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Questions and answers

Positive opinion on the change to the marketing authorisation for Vectibix (panitumumab)

Outcome of re-examination

On 23 June 2011, the Committee for Medicinal Products for Human Use (CHMP) recommended that a change to the marketing authorisation for the medicinal product Vectibix be granted. The change concerns an extension of indication in the treatment of patients with metastatic colorectal carcinoma (mCRC). The company that applied for the change to the authorisation is Amgen Europe B.V.

On 17 March 2011, the CHMP had originally adopted a negative opinion on the proposed use of Vectibix in combination with chemotherapy in patients with mCRC. At the request of the applicant, the CHMP started a re-examination of its opinion. Following the re-examination, the CHMP adopted a final positive opinion on 23 June 2011 recommending a change to the marketing authorisation for Vectibix to add a new indication for use in combination with specific chemotherapy treatments.

What is Vectibix?

Vectibix is a concentrate that is made up into a solution for infusion (drip into a vein). It contains the active substance panitumumab.

Vectibix is used to treat 'non-mutated (wild-type) *KRAS* metastatic colorectal carcinoma'. This is a cancer of the large intestine (bowel) that has spread to other parts of the body. Vectibix is used on its own after treatment has stopped working with combinations of anti-cancer medicines that include a 'fluoropyrimidine' (such as 5-fluorouracil), oxaliplatin and irinotecan.

Vectibix has been authorised in the EU since December 2007. It is marketed in all EU Member States, as well as Iceland and Norway.

What is Vectibix to be used for?

In addition to the approved uses, Vectibix is to be used in combination with specific chemotherapy (medicines to treat cancer) in first line treatment (patients who have not been treated before) and second line treatment (patients who have already received one type of treatment). In first-line

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treatment it is to be used in combination with 'FOLFOX' chemotherapy (oxaliplatin, 5-fluorouracil and folinic acid). In second-line treatment it is to be used in combination with 'FOLFIRI' chemotherapy (irinotecan, 5-fluorouracil and folinic acid) in patients who have already received fluoropyrimidine-based chemotherapy (excluding irinotecan).

How does Vectibix work?

Vectibix in combination with chemotherapy is expected to work in the same way as it does on its own.

The active substance in Vectibix, panitumumab, is a monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and attach to a specific structure (called an antigen) that is found on certain cells in the body. Panitumumab has been designed to attach to EGFR, which can be found on the surface of certain cells, including cells in some tumours. As a result, these tumour cells can no longer receive the messages transmitted via EGFR that they need for growth, progression and spreading (metastasis).

Panitumumab does not seem to work in tumour cells that contain mutated *KRAS* gene. This is because their growth is not controlled by signals transmitted via EGFR and they continue to grow even when the EGFR is blocked.

What did the company present to support its application?

The company presented data from two main studies involving a total of 2,369 patients with mCRC. In the first study, Vectibix in combination with FOLFOX chemotherapy was compared with chemotherapy alone in patients who had not been treated before for their metastatic cancer. The main measure of effectiveness was progression-free survival (how long the patients lived without their disease getting worse). The second study compared Vectibix in combination with FOLFIRI chemotherapy with chemotherapy alone in patients who had been treated before. The main measures of effectiveness were progression-free survival and overall survival (the length of time the patients lived).

What were the CHMP's main concerns that led to the initial negative opinion?

At the time of the initial opinion, the CHMP was concerned about the clinical relevance of the relatively small increase in progression-free survival (how long patients lived without their disease getting worse) and the lack of improvement in overall survival (the average length of time the patients lived) seen in the studies with Vectibix in combination with chemotherapy. The Committee was also concerned about the toxicity of the combination treatment and about the risk of patients with the mutated *KRAS* gene being treated with Vectibix if they were not identified through appropriate tests.

Therefore, at that point in time, the CHMP was of the opinion that the benefits of Vectibix in combination with chemotherapy did not outweigh its risks. Hence, the CHMP recommended that the change to the marketing authorisation be refused.

What happened during the re-examination?

During the re-examination the Committee looked again at the data from the main studies. A key element of the re-examination was an investigation into whether certain patients were more likely to benefit from Vectibix in combination with chemotherapy. The Committee also took advice from a group of experts specialising in cancer treatment.

What were the conclusions of the CHMP following the re-examination?

Following advice from the experts and discussions within the Committee, the CHMP concluded that although the benefits were relatively small, Vectibix in combination with chemotherapy could benefit certain patients and the toxicity could be monitored and managed appropriately, based on experience of using this type of combination treatment in clinical practice. The Committee decided that prescribers were best placed to judge this based on individual characteristics (such as overall health status, other medical problems and age) and that warnings should be included in the product information regarding the risks particularly for patients who are less likely to benefit and more likely to be harmed by the combination treatment.

The Committee also considered further information regarding tests to identify the mutated *KRAS* gene. The CHMP was satisfied that the tests are effective and would be carried out. It agreed that a new contraindication in patients with the mutated KRAS gene should be included in the product information to ensure the medicine is not used with FOLFOX chemotherapy in these patients.

Therefore, the CHMP concluded that the benefits of Vectibix outweigh its risks in the treatment of wild-type *KRAS* mCRC in combination with specific chemotherapy in first and second line treatment. The Committee recommended that the change to the marketing authorisation for Vectibix be granted.

The full European Public Assessment Report for Vectibix can be found on the Agency's website ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.

The summary of the positive opinion of the CHMP is is published on the Agency's website ema.europa.eu/Find medicine/Human medicines/Pending EC decisions.