HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

26 April 2006

XELODA 150 mg, film-coated tablet
6 PVC/PE/ PVDC blister of 10 tablets: 365 745-6

XELODA 500 mg, film-coated tablet
12 PVC/PE/ PVDC blister of 10 tablets: 365 746-2

Applicant: ROCHE

capecitabine

List I
Medic for hospital prescription only. Prescription restricted to oncology or haematology specialists, or physicians qualified in oncology. Medic requiring special monitoring during treatment.

Date of centralised European Marketing Authorisation: 02 February 2001
Amendments: 21 March 2002 and 30 March 2005

Reason for application: inclusion on the list of products reimbursed by National Insurance and approved for use in hospitals in the extension of indication " Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer ."

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

capecitabine

1.2. Indications

Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer .
Xeloda is indicated for first line monotherapy of metastatic colorectal cancer.
Xeloda is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen .
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 should 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 anthracyclinecontaining chemotherapy regimen or for whom further anthracycline therapy is not indicated.

1.3. Dosage

Xeloda should only be prescribed by a qualified physician experienced in the utilisation of antineoplastics agents.

Recommended posology:
The recommended dose is 1250 mg/m² administered twice a day (morning and evening), i.e. a total daily dose of 2500 mg/m² for 14 days, followed by a seven day rest-period.
Xeloda tablets should be swallowed with water, within 30 minutes after a meal.
Treatment should be discontinued if progressive disease or intolerable toxicity is observed.
In combination with docetaxel: the recommended dose of Xeloda is 1250 mg/m² twice a day for 14 days, followed by a 7 day rest-period, combined with 75 mg/m² of docetaxel as 1 hou I.V. infusion, every three weeks.
For patients receiving the combination of Xeloda plus docetaxel, premedication with an oral corticosteroid, such as dexamethasone, should be started prior to docetaxel administration (in accordance with the SPC for docetaxel).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L : Antineoplastic and immunomodulating agents
L01 : Antineoplastic agents
L01B : Antimetabolites
L01BC : Pyrimidine analogues
L01BC 06 : capecitabine

2.2. Medicines in the same therapeutic category

Pyrimidine analogues indicated as adjuvant therapy to surgery for colorectal cancer (administered by injection):

5 Fluorouracil (5FU):
- Fluorouracil ICN
- Fluorouracil Dakota
- Fluorouracil Meram
- Fluorouracil Merck
- Fluorouracil Teva

2.3. Medicines with the same therapeutic aim

- folinic acid (FA) indicated in combination with 5 fluorouracil.
- Calcium levofolinate (Elvorine)
- Calcium folinate Aguettant
- Calcium folinate Dakota Pharm
- Disodium folinate (Nafoline)

- oxaliplatin (Eloxatin)

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and safety of Xeloda in stage III (Dukes' C) colon cancer as an adjuvant therapy has been evaluated in the pivotal X-ACT[1] study.
An open, randomised clinical trial comparing Xeloda monotherapy with folinic acid and a 5-FU bolus (Mayo Clinic FUFOL regimen) in 1987 patients with stage III colon cancer (Dukes' C) following resection.

Methodology:
The main analysis of the study was a non-inferiority analysis assessing disease-free survival. A second planned statistical analysis was a superiority test on disease-free survival and an equivalence test on disease-free survival at 3 years.
The statistical analysis was based on the following hypothesis: non-inferiority was established if the upper limit of the 95% confidence interval for relativeCI riskwas lower than 1.25.

Patients were randomised to receive one of the following treatments for 24 weeks (6 months):
- treatment with Xeloda given orally: 1250 mg/m^2 twice daily from D1 to D14 every 3 weeks (8 cycles)
- or 5-FU/FA given as an IV bolus according to the Mayo Clinic regimen: folinic acid 20 mg/m^2 + 5-FU 425 mg/m^2) from D1 to D5 every 4 weeks (6 cycles).

Primary endpoint: disease-free survival defined as the number of days between randomisation and onset of first relapse, onset of a second colon cancer or death from any cause, or the last date on which the patient was assessed as being disease-free.

1 Twelves et al. Capecitabine as adjuvant treatment for stage III Colon Cancer. N Engl J Med 2005: 2696-2748.

Secondary endpoints:
- Relapse-free survival, and the same assessment as for disease-free survival, excluding deaths unrelated to treatment or disease progression.
- Overall survival, defined as the number of days between randomisation and date of death or the last date on which the patient was alive.
- Quality of life measured by the EORTC QLQ-C30 questionnaire on entry into the study and before the treatment cycle at weeks 7, 16, 25 in the capecitabine group and at weeks 9, 17 and 25 in the 5-FU/FA group.

Results:
Median age of patients was 62 years (25–80 years)
After a median follow-up of 3.8 years, the relative risk concerning disease-free survival (primary endpoint) was 0.87 [95% CI 0.75–1.00] for ITT and 0.89 [95% CI 0.76–1.04] in the per protocol analysis.

Results of the superiority test showed, in the ITT analysis, that there was no difference in disease-free survival (primary endpoint) at 3 years between the two arms of treatment (64.2% compared with 60.6% in the 5-FU/FA group, with a 13% of reduction in risk of relapse).

Secondary endpoints showed a significantly longer relapse-free survival in the Xeloda arm (65.5% compared with 61.9% with the Mayo clinic FUFOL regimen; p=0.041). However, there was no difference in overall survival at 3 years between the two groups (81.3% with Xeloda compared with 77.6% with FUFOL).
Quality of life measured by the EORTC QLQ-C30 questionnaire showed no difference between the two treatment arms .

Note:
The bolus administration of 5-FU (Mayo clinic FUFOL regimen) is not current practice in Europe, where the preference is to give 5-FU as a continuous infusion, e.g. LV5FU2 (5FU 400 mg/m^2 IV bolus followed by infusion of 600 mg/m^2 D1, D2,/F A: 200 mg/m^2 on D1, administered every 2 weeks), which has equivalent efficacy with lower toxicity, as shown by a comparative study (T André et al. Semimonthly Versus Monthly Regimen of Fluorouracil and Leucovorin Administered for 24 or 36 Weeks as Adjuvant Therapy in Stage II and III Colon Cancer: Results of a Randomized Trial. J Clin Oncol 2003: 21(15): 2896-2903).

Additional data:

In a comparative study (MOSAIC) (oxaliplatin combined with LV5FU2, the FOLFOX4 regimen compared with LV5FU2) in 2,246 patients with colon cancer requiring adjuvant therapy after resection, 3-year disease-free survival in stage III patients was 72.8% in the FOLFOX4 group compared with 65.8% in the LV5FU2 group (relative risk 0.75, 95 % CI 0.62–0.90; p = 0.002). The FOLFOX4 combination induced additional adverse events, in particular neurological toxicity.

3.2. Undesirable effects:

Treatment discontinuation due to undesirable effects were more frequent in the Xeloda group (150 patients, 15.1%) than in the FUFOL group (48 patients, 4.9%) [mainly hand-foot syndrome]: 3% with Xeloda and fewer than 1% with FUFOL.

The most frequent undesirable effect observed with Xeloda was hand-foot syndrome[2]: 60% compared with 9% with FUFOL, all grades included. Grade 3 was 17% with Xeloda compared with 0.5% with FUFOL. Bilirubin increase was also more frequent in the Xeloda group (50%, including 20% grade 3/4) than in the FUFOL group (20% including 6% grade 3/4).
The incidence of other types of grade 3/4 toxicity was lower withXeloda than with FUFOL: diarrhoea (11% versus 13% with FUFOL), stomatitis (2% versus 14% with FUFOL), neutropenia (2% versus 26% with FUFOL).

3.3. Conclusion

The primary endpoint of this comparative study was to establish the non-inferiority of Xeloda therapy compared with the combination 5 FU and folinic acid (Mayo Clinic FUFOL regimen) in 1,987 patients with stage III (Dukes' C) colon cancer after resection, the main study analysis showed that Xeloda was not inferior to the 5FU/AF regimen (bolus administration) which is used differently in Europe (continuous infusion). The secondary analysis planned in the protocol did not establish that Xeloda was superior to that combination in terms of disease-free survival.
The safety profile was different for both treatments, within particular hand-foot syndrome and hyperbilirubinaemia being more frequent in the Xeloda group. Diarrhoea, stomatitis and neutropenia were more frequent in the FUFOL group.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Colorectal cancer is a serious life-threatening disease. There is a high risk of recurrence after surgical resection of the primary tumour;
Xeloda is an adjuvant therapy administered after a curative resection of the primary tumour, in patients with stage III (Dukes' stage C) colon cancer.

Anticipated Public Health impact

The public health burden of stage III (Dukes' stage C) colon cancer is substantial. The public health burden for the population that could receive Xeloda, i.e. patients who are not candidates for oxaliplatin, is low, because by definition this population is fairly limited.

There is a public health need which is only partly covered by existing therapies. Based on the available data, it cannot be assumed that Xeloda would satisfy this need.

In view of the only study available in which the comparator is not the current gold standard adjuvant therapy (oxaliplatin-based regimens), it is not anticipated that there would be any impact on mortality or morbidity compared with drugs used in current practice.

The result of a health economics study included in the dossier provides insufficient data to assess the impact on the health system. In fact, this study did not compare Xeloda with current oxaliplatin-based regimens. Nevertheless, in view of the marginal role of Xeloda used as monotherapy in this indication, there is no anticipated impact on the health system, despite the benefit of an oral form.

Consequently, in the context of this extension of indication, and in the current state of knowledge, it is not anticipated that Xeloda would have any impact on public health.

2 Hand-foot syndrome is palmar-plantar erythrodysaesthesia characterised by redness and/or pain in the extremities which may lead to functional disability.

Xeloda is a first-line drug;
The /undesirable effects ratio for the drug is high;
Alternative drug therapies are available;

The actual benefit of Xeloda is substantial.

4.2. Improvement in actual benefit:

Xeloda does not contribute any improvement in actual benefit (level V) compared with the combination 5-Fluorouracil and folinic acid. However, the Committee is aware that the current gold standard adjuvant therapy in stage III colon cancer is an oxaliplatin-based regimen.

4.3. Therapeutic use

In non-metastatic colon cancer, surgery is the first-line treatment in most patients, including elderly patients. Nevertheless, 40–50% of patients relapse and subsequently require further treatment[3].
The risk of relapse after resection depends in particular on the tumour stage at the time of tumour resection. In tumours with a deep invasion of the intestinal wall (stage II, Dukes' stage B2) and/or locoregional lymph node metastases (stage III, Dukes' stage C), the risk of residual or distant microscopic metastases is significantly higher than in localised disease (stage I, Dukes' stages A and B1).
In stage III (Dukes' stage C) colon cancer, the benefit of systematic adjuvant chemotherapy after resection, with a combination of 5-fluorouracil and folinic acid (LV5FU2) given for 6 months has been well-established. The clinical benefit is expressed as improved survival, with a reduction in mortality of about 33% and a reduced risk of recurrence at 5 years.
Three-year results of the MOSAIC clinical trial show that the oxaliplatin + LV5FU2 regimen (FOLFOX4) contributed benefit in terms of recurrence-free survival compared with LV5FU2 alone, at the cost of mainly neurological toxicity.
Xeloda is an interesting alternative to intravenous 5FU because of its efficacy which is equivalent, and its oral route of administration. However, Xeloda monotherapy cannot currently replace oxaliplatin-based regimens.

4.4. Target population

In 1995, the annual incidence of colorectal cancer was 33,405[4]. As the incidence increased by 10% between 1985 and 1995, the estimated current annual incidence is 37,000 patients/year[5].

The following hypotheses were used:
- among these 37,000 patients, 2/3 had colon cancer and 1/3 had rectal cancer [6], i.e. an annual incidence of colon cancer of 24,600.

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3 Obrand DI, Gordan PH. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. Dis Colon Rectum 1997 ; 40(1): 15-24

4 Eilstein D, Hédelin G, Schaffer P. Incidence du cancer colorectal dans le Bas-Rhin: tendance et projection jusqu'en 2009. Bull Cancer 2000; 87 (7-8) : 595-599.

5 Bouvier AM. Côlon-rectum. In: Remontet L, Buemi A, Velten M, Jougla E, Estève J: Évolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000; 2003: 53-59. http://www.invs.sante.fr/publications/2003/rapport_cancer_2003

6 PMSI [footnote PMSI = the French national computerised medical information system program] – Statistics. http://stats.atih.sante.fr/mco/statone.php

- among the patients with a colon cancer resection, 30–40%[7] would be diagnosed at stage III every year, i.e. 7,500–10,000 patients.
Consequently, the number of patients likely to receive adjuvant therapy after a resection of a stage III colon cancer is around 7,500–10,000 a year.
However, in view of the progress in the current treatment strategy (oxaliplatin-based chemotherapy regimens), the target population for Xeloda could be patients who are not candidates for oxaliplatin. According to experts, this population is fairly limited and difficult to quantify.

4.5. Transparency Committee recommendations

Approval of 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 in this extension of indication

4.5.1. Packaging:
The packaging is appropriate for the prescription conditions.

4.5.2. Reimbursement level: 100%

7 Hamilton JM, Grem JL. Lower gastrointestinal cancer. In: Current Cancer Therapeutics, Third Edition. Philadelphia: Churchill Livingstone. Kirkwood JM, Lotze MT, Yasko JM eds. 1998: 156-160.