HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

30 April 2008

VECTIBIX 20 mg/ml concentrate for solution for infusion - 5 ml vial
Pack of 1 (CIP: 571 818-5)

VECTIBIX 20 mg/ml concentrate for solution for infusion - 10 ml vial
Pack of 1 (CIP: 571 819-1)

VECTIBIX 20 mg/ml concentrate for solution for infusion - 20 ml vial
Pack of 1 (CIP: 571 821-6)

Applicant: AMGEN S.A.S.

panitumumab

ATC code: L01XC08

List I
Medicinal product for hospital use only.
To be prescribed only by specialists in oncology or haematology or by doctors competent in oncology.
Medicinal product requiring special surveillance during treatment.

Date of conditional marketing authorisation (European centralised procedure): 3 December 2007

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

panitumumab

1.2. Background

Panitumumab is a fully human recombinant IgG2 monoclonal antibody that binds with high affinity and specificity to the human EGFR. EGFR promotes cell growth in normal epithelial tissues, including the skin and hair follicle, and is expressed on a variety of tumour cells.
The *KRAS* (Kirsten rat sarcoma 2 viral oncogene homologue) gene encodes a small, GTP-binding protein involved in signal transduction. A variety of stimuli, including that from the EGFR activates *KRAS*, which in turn stimulates other intracellular proteins to promote cell proliferation, cell survival and angiogenesis.
Panitumumab is a targeted therapeutic agent for patients who have a non-mutated *KRAS* gene.

1.3. Indication

"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."

1.4. Dosage

"Vectibix treatment should be supervised by a physician experienced in the use of anti-cancer therapy.
Detection of non-mutated *KRAS* expression should be performed by an experienced laboratory using a validated test method.

The recommended dose of Vectibix is 6 mg/kg of body weight given once every two weeks. Prior to infusion, Vectibix should be diluted in 0.9% sodium chloride injection to a final concentration not to exceed 10 mg/ml.
Vectibix must be administered as an intravenous (IV) infusion via an infusion pump, using a low protein binding 0.2 or 0.22 micrometer in-line filter, through a peripheral line or indwelling catheter. The recommended infusion time is approximately 60 minutes. Doses higher than 1000 mg should be infused over approximately 90 minutes."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

L	:	Antineoplastic and immunomodulating agents
L01	:	Antineoplastic agents
L01X	:	Other antineoplastic agents
L01XC	:	Monoclonal antibodies
L01XC08	:	panitumumab

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

- FLUOROURACIL ICN solution for infusion (fluorouracil) and proprietary drugs containing fluorouracil
- ELVORINE (folinic acid) and proprietary drugs containing folinic acid, indicated in combination with fluorouracil.
- ELOXATIN (oxaliplatin)
- CAMPTO (irinotecan)
- TOMUDEX (raltitrexed)
- AMETYCINE (mitomycin C)
- ERBITUX (cetuximab)[1]
- AVASTIN (bevacizumab)
- XELODA (capecitabine)
- UFT (tegafur).

[1] The marketing authorisation includes the indication “Erbitux in combination with irinotecan is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer who have failed irinotecan-based therapy.”

3 ANALYSIS OF AVAILABLE DATA

The dossier includes two studies:

- pivotal study 20020408
- non-comparative follow-up study 20030194, which included the patients from the palliative treatment arm of the pivotal study who were put on Vectibix secondarily after progression of their disease.

3.1. Efficacy

Study 20020408
Phase III, controlled, randomised, open-label study comparing the efficacy and safety of Vectibix combined with palliative treatment versus palliative treatment alone in 463 patients with metastatic colorectal cancer after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

Inclusion criteria: patients aged 18 or older with a confirmed diagnosis of metastatic colorectal carcinoma with radiological progression documented during or after prior fluoropyrimidine, oxaliplatin and irinotecan therapy given at adequate prescribed doses.
Patients should have a measurable lesion (≥ 20 mm), an ECOG status of 0 to 2, more than 1% of tumour cells expressing EGFR at the time of assessment and a suitable haematological, renal and hepatic profile.

Vectibix was given at a dose of 6 mg/kg once every two weeks in combination with palliative care (not including chemotherapy). Patients were treated until disease progression or unacceptable toxicity occurred.

Endpoints:
Tumour response according to modified-RECIST criteria was determined in weeks 8, 12, 16, 24, 32, 40 and 48, and then every three months until disease progression. Response was assessed by the investigators and then via a blinded centralised review of the scans by an independent panel.

The primary endpoint was progression-free survival[2].

The secondary endpoints were: overall survival (from baseline to patient death), objective response rate, duration of response, time to response, time to disease progression, time to treatment failure, duration of stable disease, patient-reported quality of life, and safety.

Results:
Of the 463 patients included (231 in the Vectibix plus palliative care arm and 232 in the palliative care alone arm), 63% were male.
The median age was 62 years (range 27 to 83). Three hundred and ninety-six patients (86%) had a baseline ECOG Performance Status of Two thirds of the patients had colon cancer and one third had rectal cancer.

The ITT results for the primary endpoint showed a progression-free survival of 8.0 (7.9-8.4) weeks in the Vectibix + palliative care arm vs 7.3 (7.1-7.7) weeks in the palliative care alone arm ($p < 0.0001$), i.e. an absolute gain of 5 days.
Over 50% of patients in both arms showed disease progression before the first scheduled visit (in the 8th week): 52% in the combination arm and 70% in the palliative care alone arm.

[2] Defined as the time between randomisation and the onset of disease progression or death from any cause.

No difference was seen in overall survival between the two arms: 52% deaths were observed in the combination arm vs 56% in the palliative care alone arm, p=0.60).
A partial response was observed in 19 patients (8%) in the combination arm and in none in the palliative care alone arm. No significant difference was observed in the quality-of-life assessment.

In all, the results of the prospective analysis showed no clinically relevant difference between the two arms in the number of weeks of progression-free survival (primary endpoint). Accordingly, on 24 May 2007 the CHMP issued an opinion against granting a marketing authorisation for this proprietary product.

Recent scientific publications have reported that a *KRAS* gene mutation in tumours has predictive value for an objective response to anti-EGFR treatments in colorectal cancer. In light of these data, a second analysis of study 20020408 was performed *post hoc* to include the presence or absence of *KRAS* mutation.

Results of the *post hoc* analysis:
In the subgroup of 427 patients eligible for analysis of their *KRAS* status, 184 patients (43%) had this mutation and 243 (57%) had a non-mutated, wild-type *KRAS* gene (marketing authorisation population).
KRAS mutation status could not be assessed in 4% of patients because insufficient tissue was available.

For patients with wild-type *KRAS* genes in their tumours, median progression-free survival (primary endpoint) was 16 weeks in the combination arm and 8 weeks in the palliative care alone arm. The hazard ratio was 0.49 (95% CI: 0.37-0.65), i.e. a 51% reduction in the risk of progression or death in favour of Vectibix. The primary endpoint results were not different in the mutant *KRAS* subpopulation.
No difference in survival was observed between the two groups.
The percentage of partial tumour response (assessed by a blinded independent central review panel) was 17% in the combination arm vs 0% in the palliative care alone arm. Disease progression was observed in 36% of patients in the combination arm vs 75% of patients in the palliative care alone arm.
The percentages for stable disease and disease control rate did not differ between the two arms.

Study 20030194
Study 20030194 is a non-comparative study including 175 patients from the palliative care alone arm of the pivotal study (20020408) who showed disease progression.
The primary objective of this follow-up study was to evaluate safety.
The wild-type *KRAS* gene was present in the tumours of 119 patients, 91 of whom were given Vectibix.
Approximately one third (59/175) of the patients stopped treatment for reasons other than disease progression; this proportion was higher than that observed in the pivotal study (22%).

The median follow-up time for all patients was 10.7 weeks (7.4-18.3). The median follow-up time for patients withdrawing from the study[3] was 8 weeks; this was shorter than in the pivotal study (17.9 weeks). The objective response rate was 10% (17/174).

3.2. Adverse events

Analysis of all patients who received Vectibix monotherapy (n=920) reveals that the most commonly reported adverse effects were skin reactions, observed in approximately 90% of

[3] The time to appearance of the event for these patients is unknown in this follow-up period.

patients. Most of them were mild to moderate in intensity, and roughly 10% were severe (NCI-CTC grade 3 or higher). Diarrhoea was reported with an incidence ≥ 1/10.
Other adverse effects described as common (>1/100 to <1/10) included infusion-related reactions (pyrexia and chills), stomatitis and dyspnoea.
The safety profile for Vectibix in patients with tumours expressing wild-type *KRAS* (n=123) was generally similar to that described above in the global population of metastatic colorectal cancer patients treated with Vectibix monotherapy. The only differences were the frequency of nausea, vomiting, dyspnoea and cough, which were very common (≥1/10) in the wild-type *KRAS* group and common (≥1/100 to <1/10) in the global population of metastatic colorectal cancer patients treated with Vectibix monotherapy.

3.3. Conclusion

Assessment of the therapeutic value of Vectibix was based on *post hoc* analysis of a phase III, controlled, randomised, open-label study comparing the efficacy and safety of Vectibix combined with palliative treatment versus palliative treatment alone in 463 patients with metastatic colorectal cancer after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

The results of the prospective analysis of the study in the global population did not show any clinically relevant gain in the Vectibix arm: an absolute gain of 5 days in terms of survival-free progression (primary endpoint). No difference was seen in overall survival between the two arms: 52% deaths were observed in the combination arm vs 56% in the palliative care alone arm, p=0.60). Accordingly, on 24 May 2007 the CHMP issued an opinion against granting Vectibix a marketing authorisation.

A second analysis of the study was performed *post hoc* to include the presence or absence of *KRAS* mutation. It was performed on subpopulations distinguishing 2 types of genetic profile: patients whose tumours had a mutant *KRAS* gene and those with a wild-type (non-mutated) *KRAS* gene.
Of 427 patients eligible for analysis of their *KRAS* status, 184 patients (43%) had this mutation and 243 (57%) had a wild-type *KRAS* gene (marketing authorisation population).
For patients with wild-type *KRAS* genes, progression-free survival (primary endpoint) was 16 weeks in the Vectibix combined with palliative care arm versus 8 weeks in the palliative care alone arm. No difference in survival was observed between the two groups.
Safety data are currently limited. The principal risks identified are skin toxicity (roughly 10% severe skin reactions, grade 3 or higher) and digestive toxicity (diarrhoea).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Colorectal cancer is a serious, life-threatening condition.
These proprietary products are intended for curative treatment:
They are for use as third-line treatment.
There are few alternatives at this stage of the disease.

Public health benefit:

> Colorectal cancer is a common, serious clinical condition and represents a major public health burden. The burden represented by metastatic colorectal cancer is considerable. That represented by the population of patients likely to benefit from this proprietary product (EGFR-expressing and with a wild-type *KRAS* gene, after failure of fluoropyrimidine, oxaliplatin and irinotecan-containing chemotherapy regimens) may be considered moderate.

Improving the management of this condition is a public health need that falls within an established priority (GTNDO[4]: cancer management).
In light of the available data (from just one *post hoc* analysis on subgroups of the pivotal study), the impact of VECTIBIX on morbidity, mortality and quality of life cannot be quantified.
In addition, it is not clear whether the results of the trial can be transposed into clinical practice because of uncertainty regarding the effectiveness of the genetic test to identify patients with a wild-type *KRAS* gene.
VECTIBIX is therefore unlikely to be able to fulfil the identified public health need.
Consequently, in the current state of knowledge, VECTIBIX is not expected to provide any public health benefit.

On the basis of currently available data, the efficacy/safety ratio for VECTIBIX is insufficiently well established (results are from a single *post hoc* exploratory subgroup analysis). However, in view of the seriousness of the disease and pending the results of two ongoing studies to be reported to the EMEA, the Committee considers that the actual benefit provided by VECTIBIX is substantial.

4.2. Improvement in actual benefit

In the absence of comparative data based on rigorous methodology, it is not possible to assess the therapeutic benefit of this medicine in this clinical situation. Consequently, the Transparency Committee considers that in the current state of knowledge Vectibix does not provide any improvement in actual benefit (level V) in the management of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

[4] National Technical Group for Defining Public Health Objectives (DGS) 2003.

4.3. Therapeutic use

Treatment for metastatic colorectal cancer has undergone major advances in recent years. Overall survival was first of all significantly increased due to the routine use of irinotecan and oxaliplatin in combination with 5-fluorouracil (5FU) and folinic acid (FA) in the form of LV5FU2, combinations known as Folfiri and Folfox, respectively. A study showed that the first- and second-line treatment sequences Folfiri – Folfox and Folfox – Folfiri were equally effective[5].

With the appearance of targeted therapies, the use of a combination of chemotherapy and targeted therapy as first- and second-line treatments was established[6].

The anti-VEGF antibody bevacizumab and the anti-EGFR antibody cetuximab were assessed as first-line treatments. In terms of progression-free survival, combining bevacizumab with Folfiri produces a 47% gain, whereas cetuximab provides only an 11% gain[7]. Bevacizumab therefore remains the product of choice for combining with first-line chemotherapy. No factor predicting response to bevacizumab has yet been identified.

For second-line therapy, where there is disease progression on irinotecan plus bevacizumab, the choice is either to change the chemotherapy by replacing irinotecan with oxaliplatin, or to change the targeted therapy by introducing cetuximab, an anti-EGFR antibody. Testing for EGFR status by means of immunohistochemistry is no longer recommended, since the method is unreliable and not response-predictive, but the latter choice requires testing for a mutation in the *KRAS* gene within the tumour.

For third-line treatment, in the event of disease progression on irinotecan and oxaliplatin (with or without bevacizumab):

- no *KRAS* mutation:
    - either cetuximab plus irinotecan
    - or Vectibix
- *KRAS* mutation: palliative care or therapeutic trial.

In conclusion, use of Vectibix (panitumumab) would seem to be reserved for third-line treatment of metastatic bowel cancer in the event of disease progression after irinotecan and oxaliplatin (with or without bevacizumab) in patients who do not have mutant *KRAS* in their tumours. The alternative in these patients is cetuximab combined with irinotecan, although no direct comparison with panitumumab (Vectibix) has been performed.

4.4. Target population

In 2000, the incidence of colorectal cancer was approximately 36,000 cases[8].

Metastatic stages were observed in about half of the cases[9].

An unpublished in-house study by the company indicates that third-line chemotherapy is started in roughly half of the cases.

According to the literature, approximately 60% of these cancers express wild-type *KRAS*.

On these grounds, the target population for VECTIBIX may be estimated at 5,400 patients a year.

5 Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A.J Clin Oncol. 2004 ; 22: 229-37.

6 Thésaurus de cancérologie digestive SNFGE, 2007.

7 Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005; 352: 476-87.

8 Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000 [Changes in cancer incidence and mortality in France from 1978 to 2000] (INVS 2003).

9 EPAR for Erbitux, 2004.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services for the indication and at the dosage stated in the marketing authorisation.

The Transparency Committee would like a descriptive study to be conducted on patients treated with VECTIBIX in France for colorectal cancer. The objective is to document the circumstances in which this product is used in real-life treatment situations:

- characteristics of prescribing physicians (specialty, status of the healthcare organisation, etc.)
- characteristics of the patients treated: age, gender, disease stage, previous treatments, diagnostic factors (EGFR status, *KRAS* expression, etc.)
- dosage used and combined treatments.

The duration of the study must be justified by an independent scientific committee.
If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, cannot answer all the questions raised by the Transparency Committee, a specific study must be conducted.