicity considered unacceptable by the investigator.

- platinum-based chemotherapy by intravenous infusion according to one of the following regimens:
  - cisplatin plus docetaxel: cisplatin 75 mg/m² on day 1 and docetaxel 75 mg/m² on day 1. This regimen was repeated every 3 weeks.
  - or
  - cisplatin plus gemcitabine: cisplatin 75 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8. This regimen was repeated every 3 weeks.

If patients were not eligible for treatment with cisplatin, it could be replaced by carboplatin according to the following schedules:
- docetaxel 75 mg/m² on day 1 and carboplatin AUC = 6 on day 1, every 21 days.
- gemcitabine 1000 mg/m² on days 1 and 8 and carboplatin AUC = 5 on day 1, every 21 days.

The chemotherapy was administered until a maximum of four cycles.

The inclusion criteria included:
- histologically confirmed diagnosis of advanced (stage IIIB) or metastatic (stage IV) non-squamous cell cancer.
- confirmed deletion of exon 19 and confirmed mutation of exon 21 L 858R of the tyrosine kinase domain of the EGFR.
- measurable disease according to the RECIST criteria.
- ECOG performance status (PS) ≤ 2.
- granulocytes > 1500/mm³; platelets > 100,000/mm³; haemoglobin > 9 g/dl.
- AST/SGOT and ALT/SGPT < 1.5 times the upper normal limit in the absence of liver metastases and up to 5 times the upper normal limit in the presence of liver metastases.

The noninclusion criteria included:
- previous treatment with chemotherapy for metastatic disease. The administration of neoadjuvant or adjuvant chemotherapy was allowed as long as it was completed ≥ 6 months before entering the study.
- Previous treatment with therapeutic agents targeting EGFR.
The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to the first documented occurrence of progressive disease, or death from any cause.

Secondary endpoints were:
- overall survival, defined as the time between randomisation and the date of death from any cause;
- the response rate determined in accordance with the RECIST criteria,\(^1\)
- safety profile,
- quality of life assessed by the the “lung cancer symptom scale”.

**Results:**

A total of 154 Caucasian patients were randomised: 77 patients to each treatment arm. The patients’ median age was 65 years in the TARCEVA group and 64 years in the chemotherapy group, 68% were women in the TARCEVA group and 79% in the chemotherapy group. The proportion of smokers was 70% in the TARCEVA group and 74% in the chemotherapy group.

In a pre-planned interim analysis (performed after 92 progression-free survival events), median progression-free survival (primary efficacy endpoint) was 9.4 months in the TARCEVA group versus 5.2 months in the chemotherapy group, an absolute gain of 4.2 months in favour of TARCEVA (HR = 0.42 95% CI [0.27-0.64], p<0.0001). These results are probably overestimated given that the study was stopped after an interim analysis.

Median overall survival did not differ between the two groups (22.9 months in the TARCEVA group versus 18.8 months in the chemotherapy group; HR = 0.80 95% CI [0.47 – 1.37]). At the time of that analysis, 36% of the patients in the TARCEVA group and 67% of the patients in the chemotherapy group had received other lines of treatment.

The Best Overall Response Rate was greater in the TARCEVA group than in the comparator group: 54.5% versus 10.5%. About half of the tumour responses in the TARCEVA group were partial responses.

The number of patients for whom quality of life data were collected was too small to allow their analysis.

**3.2. Adverse effects**

Treatment discontinuations due to adverse events affected 12% of the patients in the TARCEVA group and 14.9% of the patients in the chemotherapy group. The percentage of patients who had serious adverse events was 26.7% in the TARCEVA group and 25.7% in the chemotherapy group. Events of grades ≥ 3 affected 31 patients (41.3%) in the TARCEVA group and 49 patients (66.2%) in the chemotherapy group. The most common events in the chemotherapy group were neutropenia and asthenia and in the TARCEVA group, skin and gastrointestinal disorders.

\(^1\) RECIST criteria: evaluation of tumour response in solid tumours as: complete response (disappearance of the target lesions), partial response (reduction of 30% in the target lesions in their largest diameter), progression of the disease (increase of 20% in the target lesions in their largest diameter) and stabilisation.
3.3. Conclusion

In an open-label randomised study, TARCEVA was compared with platinum-based chemotherapy in 154 treatment-naïve Caucasian patients with locally advanced or metastatic (stage IIIb or IV) non-small cell lung cancer (NSCLC) whose tumour had an EGFR mutation (deletion of exon 19 or mutation of exon 21).

The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to the first documented occurrence of disease progression, or death from any cause.

The results are those of a pre-planned interim analysis after 92 events, based on progression-free survival, at the end of which the study was stopped.
- median progression-free survival was greater in the TARCEVA group than in the chemotherapy group: 9.4 months versus 5.2 months, an absolute gain of 4.2 months in favour of TARCEVA (HR = 0.42 95% CI [0.27-0.64], p<0.0001). These results are probably overestimated given that the study was stopped.
- median overall survival did not differ between TARCEVA and chemotherapy group (22.9 months versus 18.8 months; HR = 0.80 95% CI [0.47 – 1.37]).
- the percentage of patients who received other lines of treatment was 36% in the TARCEVA group and 67% in the chemotherapy group.
- the Best Overall Response Rate was greater in the TARCEVA group compared with the chemotherapy group: 54.5% versus 10.5%. About half of the tumour responses in the TARCEVA group were partial responses.
- the level of data collected was low and does not allow an assessment of quality of life.

Discontinuations of treatment due to adverse events (12% versus 14.9% in the chemotherapy group) and the percentage of serious adverse events (26.7% versus 25.7% in the chemotherapy group) were similar in the two groups.
The most common events in the chemotherapy group were neutropenia and asthenia and in the TARCEVA group, skin and gastrointestinal disorders.
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/adverse effects ratio is high.

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 itself substantial. The burden of the population likely to benefit from TARCEVA (patients who have a tumour with an EGFR activating mutation) can be considered moderate due to the prevalence of EGFR activating mutations, estimated as 16.5% of patients with NSCLC in France.

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

In light of the available clinical data (an interim analysis of a study conducted in Caucasian patients which was stopped early showing an absolute gain of 4.2 months in progression-free survival with no gain in terms of overall survival or no demonstrated improvement in quality of life), an impact in terms of morbidity and mortality is expected, like the proprietary medicinal product IRESSA, in patients treated with TARCEVA as first-line therapy by comparison with platinum-based chemotherapy. In addition, like oral chemotherapies, TARCEVA may have an impact on the way the healthcare system is organised (stays in hospital avoided, management transferred to consultations).

The proprietary medicinal product TARCEVA is therefore likely to meet an identified public health need.

Consequently, TARCEVA is expected to benefit public health in its first-line indication. Like the proprietary medicinal product IRESSA, that benefit is low.

It is a first-line treatment. Alternative medicinal products exist.

The actual benefit of TARCEVA in this indication is substantial.

4.2. Improvement in actual benefit (IAB)

In the first-line indication of the treatment of NSCLC with EGFR activating mutations, TARCEVA, like IRESSA, provides a minor improvement in actual benefit (level IV) compared to platinum-based chemotherapy.

4.3. Therapeutic use

Surgery is the treatment of choice for the early stages of NSCLC. However, a large proportion of patients are diagnosed at an advanced stage of the disease (about 30% at a locally advanced stage and 40% at the metastatic stage) and the early stage accounts for only about 25 to 30%.
The professional guidelines of the National Cancer Institute (INCa) published in September 2010 indicate that therapeutic use in inoperable patients must, in first-line treatment, be determined by the presence or not of these mutations. In those patients who have a tumour with no EGFR mutation, platinum-based chemotherapy is still the reference. In cases with a mutation, the recommended treatment is a tyrosine kinase inhibitor. Today, two tyrosine kinase inhibitors are indicated in the first-line treatment of patients who have a tumour with EGFR activating mutations: gefitinib (IRESSA) and more recently erlotinib (TARCEVA). In the absence of any comparative data, the place of erlotinib by comparison with gefitinib in first-line treatment has still to be determined.

To date, the benefit of tyrosine kinase inhibitors has been established compared to chemotherapy mainly in terms of progression-free survival and with no demonstrated impact on overall survival.

4.4. Target population

The target population for TARCEVA in its new indication consists of patients with locally advanced or metastatic NSCLC whose tumour has EGFR activating mutations. The incidence of lung cancer in France was last estimated in 2009 by the National Cancer Institute (INCa), who notes 34,185 new cases per year. Of these, about 85% are non-small cell cancers (KBP French population of lung cancers followed up in 2000), i.e. 29,057 new cases a year.

At initial diagnosis of the disease, it was estimated that:
- 65% (18,887 patients) were at inoperable stages IIIB and IV,
- 35% (10,170 patients) had localised cancer and are eligible for initial management by surgery or radiotherapy, but of these 2 out of 5 would relapse (4068 patients) and be eligible for systemic treatment.

Thus, 22,950 patients are therefore potentially eligible for first-line treatment of stage IIIB and IV lung cancer. The EGFR activating mutation is found in France in about 10.3% to 13.7% of NSCLC cases.

Thus, the target population for first-line TARCEVA can be estimated at about 2360 to 3150 patients per year.

4.5. Transparency Committee recommendations

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

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