HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

13 May 2009

ERBITUX 5 mg/ml, solution for infusion
1 bottle of 20 ml (CIP: 570 750-8)
1 bottle of 100 ml (CIP: 570 752-0)

Applicant: MERCK LIPHA SANTE

Cetuximab

ATC Code: L01XC06

List I
Medicinal product for hospital use only
Prescription restricted to oncologists and cancerologists.

Date of MA (centralised): 29 June 2004 – Variations: 29 March 2006 – 17 July 2008

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the extension of indication "treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer:
• in combination with chemotherapy,
• as a single agent in patients who have failed oxaliplatin and irinotecan based therapy and who are intolerant to irinotecan"

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Cetuximab

1.2. Novel aspects

Cetuximab is a chimeric monoclonal IgG1 antibody specifically directed against the epidermal growth factor receptor (EGFR). In tumours, activation of the KRAS (Kirsten rat sarcoma) gene by EGFR contributes to EGFR-mediated increased proliferation, survival and the production of pro-angiogenic factors.

1.3. Indications

"Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer
• in combination with chemotherapy,
• as monotherapy in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck
- in combination with radiotherapy in the case of locally advanced disease,
- in combination with platinum-based chemotherapy for recurrent and/or metastatic disease[1]."

1.4. Dosage

"Erbitux must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.
Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions.

In all indications, Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m^2 body surface area. All subsequent weekly doses are 250 mg/m^2 each.

Colorectal cancer:
In patients with metastatic colorectal cancer, cetuximab is used in combination with chemotherapy or as a single agent. It is recommended that the detection of KRAS mutational status be performed by an experienced laboratory using a validated test method.
It is recommended that cetuximab treatment be continued until progression of the underlying disease."

1 This indication has not yet been evaluated by the French Transparency Committee. It will form the subject of a separate application.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic drugs
L01XC	Monoclonal antibodies
L01XC06	Cetuximab

2.2. Medicines in the same therapeutic category

2.2.1. Comparator drugs

VECTIBIX (panitumumab)
"Vectibix is indicated as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens."

2.3. Medicines with a similar therapeutic aim

- FLUOROURACIL ICN solution for infusion (fluorouracil) and proprietary medicines containing fluorouracil
- ELVORINE (folinic acid) and proprietary medicines containing folinic acid indicated in combination with fluorouracil.
- ELOXATINE (oxaliplatin)
- CAMPTO (irinotecan)
- TOMUDEX (raltitrexed)
- AMETYCINE (mitomycin C)
- AVASTIN (bevacizumab)
- XELODA (capecitabine)
- UFT (tegafur)

3 ANALYSIS OF AVAILABLE DATA

Since June 2004, ERBITUX is indicated in combination with irinotecan, in the treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer in patients failing irinotecan-based chemotherapy. This indication was evaluated by the French Transparency Committee on 16 March 2005.
On 17 July 2008, this indication was extended to first-line and subsequent treatment of metastatic colorectal cancer with a restriction to tumours expressing the non-mutated KRAS gene.

3.1. Efficacy

A/ First-line treatment
The dossier comprises two studies: a phase II study (EMR62202-47) and a phase III study (EMR62202-013).

Study EMR62202-47
Open-label, randomised, phase II study evaluating the efficacy and safety of ERBITUX in combination with the FOLFOX regimen vs FOLFOX only, in 337 patients with EGFR-expressing, metastatic colorectal cancer who had not received prior treatment.

The FOLFOX-4 chemotherapy regimen was administered every two weeks and combined:
- oxaliplatin: 85 mg/m² IV on day 1
- folinic acid: 200 mg/m², IV on days 1 and 2
- 5-FU: 400 mg/m², followed by 600 mg/m² IV on days 1 and 2.

ERBITUX was administered once weekly: the initial dose was 400 mg per m² body surface area and all subsequent doses were 250 mg/m².

The primary endpoint was the percentage overall response (sum of complete and partial responses)[2].
The secondary endpoints were progression-free survival (defined as the time between randomisation and disease progression or death of any cause), overall survival and resectability.

Results:
The median age of patients was 62 years in the ERBITUX + FOLFOX arm and 60 years in the FOLFOX only arm.
Approximately 90% of the study patients were in good general condition (ECOG performance status of from 0 to 1).
No difference was observed between the two groups for percentage overall response (46.2% vs 39.9% in the FOLFOX arm, p=0.243) and median progression-free survival (7.2 months in each group).
There was no data for overall survival (the median survival was not reached at the time of the analysis).
The percentage of complete microscopic resection was 4.7% in the ERBITUX + FOLFOX arm and 2.4% in the FOLFOX arm.

2 Corresponding to the endpoints used to evaluate the response in solid tumours summarised as follows:
Complete response: disappearance of all tumour lesions
Partial response: 30% reduction in the largest diameter of the lesions

A post-hoc analysis including patients with a tumour expressing the KRAS gene was performed. In the 134 patients (40% of the study population) with a wild-type KRAS tumour, the percentage of patients with an overall response was 60.7% in the ERBITUX + FOLFOX arm vs 37% in the Folfox only arm (p = 0.011). A gain of 0.5 months in progression-free survival in favour of the ERBITUX + FOLFOX arm was observed (7.7 vs 7.2 months, p=0.0163).

Study EMR62202-013
Open-label, randomised, phase III study evaluating the efficacy and safety of ERBITUX in combination with the FOLFIRI protocol vs FOLFIRI alone, in 1198 patients with EGFR-expressing, metastatic colorectal cancer who had not received prior treatment.

The primary endpoint was progression-free survival defined as the time between randomisation and disease progression or death from any cause.

Secondary endpoints were the percentage objective response, response duration, overall survival, resectability and quality of life (EORTC QLQ C30 questionnaire).

The FOLFIRI chemotherapy regimen was administered every two weeks and combined :
- irinotecan: 180 mg/m² IV on day 1
- folinic acid: 200 mg/m², IV on day 1
- 5-FU: 400 mg/m ² bolus dose on day 1 followed by IV infusion of 2400 mg/m² over 46 hours.
ERBITUX was administered in a first dose of 400 mg per m² body surface area during the first week and then 250 mg/m² weekly.

Results:
The median age of patients was 61 years in both arms.
Nearly all enrolled patients (97%) were in good general condition (ECOG performance status of from 0 to 1).

Median progression-free survival (primary endpoint) was 8.9 months in the ERBITUX + FOLFIRI arm vs 8.0 months in the FOLFIRI only arm, p=0.0479.
The percentage objective responses was 46.9% in the ERBITUX + FOLFIRI arm vs 38.7% in the FOLFIRI alone group, p=0.038.
There were no data for overall survival (median survival was not reached at the time of the analysis).
The quality of life analysis showed an improvement for two items, overall health and social function, in favour of the FOLFIRI only arm.
The percentage complete microscopic resection was 4.3% in the ERBITUX + FOLFIRI arm and 1.5% in the FOLFIRI only arm.

A post-hoc analysis including patients with a tumour expressing the KRAS gene was performed. In the 348 patients (29% of the study population) with a wild-type KRAS tumour, the median progression-free survival was 9.9 months in the ERBITUX + FOLFIRI arm vs 8.7 months in the FOLFIRI only arm (p = 0.0167).
In the subgroup of patients with a tumour with a mutated KRAS gene, there was no difference in the median progression-free survival between the two arms.

B/ Second-line or subsequent treatment

The dossier comprises two phase III studies (studies CA225006 and CA225025).

Study CA225006
Randomised open-label study evaluating the efficacy and safety of ERBITUX combined with irinotecan versus irinotecan alone in 1298 patients with EGFR expressing, metastatic colorectal cancer, failing oxaliplatin- plus fluoropyrimidine-based chemotherapy.

The primary endpoint was overall survival.
Secondary endpoints were the percentage of objective responses, progression-free survival and safety.

ERBITUX was administered weekly: the initial dose was 400 mg per m^2 body surface area and subsequent weekly doses were 250 mg/m^2.
Irinotecan was administered at the dose of 350 mg/m^2 in patients aged under 70 years and 300 mg/m^2 in those over 70 years, or those with a PS score of 2, or those who received pelvic or abdominal radiotherapy.

Results:
The median age of patients was 61 years in the ERBITUX + irinotecan arm and 62 years in the irinotecan monotherapy arm.
Approximately 95% of the study patients were in good general condition (ECOG performance status of from 0 to 1).
There was no difference in median overall survival (primary endpoint) between the two groups.
The median progression-free survival was 4 months in the ERBITUX + irinotecan group versus 2.6 months in the irinotecan only group ($p < 0.0001$).
The percentage of complete responses was 16.4% in the ERBITUX plus irinotecan group versus 4.2% in the irinotecan only group ($p < 0.0001$).

A post-hoc analysis including patients with a tumour expressing the KRAS gene was performed. In the 300 patients (23% of the study population) with a tumour with a wild-type KRAS gene, no difference was demonstrated between the two groups for :
- Median overall survival
- Progression-free survival
- Response rate

Study CA225025
Randomised, open-label study comparing ERBITUX combined with Best Supportive Care (BSC) with BSC alone in 572 patients with metastatic colorectal cancer expressing EGFR who failed treatment based on oxaliplatin, irinotecan and fluoropyrimidine for their metastatic disease.

The primary endpoint was overall survival.
Secondary endpoints were the percentage of objective responses and progression-free survival.

ERBITUX was administered weekly: the initial dose was 400 mg per m^2 body surface area and subsequent weekly doses were 250 mg/m^2.

Results:
The median age of patients was 63 years.
Approximately three quarter of patients were in good general health (ECOG PS score 0 to 1).
Median overall survival (primary endpoint) was 6.1 months in the ERBITUX arm versus 4.6 months in the BSC only arm, p= 0.0046.
Median progression-free survival was 1.9 months in the ERBITUX arm versus 1.8 months in the BSC only arm (p= 0.0001).
Post-hoc analysis was performed on patients whose tumour expressed the KRAS gene. In the 111 patients (19% of the study population) with a tumour with a wild-type KRAS gene, there was no difference in median overall survival between the two groups.
Median progression-free survival was 3.6 months in the ERBITUX group versus 1.9 months in the BSC only arm (p< 0.0002).

3.2. Advers effects

During the randomised studies, grade 3 or 4 adverse events that were more frequently observed in patients treated with ERBITUX were skin reactions, stomatitis and diarrhoea.
In study CA225006, 25.9% of patients in the ERBITUX arm discontinued treatment because of adverse events compared to 15.3% in the irinotecan monotherapy arm group. The incidence of cardiac adverse events was 6.4% including 3% with grades 3-4 in the ERBITUX arm and 3.8% including 2.1% with grades 3-4 in the irinotecan alone arm.

3.3. Conclusion:

The benefit of adding ERBITUX to first-line chemotherapy for epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type, metastatic colorectal cancer was evaluated by post-hoc analysis of two randomised studies.
In the prospective analysis of the phase II study evaluating the merits of adding ERBITUX to the FOLFOX protocol, the primary objective was not reached (no difference in percentage of overall responses). In the phase III study, there was no clinically relevant improvement in progression-free survival (8.9 vs 8.0 months, p=0.0479) when ERBITUX was added to FOLFIRI.
A post-hoc analysis including patients with a tumour expressing the KRAS gene was performed for both of these studies. In the 40% of the phase II study population with a tumour with a wild-type KRAS gene, the percentage of overall responses was improved in the ERBITUX arm (60.7% vs 37% in the Folfox only arm (p = 0.011) with no clinically relevant gain in progression-free survival (0.5 months).
In the 29% of the phase III population with a wild-type KRAS tumour, a gain in median progression-free survival was observed in the ERBITUX + FOLFIRI arm (9.9 months vs 8.7 months in the FOLFIRI only arm p = 0.0167).
There are no overall survival data in these two studies.

In the second and subsequent lines of treatment of metastatic colorectal cancer, the dossier comprised two phase III studies. In the prospective analysis of the study which evaluated the benefit of adding ERBITUX to irinotecan after failure of oxaliplatin plus fluoropyrimidine-based chemotherapy, the primary objective was not reached. In the study which evaluated ERBITUX monotherapy after failure of treatments based on oxaliplatin, irinotecan and fluoropyrimidine, the median overall survival (primary endpoint) was improved by 1.5 months in the ERBITUX arm compared to the BSC alone arm (6.1 versus 4.6 months, p= 0.0046).
The post-hoc analysis on the subgroup of patients with a tumour expressing the KRAS gene was performed for each of these studies. It showed that no benefit was obtained by adding ERBITUX to irinotecan for all endpoints. In the case of monotherapy, there was an improvement of 1.7 months in progression-free survival (3.6 months vs 1.9 for the BSC alone group) with no difference on median overall survival.

During the randomised studies, grade 3 or 4 adverse events more frequently observed in the ERBITUX groups were skin reactions, stomatitis and diarrhoea.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Colorectal cancer is a serious and life-threatening condition;
This proprietary drug is intended to provide curative treatment;
Public health benefit:

Colorectal cancer is a frequent and serious clinical condition which represents a major public health burden. The burden of metastatic colorectal cancer is considerable and that of the population of patients likely to benefit from ERBITUX (expressing EGFR with a non-mutated KRAS gene) may also be considered as considerable.

The need to improve the management of these patients comes within the scope of an identified public health priority (GTNDO4: management of cancer).
Based on available data (post hoc analyses, in sub-groups), ERBITUX is only expected to have a positive impact on morbidity and mortality in patients expressing the EGFR receptor with a wild-type KRAS gene though this impact cannot be quantified.
In addition, the transposability of the results (post hoc analyses, sample sizes and uncertainty about the population likely to benefit from this targeted therapy) is not certain.
Consequently, given our current knowledge, the expected public health benefit of the proprietary medicine ERBITUX as first-line treatment and as second and subsequent lines of treatment for metastatic colorectal cancer cannot be evaluated. This product is not expected to benefit public health.

<u>As first-line treatment:</u>
Alternative drugs are available;
The efficacy/adverse effects ratio is moderate;
The actual benefit is susbtantial.

<u>For second and further lines of treatment:</u>
There are very few alternative medications at this stage of the disease;
The efficacy/ adverse effects ratio is moderate;
The actual benefit is susbtantial.

4.2. Improvement in actual benefit

Based on available data, the Transparency Committee considers that:
- as first- and second-line treatment, ERBITUX combined with standard chemotherapy does not improve actual benefit (level V) compared to usual management.
- as monotherapy after failure of irinotecan or oxaliplatin-based treatment, ERBITUX provides a minor improvement in actual benefit (level IV) compared to best supportive care alone.

4.3. Therapeutic use

There has been considerable progress in the treatment of metastatic colorectal cancer during recent years. Overall survival was first significantly increased following the routine use of irinotecan and oxaliplatin, in combination with 5-fluorouracil (5FU) and folinic acid (AF) in the form of LV5FU2, called the Folfiri and Folfox regimens respectively. A study showed that the Folfiri-Folfox and Folfox-Folfiri sequences had an equivalent efficacy when used for first- and second-line treatments[3].

Since the development of targeted therapies, the benefit of combining chemotherapy and a targeted therapy for first- and second-line treatment seems to have been established[4].

As first-line treatment, the anti-VEGF antibody, bevacizumab and the anti-EGFR antibody cetuximab have been evaluated. Bevacizumab in combination with chemotherapy has already been validated for first-line treatment**Erreur ! Signet non défini.**. Currently, no predictor of response to bevacizumab has been identified. In the absence of any direct comparative data, the place of ERBITUX with respect to bevacizumab is unknown.

For second-line therapy, after progression with irinotecan plus bevacizumab, the choice is either to modify chemotherapy by replacing irinotecan with oxaliplatin or to change targeted therapy by introducing cetuximab, an anti-EGFR antibody. It is no longer recommended to test the EGFR status by immunohistochemistry as the method is unreliable and not predictive of response but this choice involves the test for a KRAS gene mutation in the tumour.

For third-line therapy after progression with irinotecan and oxaliplatin (with or without bevacizumab):

- no KRAS gene mutation:
  - either cetuximab
  - or Vectibix
- presence of a KRAS gene mutation: palliative care or clinical trial.

4.4. Target Population

The target population for first-line treatment with ERBITUX comprises all patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer.

In 2000, the incidence of colorectal cancer was approximately 36,000 cases[5] .

Metastatic stages are observed in about half the cases[6].

Approximately 75% of patients with metastatic colorectal cancer have a tumour expressing EGFR.

The incidence of KRAS gene mutations is between 30 and 50% in metastatic colorectal cancer[7].

Thus the target population of ERBITUX as first-line treatment may be estimated to be between 4,100 to 6,800 patients per year.

For second-line and subsequent therapy, the target population of ERBITUX comprises patients with EGFR-expressing, KRAS wild-type, metastatic colorectal cancer who have already been treated for their metastatic disease and have failed at least one treatment.

According to the experts, approximately 80% of patients receiving first-line treatment will relapse and thereafter receive second- or even third-line treatment (approximately 20% of patients are not candidates for subsequent treatment as there life expectancy is two short or

3 Tournigand C, André T, Achille E, et Al. J Clin Oncol. 2004 ;22(2):229-37
4 SNFGE Thesaurus of gastrointestinal oncology, 2007 (metastatic colonic cancer. Updated on 29/01/2009)
5 Changes in cancer incidence and mortality in France from 1978 to 2000 (INVS 2003)
6 EPAR Erbitux 2004
7 EPAR Erbitux 2009

they have various contraindications). Hence the target population of ERBITUX as second-line and subsequent treatment may be estimated to be 3,300 to 5,500 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicinal products approved for use by hospitals and various public in these extensions of indication.