HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 December 2007

TARCEVA 25 mg, film-coated tablet (369 232-3)
TARCEVA 100 mg, film-coated tablet (369 234-6)
TARCEVA 150 mg, film-coated tablet (369 235-2)
Pack of 30

Applicant: ROCHE

erlotinib

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

Date of Centralised Marketing Authorisation: 19 September, 2005 – Variation: 24 January 2007 (extension of indication to be evaluated)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use in the extension of indication "Tarceva, in combination with gemcitabine, is indicated in the treatment of metastatic pancreatic cancer".

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

erlotinib

1.2. Indications

"- 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.

- Non-small cell lung cancer (NSCLC):

Tarceva is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer 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 treatment have been demonstrated in patients with EGFR-negative tumours."

1.3. Dosage

Pancreatic Cancer:

The recommended daily dose of Tarceva is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the summary of product characteristics of gemcitabine for the pancreatic cancer indication).
In patients who do not develop a skin rash within the first 4 – 8 weeks of treatment, further Tarceva treatment should be re-assessed.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2007 Classification

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

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

GEMZAR (gemcitabine)

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and safety of Tarceva combined with gemcitabine in first-line treatment were evaluated during a randomised, controlled, double-blind trial versus placebo, in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer.
Patients were randomised (1:1) to receive either gemcitabine alone or Tarceva 100 mg or 150 mg per day in combination with gemcitabine.

The primary endpoint of the study was overall survival.

Secondary endpoints were:
- Progression-free survival defined as the time between randomisation and disease progression or death from whatever cause.
- Objective response rate:
- The objective response duration defined as the time between the first objective response and disease progression or death.
- Quality of life (EORTC QLQ-C30 questionnaire),
- Safety.

Results:

At baseline, the demographic and disease characteristics of patients were similar in the two treatment groups except for a slightly higher proportion of women in the erlotinib/gemcitabine group than in the placebo/gemcitabine group.
Nearly half of the patients were aged ≥ 65 years.
A quarter of the patients had locally advanced disease and three quarters were at the metastatic stage. Approximately 80% of patients had a good general health status (ECOG performance score (PS) = 0-1).

285 patients received gemcitabine combined with Tarceva (261 patients with 100 mg and 24 patients with 150 mg) and 284 patients gemcitabine alone.

Survival (primary endpoint) was evaluated for the intention-to-treat population and the results are shown in table 1.

Table 1 (results for the primary endpoint)

	Tarceva (months)	Placebo (months)	Δ (months)	CI of Δ	HR	CI of HR	p
Overall population							
Median overall survival	6.4	6.0	0.41	-0.54-1.64	0.82	0.69-0.98	0.028
Mean overall survival	8.8	7.6	1.16	-0.05-2.34			
Metastatic population							
Median overall survival	5.9	5.1	0.87	-0.26-1.56	0.80	0.66-0.98	0.029
Mean overall survival	8.1	6.7	1.43	0.17-2.66			
Population with locally advanced disease							
Median overall survival	8.5	8.2	0.36	-2.43-2.96	0.93	0.65-1.35	0.713
Mean overall survival	10.7	10.5	0.19	-2.43-2.69			

The ITT results for the primary endpoint showed a median survival of 6.4 months in the Tarceva-gemcitabine combination group vs 6 months for the gemcitabine monotherapy group showing an absolute gain of 12 days.
The results for the groups of metastatic and locally advanced patients were obtained by exploratory subgroup analysis. An absolute gain of 26 days was observed in favour of the group treated with the combination (5.9 months vs 5.1 months) in terms of median survival in the metastatic subgroup. However, no difference was observed between the two treatments in the locally advanced subgroup (8.5 months in the combination group vs 8.2 months with gemcitabine alone).

Because of the small sample size of patients treated with the dosage of 150 mg per day , it was impossible to draw any conclusions about the efficacy of this dosage. EMEA[1] only approved the indication for the sub-group of patients in the metastatic stage receiving Tarceva at the dosage of 100 mg/day.

Results for secondary endpoints:
No significant difference between the two groups was observed for the following secondary endpoints:
- Median progression-free survival: 3.58 months with Tarceva vs 3.22 months with placebo (NS).
- Objective response rate: 9.3% with Tarceva vs 8.1% with placebo (NS).
- Median response duration: 23.9 weeks with Tarceva vs 23.3 with placebo (NS).

No improvement in quality of life was observed in Tarceva-treated patients. A higher incidence of diarrhoea was observed in the Tarceva group.

3.2. Safety

Safety data are presented for the population treated by Tarceva at 100 mg (MA dosage).
The incidence of serious adverse events was 51% in the Tarceva group and 39% in the placebo group: infections (16% versus 11%), respiratory, chest and mediastinal disorders (7% vs 4%), nervous system disorders (4% vs <1%), hepatic disorders (4% vs 2%) and renal and urinary disorders (2% vs 0%).

[1] European Medicines Agency

The incidence of treatment discontinuation was 10% in the Tarceva group and 5% in the placebo group. The main causes were: diarrhoea, skin rashes and elevated transaminases.
The following adverse events were more frequent in patients who received Tarceva: rash (69% vs 30%), diarrhoea (48% vs 36%), weight loss (39% vs 29%) and stomatitis (22% vs 12%).

3.3. Conclusion

The efficacy and safety of Tarceva combined with gemcitabine in first-line treatment were evaluated during a controlled, randomised, double-blind trial versus placebo, in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer.
The ITT results for the primary endpoint showed a median survival of 6.4 months in the Tarceva-gemcitabine combination group vs 6 months in the gemcitabine monotherapy group (p=0.028), i.e. an absolute gain of 12 days.
The results for the group of metastatic (MA population) and locally advanced patients were obtained by an exploratory subgroup analysis.
An absolute gain in terms of median survival of 26 days in favour of the group treated with the combination was observed (5.9 months vs 5.1 months, p=0.029) in the metastatic subgroup. However, no difference was observed between the two treatments in the locally advanced subgroup (8.5 months in the combination group vs 8.2 months with gemcitabine alone).

No significant difference was observed between the two groups for the secondary endpoints, progression-free survival, objective response rate and median response duration.
No improvement in quality of life was observed in Tarceva-treated patients. However, a significant deterioration was observed for diarrhoea in the Tarceva group.

The incidence of serious adverse events was 51% in the Tarceva-gemcitabine group and 39% in the gemcitabine group. The main side effects were gastrointestinal (diarrhoea) and cutaneous reactions.

To conclude, the therapeutic benefit of Tarceva in metastatic pancreatic cancer was evaluated by exploratory subgroup analysis which showed a small gain of 26 days in median overall survival in favour of the Tarceva – gemcitabine combination vs gemcitabine alone at the price of an increase in the incidence of diarrhoea and skin reactions.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In more than 90% of cases, pancreatic cancer is diagnosed at a locally advanced or metastatic stage. The 5-year survival rate is less than 5% in inoperable patients[2];
Tarceva is intended for curative treatment;
The efficacy/safety ratio is low;
This proprietary drug is intended for first-line therapy;
There is an alternative medication;
Expected public health benefit:

Metastatic pancreatic cancer represents a moderate public health burden.

Because of the seriousness of its prognosis, improving its management is a public health need.

A review of the study results shows that the Tarceva + gemcitabine combination is not expected to have any impact in terms of a reduction in morbidity and mortality compared to gemcitabine monotherapy. It only had a marginal effect on survival in the clinical study with no improvement in quality of life and it is not clear if these results can be extrapolated to clinical practice. Moreover, the possibility of a negative impact on quality of life cannot be ruled out in a real-life setting in particular because of the high incidence of diarrhoea in the treated population.

Consequently, Tarceva used in combination with gemcitabine is not expected to benefit public health in this indication.

The actual benefit of this medicinal product is insufficient in view of the available clinical data: results obtained by an exploratory subgroup analysis which showed a 26-day gain in median overall survival in favour of the Tarceva – gemcitabine combination vs gemcitabine alone with no improvement in patient quality of life and an increase in the incidence of diarrhoea and skin reactions with Tarceva – gemcitabine.

4.3. Transparency Committee recommendations

The Transparency Committee did not recommend inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services in this extension of indication.

[2] EPAR Tarceva 2006