HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 February 2008

XELODA 150 mg, film-coated tablet
6 PVC/polyethylene/PVDC blister packs of 60 tablets (CIP 365 745-6)

XELODA 500 mg, film-coated tablet
12 PVC/polyethylene/PVDC blister packs of 120 tablets (CIP 365 746-2)

Applicant: ROCHE

capecitabine

ATC code: L01BC 06

List I
Medicinal product available only on hospital prescription. Prescription restricted to specialists in oncology or haematology or oncologists. Medicinal product requiring specific monitoring during treatment.

Date of Marketing Authorisation (centralised European procedure): 2 February 2001
Revisions: 21 March 2002 - 30 March 2005 - 28 March 2007 (indication to be assessed)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication "Xeloda is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen".

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

capecitabine

1.2. Therapeutic Indications

"Xeloda is indicated for first-line treatment of advanced gastric cancer in combination with a platinum–based regimen.

Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III colon cancer (Dukes' stage C).

Xeloda is indicated for the treatment of metastatic colorectal cancer.

Xeloda, in combination with docetaxel, is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy shoud have included an anthracycline. Xeloda is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen, or for whom further anthracycline therapy is not indicated."

1.3. Dosage

"Advanced gastric cancer:
In combination with a platinum-based regimen, the recommended dose of Xeloda is 1,000 mg/m^2 twice a day for fourteen days, followed by seven days without treatment. The first dose of Xeloda is administered on the evening of day one and the last dose on morning of day fifteen. If the treatment also includes epirubicin, the recommended dose of Xeloda is 625 mg/m^2 twice a day without interruption. Epirubicin should be administered at a dose of 50 mg/m^2 as a bolus injection on day one every three weeks. The platinum-based regimen (cisplatin, at a dose of 60 mg/m^2 (in tritherapy) - 80 mg/m^2 (in bitherapy) or oxaliplatin at a dose of 130 mg/m^2) should be administered on day one, as a two-hour intravenous perfusion, every three weeks.
For patients receiving Xeloda in combination with cisplatin, premedication designed to maintain good hydration and an antiemetic should be initiated before cisplatin administration (in accordance with the SPC for cisplatin)."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

L	:	Antineoplastic and immunomodulatory agents
L01	:	Antineoplastics
L01B	:	Antimetabolites
L01BC	:	Pyrimidine analogues
L01BC06	:	capecitabine

2.2. Medicines in the same therapeutic category

Pyrimidine analogues indicated in the treatment of gastric cancer (i.v. route) and included in the list of medicines approved only for use in hospitals:

- FLUOROURACIL ICN
- FLUOROURACIL DAKOTA
- FLUOROURACIL ARROW
- FLUOROURACIL TEVA
- FLUOROURACIL MERCK

2.3. Medicines with a similar therapeutic aim

- CISPLATYL (cisplatin)
- FARMORUBICINE (epirubicin)
- TAXOTERE (docetaxel)
- ADRIBLASTIN (doxorubicin)
- AMETYCINE (mitomycin C)
- ELOXATIN (oxaliplatin) (Temporary Treatment Protocol referred in the guidelines of digestive oncology drug use published by the French National Cancer Institute in December 2006)

N.B.: these drugs are approved for hospital use only.

3 ANALYSIS OF AVAILABLE DATA

The efficacy and safety of XELODA in the treatment of advanced gastric cancer were assessed in the pivotal study ML17032 which compared the XELODA/cisplatin combination with the 5-FU/cisplatin combination.

The EMEA's assessment also took into account a "support" study added to the the questions' answers file. This study: REAL2 compared the efficacy and safety of XELODA to continuous 5-FU infusion as well as the efficacy and safety of oxaliplatin compared to cisplatin. This study also compared the efficacy and safety of the XELODA/epirubicin/oxaliplatin combination ("EOX" protocol) with those of the 5-FU/epirubicin/cisplatin combination ("ECF" protocol).

3.1. Efficacy

Study ML17032
This was an open-label, randomised study comparing XELODA plus cisplatin with 5 FU plus cisplatin in 316 patients suffering from locally advanced or metastatic gastric cancer.

Methodology:
The main analysis performed in the study was a non-inferiority analysis based on progression free survival.
The statistical analysis was based on the following hypothesis: non-inferiority was established if the upper limit of the 95% confidence interval for the relative risk was below 1.25.

Patients were randomised in two groups to receive at least two cycles of treatment (six weeks):
either XELODA – cisplatin (1 cycle = 21 days) [XP protocol]:
- capecitabine: 1,000 mg/m² twice a day from day 1 to day 14
- cisplatin: 80 mg/m² by two-hour infusion on day 1

or 5-FU – cisplatin (1 cycle = 21 days) [FP protocol]:
- 5-FU: 800 mg/m² by continuous infusion from day 1 to day 5
- cisplatin: 80 mg/m² by two-hour infusion on day 1

Primary endpoint: progression-free survival, defined as the period between randomisation and any disease progression or death due to any cause.

Secondary endpoints:
- Objective Response Rate: complete or partial response
- Overall Survival: time from randomisation to death (or, where relevant, the last date on which the patient was known to be still alive),
- Time To Progression: time between randomisation and the first progression,
- Duration of response: time between the first documented (complete or partial) response and the date of disease progression or date of death,
- Safety

Results:
The median age of the patients was 56.
Approximately 90% of the patients had not previously had chemotherapy.
There were 88% of the patients in the Xeloda/cisplatin group were in the metastatic stage, and 81% o in the 5-FU/cisplatin group.

- Primary endpoint: progression-free survival
The median progression-free survival in the PP population was 5.6 months in the Xeloda/cisplatin group and 5 months in the 5-FU/cisplatin group.
The hazard ratio (HR) was 0.85 with an upper limit of the 95% confidence interval of 1.11 (below the limit of 1.25 specified in the protocol).
Similar results were observed in the ITT population: HR = 0.84 with an upper limit of the 95% confidence interval of 1.09.

- Secondary endpoints:
In the ITT population:
- the objective response rate (complete and partial response) was 40.6% in the Xeloda/cisplatin group and 28.8% in the 5-FU/cisplatin group (p= 0.0295).
- the median duration of response was 7.6 months in the Xeloda/cisplatin group and 6.2 months in the 5-FU/cisplatin arm (p=0.55).
- time to progression was 5.5 months for patients in the Xeloda/cisplatin group and 5.3 months for those receiving the 5-FU/cisplatin combination; HR = 0.83 (95% CI: 0.61; 1.12).
- there was no difference between the two groups as regards overall survival: 10.4 months in the Xeloda/cisplatin group versus 8.9 months in the 5-FU/cisplatin group; HR = 0.85 (95% CI: 0.65; 1.11).
- the one-year survival rate was 36.1% in the Xeloda/cisplatin group and 34.8% in the 5-FU/cisplatin group.

REAL2 study
This was a randomised, open-label phase III study comparing Xeloda to 5-FU and oxaliplatin to cisplatin as first-line treatment for advanced oesophagogastric and gastric cancer. 1,002 patients took part in this study and were randomised in one of the four following groups using a 2x2 factorial plan:
− ECF: epirubicin (50 mg/m^2 as a bolus injection on day 1 every three weeks), cisplatin (60 mg/m^2 by two-hour perfusion on day 1 every three weeks) and 5-FU (200 mg/m^2 a day by continuous perfusion via a central route).
− ECX: epirubicin (50 mg/m^2 as a bolus injection on day 1 every three weeks), cisplatin (60 mg/m^2 by two-hour perfusion on day 1 every three weeks) and Xeloda (625 mg/m^2 twice a day by continuous administration).
− EOF: epirubicin (50 mg/m^2 as a bolus injection on day 1 every three weeks), oxaliplatin (130 mg/m^2 by two-hour perfusion on day 1 every three weeks) and 5-FU (200 mg/m^2 once a day by continuous perfusion via a central route).
− EOX: epirubicin (50 mg/m^2 as a bolus injection on day 1 every three weeks), oxaliplatin (130 mg/m^2 by two-hour perfusion on day 1 every three weeks) and Xeloda (625 mg/m^2 twice a day by continuous administration).

Methodology:
Themain analysis of the study was a non-inferiority analysis based on overall survival.
The statistical analysis was based on the following hypothesis: non-inferiority was established if the upper limit of the 95% confidence interval for the relative risk was below 1.23.

- Primary endpoint: overall survival defined as the time from the date of randomisation to the date of death from any cause.

Secondary endpoints: progression-free survival, response rate, quality of life and safety.

Results:
Forty percent of the patients had a gastric cancer.
The principal efficacy analyses in the per-protocol population showed the protocols containing Xeloda to be not inferior to those containing 5-FU in terms of overall survival (HR = 0.86; 95% CI: 0.75 to 0.99) and the protocols containing oxaliplatin to be not inferior to those containing cisplatin (HR = 0.92, 95% CI: 0.80 to 1.05). The medial overall duration of survival was 10.9 months for patients undergoing chemotherapy based on Xeloda and 9.6 months for those undergoing chemotherapy based on 5-FU. The median overall duration of survival was 10.1 months for patients undergoing chemotherapy based on cisplatin and 10.4 months for those undergoing chemotherapy based on oxaliplatin. Non-inferiority was also demonstrated in ITT.

Superiority tests were conducted, on overall survival after one year, and showed the following results:
- no difference between Xeloda based protocols (ECX+EOX) versus those based on 5-FU (ECF+EOF). The median survival duration was 10.7 months in the Xeloda group and 9.5 months in the 5-FU group (HR=0.88 [50.77-1.00]).
-no difference between oxaliplatin based protocols versus those based on cisplatin (median survival duration of 10.4 months for patients treated with oxaliplatin versus 9.9 months for those treated with 5-FU; HR= 0.91 [0.79-1.04]).
- an absolute gain of approximately one month in favour of the EOX protocol versus the ECF protocol (median survival duration of 11.2 months for patients in the EOX protocol versus 9.9 months for patients in the ECF protocol; HR=0.80 [0.66-0.97], p=0.02).

No difference between the four chemotherapy protocols was observed with regard to the secondary criteria.

The Committee notes that only 40.5% of the patients had a gastric cancer. The four groups were not evenly distributed: in particular, the number of gastric tumours was higher in the capecitabine groups, and there were more patients with performance status 0 in the XELODA groups. Three intermediate analyses were performed: the first two investigated tolerance and the third also looked at overall survival. However, it is not known whether an appropriate method to counter the alpha risk should have been applied, both in the context of a superiority hypothesis and of a non-inferiority hypothesis. Within the factorial plan, the direct comparison made in terms of superiority of the EOX protocol versus the ECF protocol can only be considered as an exploratory one, or at best as a secondary objective study (but not specified in advance), and appropriate correction of the alpha risk should also be needed.

Overall, the REAL2 study only confirmed the non-inferiority of Xeloda versus 5-FU.

3.2. Adverse effects

The tolerance data were obtained from the pivotal study ML17032.

The percentage of patients experiencing grade 3/4 adverse effects (about 50% in each group) and the rate of withdrawals from the study because of adverse events (18% in each treatment group) were similar in both groups.
Gastrointestinal adverse events were the most frequent ones in both groups, and mainly consisted of nausea and vomiting. 51% of patients being treated with XELODA/cisplatin experienced vomiting, as did 59% of patients being treated with 5-FU/cisplatin. 12% of patients being treated with XELODA/cisplatin developed stomatitis, as did 27% of patients being treated with 5-FU/cisplatin. Hand-foot syndrome affected 22% of patients in the Xeloda/cisplatin group and 4% of patients in the 5-FU/cisplatin group.

3.3. Conclusion

A comparative study (pivotal study ML17032) was carried out with the principal objective of establishing the non-inferiority of treatment by XELODA plus cisplatin to treatment by 5-FU plus cisplatin in 316 patients suffering from locally advanced or metastatic gastric cancer. The primary analysis conducted during the study showed the non-inferiority of XELODA plus cisplatin vs 5-FU plus cisplatin.
The EMEA's assessment also took into account a study added to the list of answers to the questions it had raised. This was the REAL2 study, which compared the efficacy and safety of XELODA to continuous 5-FU perfusion and the efficacy and safety of oxaliplatin compared to cisplatin. The regimens were administered in the context of chemotherapy protocols using a 2x2 factorial plan. The results of this study confirmed the non-inferiority of Xeloda as compared to 5-FU. Within the factorial plan, the direct comparison made in terms of superiority of the EOX protocol versus the ECF protocol can only be considered as an exploratory one, or at best as a secondary objective study.

The safety profile of the two treatments was different: in particular, hand-foot syndrome occurred more frequently in the XELODA group and stomatitis was more common in the 5-FU group.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Gastric cancer is a serious illness that affects patient's vital prognosis;
XELODA provides a curative treatment;
This drug is a first-line medicinal product;
Its efficacy/adverse effects ratio is important;
Alternative drugs are available;

Public health benefit:

Metastatic gastric cancer represents a considerable public health burden.
Improvement in its management is a public health need falling within the scope of the fight against cancer and the national palliative care development program.
Considering the data available, XELODA in combination with platinum -based regimenis not expected to bring any additional impact in the morbi-mortality decrease or patients' quality of life improvement compared to current management.
Consequently, XELODA is not expected to have a public health benefit for this indication.

The actual benefit of XELODA is substantial.

4.2. Improvement in actual benefit

Given the lack of data showing Xeloda to be superior to 5-fluorouracil, the Committee i considers that Xeloda does not provides IAB versus this comparator.

4.3. Therapeutic use

At the advanced stage of gastric cancer, the objective of palliative chemotherapy is to improve patient survival and quality of life in comparison with symptomatic treatment alone.
There is no consensus on the reference treatment of advanced gastric cancer.
Polychemotherapy regimens are more active than single-agent chemotherapy, they give better response rates but with a low benefit in terms of survival. The median survivals in phase III studies are still low, between 7 and 10 months at best. The reference chemotherapy regimens remain the 5-fluorouracil/cisplatin (CF) and epirubicin/cisplatin /5-fluorouracil (ECF) combinations.
The European Society for Medical Oncology (ESMO) recently recommended the ECF for patients selected on the basis of age and general condition, though this would be at the price of increased toxicity[1].
XELODA in combination with a platinum-based regimen represents an interesting alternative to 5FU administered i.v., because of its equivalent efficacy as well as its oral administration .

4.4. Target population

The target population of XELODA is represented by patients with advanced gastric cancer.
This population includes two subgroups:

- patients with a locally advanced or metastatic cancer at the time of diagnosis

1. 1 Gastric cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology 18 (Supplement 2): ii17–ii18, 2007
2.

- patients diagnosed at a localised stage and who will progress to a locally advanced or metastatic stage.

In France, the incidence of gastric cancer was 7,126 new cases in 2000[2].
At the time of diagnosis, approximately 30% of the patients are already at the metastatic stage[3] [4].
Approximately 50% to 60% of patients already have a locally advanced or metastatic form of the condition when they are first diagnosed (around 30% have a locally advanced form and 30% have a metastatic form)[3]. between 3,500 and 5,000 patients are diagnosed with an advanced form every year in France.
In order to calculate the total number of patients with advanced gastric cancer, the number of patients whose cancer was diagnosed before reaching an advanced stage, but which has now become locally advanced or metastatic should be considered as an extra group. No epidemiological data allowing such an estimate to be made are available.
As the mortality rate in the year following diagnosis at this stage results very high, we can consider that the number of patients suffering from locally advanced or metastatic gastric cancer and undergoing first-line treatment is probably the same as the number of deaths a year, i.e. 5,000 to 5,500 patients.

The target population for Xeloda in this indication is estimated at 5,000 to 5,500 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 for this extension of indication.

4.5.1. Packaging

Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 100%

2 INVS. Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000 [Evolution of the incidence of cancer and cancer mortality in France between 1978 and 2000].
3 Faycal J, Bessaguet C, Nousbaum JB, Cauvin JM, Cholet F, Bideau K, Robaszkiewic M, Gouérou H. Epidemiology and long term survival of gastric carcinoma in the french district of Finistère between 1984 and 1995
4 Fédération Nationale des Centres de Lutte Contre le Cancer (http://www.fnclcc.fr)