16th April 2010
Vectibix: DHCP Ireland

Direct Healthcare Professional Communication on Serious Hypersensitivity Including Anaphylaxis and Angioedema

Dear XXX

In agreement with the European Medicines Agency [EMA] and the Irish Medicine Board (IMB), Amgen Inc. would like to inform you of new reports of serious hypersensitivity reactions, including anaphylaxis, reported in patients receiving panitumumab (Vectibix) in the post-marketing setting, some of which have been fatal.

Summary

As a risk minimisation measure, the Vectibix Product Information (including the Summary of Product Characteristics [SmPC] and Patient Information Leaflet [PIL]) have been updated to highlight the following:

- Vectibix is contraindicated in patients with a history of severe or life threatening hypersensitivity reactions to Vectibix;
- Serious infusion-related reactions are unpredictable and can occur suddenly. Vectibix should be permanently discontinued if a severe or life threatening reaction occurs.
- In patients experiencing a mild or moderate infusion-related reaction, the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.
- Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported. Patients should be warned of the possibility of a late onset reaction and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.

The information in this letter and the updates to the Vectibix Product Information have been endorsed by the EU regulatory authorities.

Further Information on the Safety Concern

Across all clinical studies, infusion-related reactions (occurring within 24 hours of any infusion), were reported in 3% of Vectibix-treated patients, of which < 1% were severe (NCI-CTC grade 3 and 4).

One clinical trial report has been received of a fatal case of angioedema occurring 2 days after exposure, following a prior episode of angioedema which occurred 6 days after exposure. More recently two post-marketing reports of hypersensitivity reactions with fatal outcomes during and immediately following an infusion of panitumumab have been received. The patients had previously experienced hypersensitivity reactions to cetuximab and oxaliplatin, respectively.

It is important that Vectibix is permanently discontinued if a severe or life threatening reaction occurs and that patients are informed of the possibility of a late onset reaction and are aware of possible symptoms. They should also be instructed to contact their physician if symptoms of a hypersensitivity reaction occur.

Further Information on Recommendations to Healthcare Professionals

Vectibix is associated with mild to moderate infusion-related reactions, including chills, dyspnoea, flushing, hypertension, hypotension, pyrexia, tachycardia and vomiting, in about 3% of patients. However, severe infusion reactions, including anaphylaxis, angioedema, bronchospasm, cardiorespiratory arrest and hypotension requiring treatment, may occur and are potentially life-threatening.

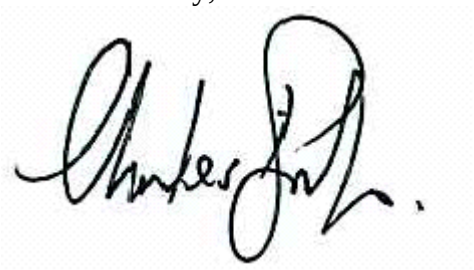
A full copy of the updated SmPC and PIL is provided as an Annex to this letter.

Call for Reporting

Suspected adverse reactions should be reported to the Pharmacovigilance Unit of the Irish Medicines Board (via the online form at www.imb.ie or using the Yellow Card reporting system) or to Amgen Drug Safety at +44 (0) 1223 436712.

Should you have any questions, require further information on product safety, please contact Amgen's Medical Information Department at +44 (0) 1223 436441.

Yours Sincerely,



Charles Brigden MB.BS FRCS MFPM MBA
Executive Medical Director
Amgen UK & Ireland

Vectibix (panitumumab)

Summary of Product Characteristics

&

Patient Information Leaflet

VECTIBIX® (panitumumab)

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Vectibix 20 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 20 mg panitumumab.

Each vial contains either 100 mg of panitumumab in 5 ml, 200 mg in 10 ml, or 400 mg in 20 ml.

When prepared according to the instructions given in section 6.6, the final panitumumab concentration should not exceed 10 mg/ml.

Panitumumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology.

Excipient:
Each ml of concentrate contains 0.150 mmol sodium, which is 3.45 mg sodium.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless solution that may contain translucent to white, visible amorphous, proteinaceous panitumumab particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

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 bodyweight 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 (for preparation instructions see section 6.6).

Method of administration

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 (for handling instructions, see section 6.6).

The infusion line should be flushed with sodium chloride solution before and after Vectibix administration to avoid mixing with other medicinal products or IV solutions.

Do not administer as an IV push or bolus.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Special populations

The safety and efficacy of Vectibix have not been studied in patients with renal or hepatic impairment.

Dose adjustment is not required in the elderly. In clinical studies no overall differences in safety or efficacy were observed between patients aged ≥ 65 years and younger patients.

There is no experience in children and Vectibix should not be used in those patients less than 18 years of age.

4.3 Contraindications

Vectibix is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to the active substance or to any of the excipients (see section 4.4).

Patients with interstitial pneumonitis or pulmonary fibrosis (see section 4.4).

4.4 Special warnings and precautions for use

Dermatological reactions

Dermatologic related reactions, a pharmacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients (approximately 90%) treated with Vectibix (see section 4.8), the majority are mild to moderate in nature. If a patient develops dermatologic reactions that are grade 3 (NCI-CTC/CTCAE) or higher, or that are considered intolerable, temporarily withhold Vectibix administration until the reactions have improved (≤ grade 2). Once improved to ≤ grade 2, reinstate Vectibix administration at 50% of the original dose. If reactions do not recur, escalate the dose of Vectibix by 25% increments until the recommended dose is reached. If reactions do not resolve (to ≤ grade 2) after withholding 1 or 2 doses of Vectibix, or if reactions recur or become intolerable at 50% of the original dose, the use of Vectibix should be permanently discontinued.

In clinical studies, subsequent to the development of severe dermatological reactions (including stomatitis), infectious complications including sepsis, in rare cases leading to death, and local abscesses requiring incisions and drainage were reported. Patients who have

severe dermatologic reactions or who develop worsening reactions whilst receiving Vectibix should be monitored for the development of inflammatory or infectious sequelae (including cellulitis), and appropriate treatment promptly initiated. It is recommended that patients wear sunscreen and hats and limit sun exposure whilst receiving Vectibix and experiencing rash/dermatological toxicities, as sunlight can exacerbate any skin reactions that may occur.

Pulmonary complications

Patients with a history of, or evidence of, interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies. As Interstitial Lung Disease (ILD) has been observed with EGFR inhibitors, in the event of acute onset or worsening pulmonary symptoms, Vectibix treatment should be interrupted and a prompt investigation of these symptoms should occur. If pneumonitis or lung infiltrates are diagnosed, Vectibix should be discontinued and the patient should be treated appropriately.

Electrolyte disturbances

Progressively decreasing serum magnesium levels leading to severe (grade 4) hypomagnesaemia have been observed in some patients. Patients should be periodically monitored for hypomagnesaemia and accompanying hypocalcaemia prior to initiating Vectibix treatment, and periodically thereafter for up to 8 weeks after the completion of treatment (see section 4.8). Magnesium repletion is recommended, as appropriate.

Other electrolyte disturbances, including hypokalaemia, have also been observed. Repletion of these electrolytes is also recommended, as appropriate.

Infusion related reactions

In a clinical study, 4% of patients experienced infusion-related reactions, and in 1% of patients, these reactions were graded as severe (NCI-CTC grade 3 and 4).

Across all clinical studies, infusion-related reactions (occurring within 24 hours of any infusion), were reported in 3% of Vectibix-treated patients, of which < 1% were severe (NCI-CTC grade 3 and 4). In the post-marketing setting, serious infusion-related reactions have been reported, including rare postmarketing reports with a fatal outcome. If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion [eg., presence of bronchospasm, angioedema, hypotension, need for parenteral medication, or anaphylaxis], Vectibix should be permanently discontinued (see sections 4.3 and 4.8).

In patients experiencing a mild or moderate (NCI-CTC grade 1 and 2) infusion-related reaction the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Hypersensitivity reactions occurring more than 24 hours after infusion have been reported including a fatal case of angioedema that occurred more than 24 hours after the infusion.

Patients should be informed of the possibility of a late onset reaction and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.

Other precautions

This medicinal product contains 0.150 mmol sodium (which is 3.45 mg sodium) per ml of concentrate. To be taken into consideration by patients on a controlled sodium diet.

Vectibix in combination with IFL

Patients receiving Vectibix in combination with the IFL regimen [bolus 5-fluorouracil (500 mg/m^2), leucovorin (20 mg/m^2) and irinotecan (125 mg/m^2)] experienced a high incidence of severe diarrhoea (see section 4.8). Therefore administration of Vectibix in combination with IFL should be avoided (see section 4.5).

Vectibix in combination with bevacizumab and chemotherapy regimens

A randomized, open-label, multicentre study of 1,053 patients evaluated the efficacy of bevacizumab and oxaliplatin- or irinotecan-containing chemotherapeutic regimens with and without Vectibix in the first-line treatment of metastatic colorectal cancer. In an interim analysis based on 947 randomised patients, shortened progression free survival time and increased deaths were observed in the patients receiving Vectibix in combination with bevacizumab and chemotherapy. A greater frequency of pulmonary embolism, infections (predominantly of dermatologic origin), diarrhoea, electrolyte imbalances and dehydration was also observed in the treatment arms using Vectibix in combination with bevacizumab and chemotherapy. An additional analysis of efficacy data by *KRAS* status did not identify a subset of subjects who benefited from Vectibix in combination with oxaliplatin- or irinotecan-based chemotherapy and bevacizumab. A trend towards worse survival was observed with Vectibix in the wild-type *KRAS* subset of the oxaliplatin cohort, and a trend towards worse survival was observed with Vectibix in the irinotecan cohort regardless of *KRAS* mutational status. Therefore, Vectibix should not be administered in combination with bevacizumab containing chemotherapy (see sections 4.5 and 5.1).

Vectibix in combination with oxaliplatin-based chemotherapy in metastatic colorectal cancer patients

Vectibix should not be administered in combination with oxaliplatin-containing chemotherapy to mCRC patients with mutant *KRAS* tumours or for whom *KRAS* tumour status is unknown. In a phase 3 study (n = 1183, 656 subjects with wild-type *KRAS* and 440 subjects with mutant *KRAS* tumours) evaluating panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) compared to FOLFOX alone as first-line therapy for mCRC, a shortened progression-free survival and overall survival time were observed in patients with mutant *KRAS* tumours who received panitumumab and FOLFOX (n = 221) vs. FOLFOX alone (n = 219).

Acute renal failure

Acute renal failure has been observed in patients who develop severe diarrhoea and dehydration.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Vectibix should not be administered in combination with IFL chemotherapy or with bevacizumab-containing chemotherapy. A high incidence of severe diarrhoea was observed when panitumumab was administered in combination with IFL (see section 4.4), and increased toxicity and deaths were seen when panitumumab was combined with bevacizumab and chemotherapy (see sections 4.4 and 5.1).

Vectibix should not be administered to mCRC patients with mutant *KRAS* tumours or for whom *KRAS* status is unknown in combination with oxaliplatin-containing chemotherapy. A shortened progression-free survival and overall survival time were observed in a clinical study in subjects with mutant *KRAS* tumours who received panitumumab and FOLFOX (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Vectibix in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Therefore, Vectibix has the potential to cause foetal harm when administered to pregnant women.

Human IgG is known to cross the placental barrier, and panitumumab may therefore be transmitted from the mother to the developing foetus. In women of childbearing potential, appropriate contraceptive measures must be used during treatment with Vectibix, and for 6 months following the last dose. If Vectibix is used during pregnancy or if the patient becomes pregnant while receiving this medicinal product, she should be advised of the potential risk for loss of the pregnancy or potential hazard to the foetus.

Breast-feeding

It is unknown whether panitumumab is excreted in human breast milk. Because human IgG is secreted into human milk, panitumumab might also be secreted. The potential for absorption and harm to the infant after ingestion is unknown. It is recommended that women do not breast feed during treatment with Vectibix and for 3 months after the last dose.

Fertility

Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys (see section 5.3). Panitumumab may impact the ability of a woman to become pregnant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. If patients experience treatment-related symptoms affecting their vision and/or ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

Based on an analysis of all clinical trial patients receiving Vectibix monotherapy (n = 1052), the most commonly reported adverse reactions are skin reactions occurring in 93% of patients. These reactions are related to the pharmacologic effects of Vectibix, and the majority are mild to moderate in nature with 12% severe (grade 3 or higher, NCI-CTC). Commonly reported adverse reactions occurring in ≥ 20% of patients were gastrointestinal disorders [nausea (30%), diarrhoea (27%), and vomiting (22%)]; general disorders [fatigue (35%)]; infections and infestations [paronychia (21%)]; and skin and subcutaneous disorders [pruritus (53%), erythema (52%), dermatitis acneiform (51%), rash (38%)].

Except where indicated, the data in the table below describe adverse reactions reported from clinical studies in patients with metastatic colorectal carcinoma who received panitumumab as a single agent (n=1052).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Adverse reactions			
MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥1/10,000 to <1/1000**
Skin and subcutaneous tissue disorders	Dermatitis acneiform Rash Exfoliative rash Erythema Skin exfoliation Pruritus Dry skin Skin fissures Acne	Palmar-plantar erythrodysaesthesia syndrome Rash papular Rash pruritic Rash erythematous Rash macular Rash maculo-papular Skin ulcer Scab Hypertrichosis Alopecia Onychoclasis Nail disorder (onycholysis)		Angioedema[1]
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain Stomatitis Constipation	Dry mouth		
General disorders and administrative site conditions	Fatigue Pyrexia	Infusion-related reaction Mucosal inflammation Chills Chest discomfort		
Infections and infestations	Paronychia	Rash pustular Eye infection Eyelid infection Cellulitis		
Metabolism and nutrition disorders		Hypomagnesaemia Hypocalcaemia Hypokalaemia Dehydration		

	Adverse reactions			
MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥1/10,000 to <1/1000**
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Epistaxis Nasal dryness	Bronchospasm	
Nervous system disorders		Headache Dizziness		
Eye disorders		Conjunctivitis Growth of eyelashes Lacrimation increased Ocular hyperaemia Dry eye Eye pruritus Eyelid irritation Eye irritation		
Immune system disorders		Hypersensitivity	Anaphylactic reaction	
Cardiac disorders		Tachycardia	Cyanosis	
Musculoskeletal and connective tissue disorders		Back pain		
Vascular disorders			Hypotension Hypertension Flushing	

[1] This adverse reaction was not reported in the monotherapy clinical studies (n=1052). Frequency was derived from reports from all clinical studies performed with Vectibix (n = 4593)

The safety profile of panitumumab in patients whose tumour express *KRAS* wild-type (n = 394) was generally consistent with overall mCRC monotherapy set (n=1052) described above. The only differences were that that nail disorder and hypomagnesaemia,were reported as very common (≥ 1/10) in the *KRAS* wild-type arm whereas these adverse reactions were reported as common (≥ 1/100 to < 1/10) in the overall mCRC monotherapy population and that stomatitis and acne were reported as common in the *KRAS* wild-type versus very common in the overall mCRC monotherapy population. In addition, bronchospasm, hypotension and hypertension were reported as uncommon (≥ 1/1000 to < 1/100) in the overall mCRC monotherapy set and reported as common (≥ 1/100 to < 1/10) in the *KRAS* wild-type group.

Gastrointestinal disorders

Diarrhoea when reported was mainly mild or moderate in severity. Two percent of patients with *KRAS* wild-type had diarrhoea reported as severe. There have been reports of acute renal failure in patients who develop diarrhoea and dehydration (see section 4.4).

Infusion related reactions

In the setting of infusion-related reactions occurring within 24 hours of infusion, adverse reactions including abdominal pain, anaphylactic reactions, angioedema, back pain, bronchospasm, cardiorespiratory arrest, chest pain, chills, cyanosis, dyspnoea, flushing, hypertension, hypotension, pyrexia, tachycardia and vomiting have been reported in clinical trials and in the post-marketing setting. Across all clinical trials, infusion-related reactions occurring within 24 hours of any infusion were reported in 3% of Vectibix-treated patients, of which < 1% were severe (NCI-CTC grade 3 and 4). In the post-marketing setting, serious infusion reactions have been reported, including rare reports with a fatal outcome.

A case of fatal angioedema occurred in a patient with recurrent and metastatic squamous cell carcinoma of the head and neck treated with Vectibix in a clinical trial. The fatal event occurred after re-exposure following a prior episode of angioedema; both episodes occurred greater than 24 hours after administration (see sections 4.3 and 4.4). Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported in the post-marketing setting.

For clinical management of infusion-related reactions, see section 4.4.

Skin and subcutaneous tissue disorders

Skin rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities. Subsequent to the development of severe skin and subcutaneous reactions, infectious complications including sepsis, in rare cases leading to death, cellulitis and local abscesses requiring incisions and drainage were reported. The median time to first symptom of dermatologic reaction was 10 days, and the median time to resolution after the last dose of Vectibix was 28 days.

Paronychial inflammation was associated with swelling of the lateral nail folds of the toes and fingers.

Dermatological reactions (including nail effects), observed in patients treated with Vectibix or other EGFR inhibitors, are known to be associated with the pharmacologic effects of therapy. In the overall monotherapy mCRC data set severe (grade 3 and grade 4) events included dermatitis acneiform (5%), erythema (4%), rash (3%), pruritus (2%), exfoliative rash (1%), acne (1%), skin fissures (1%), skin exfoliation (< 1%), dry skin (< 1%), skin ulcer (< 1%), scab (< 1%), rash erythematous (< 1%), rash papular (< 1%), and rash maculo-papular < 1%). Paronychia was observed in 1% of patients with Vectibix.

Vectibix in combination with other anti-cancer agents and/or monotherapy

Across all clinical trials, in combination with other anti-cancer agents and/or monotherapy, the most serious adverse events associated with Vectibix treatment were pulmonary embolism, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion-related reactions, and hypomagnesaemia. Adverse reactions requiring discontinuation of Vectibix were infusion-related reactions, severe skin toxicity and paronychia.

4.9 Overdose

Doses up to 9 mg/kg have been tested in clinical trials. There have been reports of overdose at doses up to approximately twice the recommended therapeutic dose. Adverse events observed included skin toxicity, diarrhoea, dehydration and fatigue and were consistent with the safety profile at the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC08

Mechanism of action

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds with high affinity and specificity to the human EGFR. EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1/c-ErbB-1), HER2, HER3, and HER4. EGFR promotes cell growth in normal epithelial tissues, including the skin and hair follicle, and is expressed on a variety of tumour cells.

Panitumumab binds to the ligand binding domain of EGFR and inhibits receptor autophosphorylation induced by all known EGFR ligands. Binding of panitumumab to EGFR results in internalisation of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin 8 and vascular endothelial growth factor production.

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.

Activating mutations in the *KRAS* gene occur frequently in a variety of human tumours and have been implicated in both oncogenesis and tumour progression.

Pharmacodynamic effects

In vitro assays and *in vivo* animal studies have shown that panitumumab inhibits the growth and survival of tumour cells expressing EGFR. No anti-tumour effects of panitumumab were observed in human tumour xenografts lacking EGFR expression. The addition of panitumumab to radiation, chemotherapy or other targeted therapeutic agents, in animal studies resulted in an increase in anti-tumour effects compared to radiation, chemotherapy or targeted therapeutic agents alone.

Immunogenicity

Data on the development of anti-panitumumab antibodies has been evaluated using two different immunoassays (an ELISA which detects high-affinity antibodies, and a Biosensor Immunoassay which detects both high and low-affinity antibodies), results from these assays indicated that the overall incidence of a post-dose anti-panitumumab antibody response was low. Pre-dose antibodies were detected in 5 of 636 patients (< 1%) and 16/635 patients (2.5%) tested by the ELISA and Biosensor Immunoassay respectively. Post-dose neutralising antibodies were detected in 1 of 447 patients (0.2%) and 7 of 447 patients (1.6%) tested by the ELISA and Biosensor Immunoassay respectively. Compared with patients who did not

develop antibodies, no relationship between the presence of anti-panitumumab antibodies and pharmacokinetics, efficacy and safety has been observed.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. The observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications and underlying disease, therefore, comparison of the incidence of antibodies to other products may be misleading.

Clinical efficacy

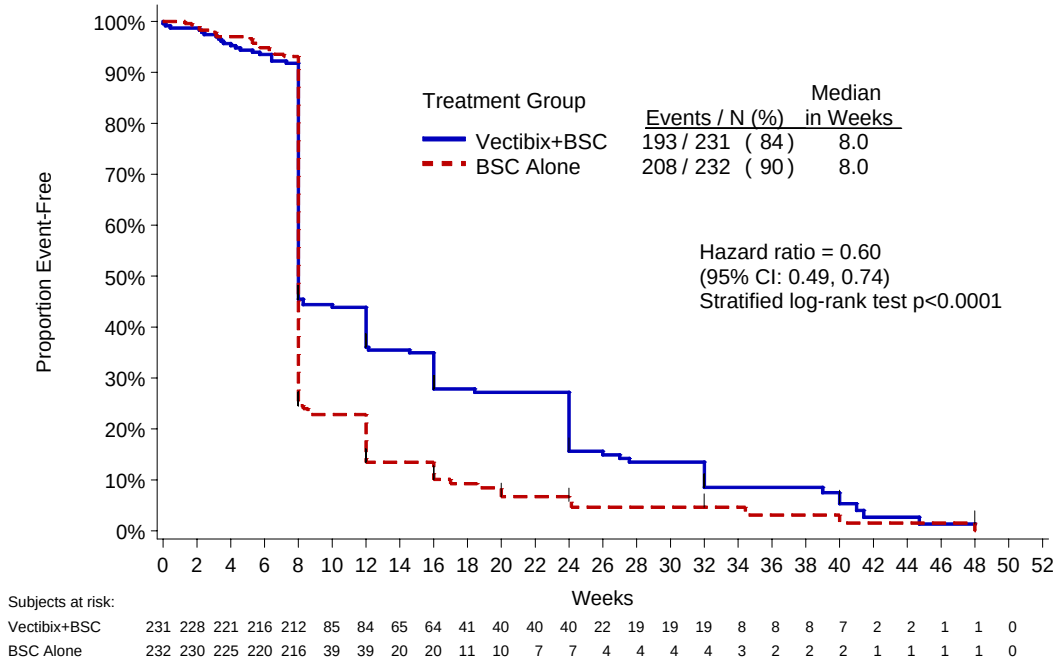
The efficacy of Vectibix in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in a randomised controlled trial (463 patients) and open-label, single-arm trials (384 patients). The safety of Vectibix in patients with mCRC who received at least one dose of Vectibix was evaluated in 920 patients. Additional studies were performed with Vectibix as a single agent in patients with other solid tumours and in combination with chemotherapy with and without bevacizumab in patients with mCRC or in combination with chemotherapy in patients with non-small cell lung cancer.

A multinational, randomised, controlled trial was conducted in 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum after confirmed failure of oxaliplatin and irinotecan-containing regimens. Patients were randomised 1:1 to receive Vectibix at a dose of 6 mg/kg given once every two weeks plus best supportive care (not including chemotherapy) (BSC) or BSC alone. Patients were treated until disease progression or unacceptable toxicity occurred. Upon disease progression BSC alone patients were eligible to crossover to a companion study and receive Vectibix at a dose of 6 mg/kg given once every two weeks.

Of 463 patients, 63% were male. The median age was 62 years (range 27 to 83), and 99% were Caucasian. Three hundred and ninety-six (86%) patients had a baseline ECOG Performance Status of 0 or 1. Sixty-seven percent of patients had colon cancer and 33% had rectal cancer.

The primary endpoint was progression-free survival (PFS). In an analysis adjusting for potential bias from unscheduled assessments, the rate of disease progression or death in patients who received Vectibix was reduced by 40% relative to patients that received BSC [Hazard Ratio = 0.60, (95% CI 0.49, 0.74), stratified log-rank $p < 0.0001$]. There was no difference seen in median PFS times as more than 50% of patients progressed in both treatment groups before the first scheduled visit. The progression-free survival rates at the first scheduled visit (week 8) were 45.5% on Vectibix plus BSC and 24.6% on BSC alone, a difference of 20.9% [95% CI: 12.4, 29.4]. No difference was seen in overall survival. This may be due to patients receiving panitumumab after progression among those randomized to BSC. Tumour response according to modified-RECIST criteria was determined by central review. Overall, 9.5% [95% CI: 6.1, 14.1] Vectibix plus BSC patients, and 0% [95% CI: 0.0, 1.6] BSC alone patients had a confirmed objective response (partial response), with stable disease in 26% and 10% patients, respectively. Among the 176 patients who received Vectibix after progression on BSC alone, the response rate (investigator assessment) was 11.4% (95% CI: 7.1, 17.0).

PFS – All Patients



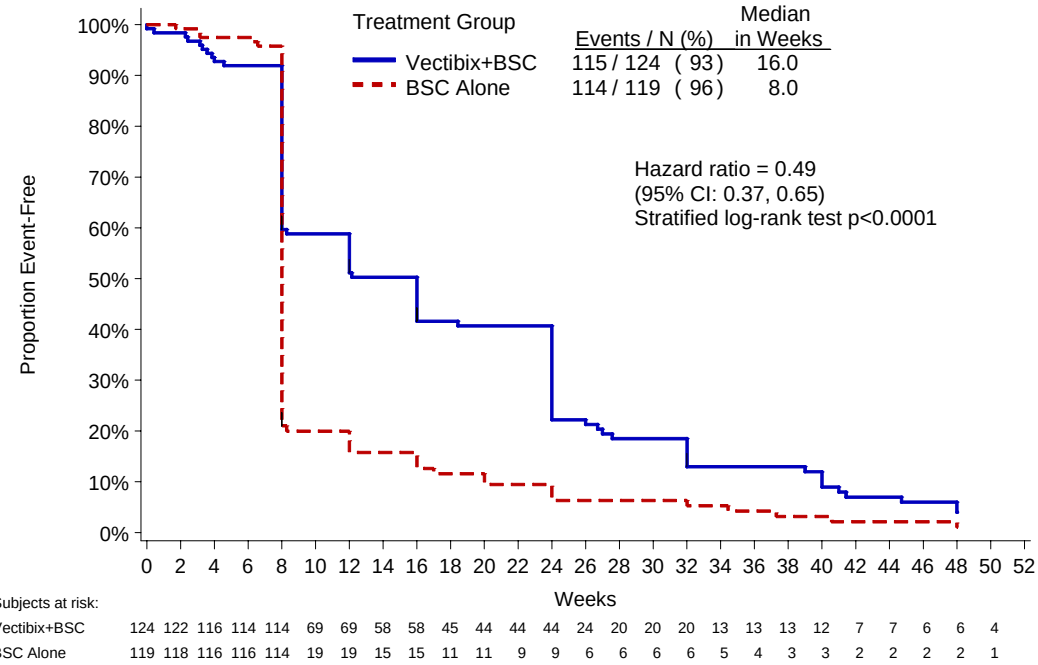
Unscheduled tumour assessments were moved to the nearest scheduled timepoint

The relationship between *KRAS* mutation status determined in archived paraffin embedded tumour tissue and clinical outcome was evaluated in a retrospective analysis.

Tumour samples obtained from the primary resection of colorectal cancer were analysed for the presence of the seven most common activating mutations in the codon 12 and 13 (Gly12Asp, Gly12Ala, Gly12Val, Gly12Ser, Gly12Arg, Gly12Cys, and Gly13Asp) of the *KRAS* gene by using an allele-specific polymerase chain reaction. 427 (92%) patients were evaluable for *KRAS* status of which 184 had mutations. In an analysis adjusting for potential bias from unscheduled assessments the hazard ratio for PFS was 0.49 (95% CI: 0.37-0.65) in favour of panitumumab in the *KRAS* wild-type group and 1.07 (95% CI: 0.77-1.48) in the *KRAS* mutant group. The difference in median PFS in the *KRAS* wild-type group was 8 weeks. The progression-free survival rates at the first scheduled visit (week 8) in the *KRAS* wild-type group were 59.7% on Vectibix plus BSC and 21.0% on BSC alone, a difference of 38.7% [95% CI: 27.4, 50.0]. The difference in median PFS in the *KRAS* mutant group was 0 weeks. The progression-free survival rates at the first scheduled visit (week 8) in the *KRAS* mutant group were 21.4% on Vectibix plus BSC and 28.0% on BSC alone, a difference of -6.6% [95% CI: -19.0, 5.9]. There were no differences in overall survival seen in either group. In the *KRAS* wild-type group the response rate was 17% for panitumumab and 0% for BSC. In the *KRAS* mutant group there were no responses in either treatment arm. Stable disease rates in the *KRAS* wild-type group were 34% for panitumumab and 12% for BSC. The stable disease rates in the *KRAS* mutant group were 12% for panitumumab and 8% for BSC. Response rate (investigator assessment) in patients that crossed over to panitumumab after progression on BSC alone was 22% (95% CI: 14.0, 31.9) for those with *KRAS* wild-type tumours and 0% (95% CI: 0.0, 4.3) for those with mutant *KRAS* tumours.

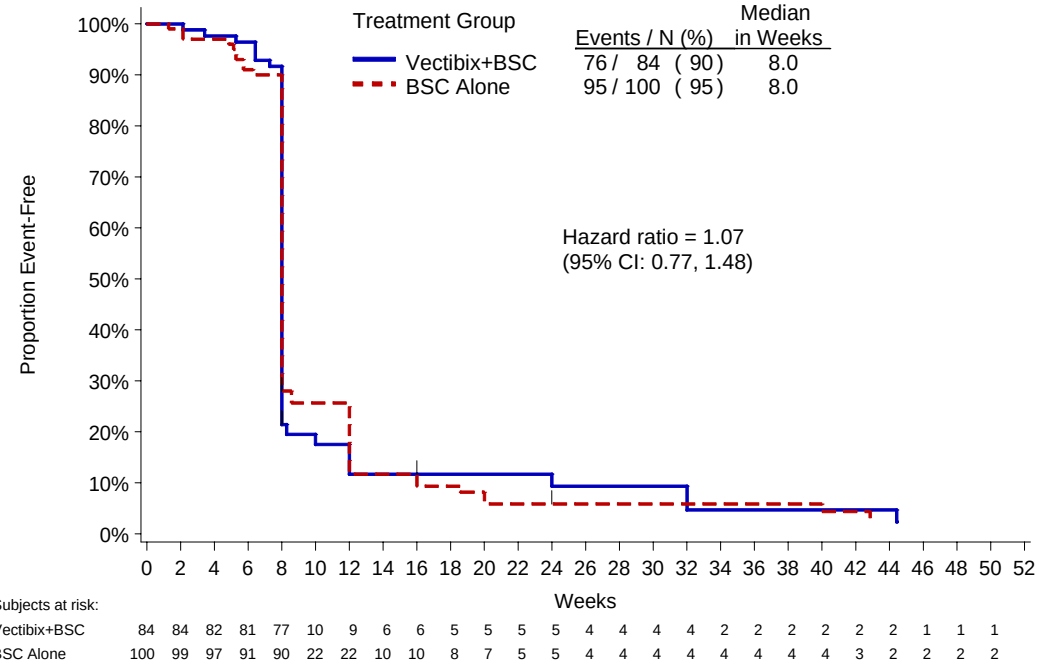
***PFS – Patients with mutant and wild type* KRAS**

Wild Type *KRAS*



Unscheduled tumour assessments were moved to the nearest scheduled timepoint

Mutant *KRAS*



Unscheduled tumour assessments were moved to the nearest scheduled timepoint

The PACCE study: In this randomised, open label, controlled clinical trial, chemotherapy (oxaliplatin or irinotecan) and bevacizumab were given with and without panitumumab in the first line treatment of patients with metastatic colorectal cancer (n=1053 [n=823 oxaliplatin cohort, n=230 irinotecan cohort]). Panitumumab treatment was discontinued due to a

statistically significant reduction in PFS in patients receiving panitumumab observed in an interim analysis.

The major study objective was comparison of PFS in the oxaliplatin cohort. In the final analysis, the hazard ratio for PFS was 1.27 (95% CI: 1.06, 1.52). Median PFS was 10.0 (95% CI: 8.9, 11.0) and 11.4 (95% CI: 10.5, 11.9) months in the panitumumab and the non-panitumumab arm, respectively. There was an increase in mortality in the panitumumab arm. The hazard ratio for overall survival was 1.43 (95% CI: 1.11, 1.83). Median overall survival was 19.4 (95% CI: 18.4, 20.8) and 24.5 (95% CI: 20.4, 24.5) in the panitumumab arm and the non-panitumumab arm.

An additional analysis of efficacy data by *KRAS* status did not identify a subset of subjects who benefited from panitumumab in combination with oxaliplatin- or irinotecan based chemotherapy and bevacizumab. For the wild-type *KRAS* subset of the oxaliplatin cohort, the hazard ratio for PFS was 1.36 with 95% CI: 1.04-1.77. For the mutant *KRAS* subset, the hazard ratio for PFS was 1.25 with 95% CI: 0.91-1.71. A trend for OS favouring the control arm was observed in the wild-type *KRAS* subset of the oxaliplatin cohort (hazard ratio = 1.89; 95% CI: 1.30, 2.75). A trend towards worse survival was also observed with panitumumab in the irinotecan cohort regardless of *KRAS* mutational status. Overall, panitumumab treatment combined with chemotherapy and bevacizumab is associated with an unfavourable benefit-to-risk profile irrespective of tumour *KRAS* mutational status.

This medicinal product has been authorised under a "conditional approval" scheme. This means that further evidence on this medicinal product is awaited, in particular data are required to confirm the effect in patients with wild-type *KRAS* tumours which is currently supported by a retrospective analysis. Further evidence is also awaited regarding the effect of panitumumab in combination with chemotherapy on PFS in patients with wild-type *KRAS* tumours. Studies investigating this effect are currently ongoing. The European Medicines Agency (EMEA) will review new information on the product every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

Vectibix administered as a single agent or in combination with chemotherapy exhibits nonlinear pharmacokinetics.

Following a single-dose administration of panitumumab as a 1-hour infusion, the area under the concentration-time curve (AUC) increased in a greater than dose-proportional manner and clearance (CL) of panitumumab decreased from 30.6 to 4.6 ml/day/kg as the dose increased from 0.75 to 9 mg/kg. However, at doses above 2 mg/kg, the AUC of panitumumab increases in an approximately dose-proportional manner.

Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour infusion), panitumumab concentrations reached steady-state levels by the third infusion with mean (± SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/ml, respectively. The mean (± SD) AUC0-tau and CL were 1306 ± 374 mcg•day/ml and 4.9 ± 1.4 ml/kg/day, respectively. The elimination half-life was approximately 7.5 days (range: 3.6 to 10.9 days).

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics. Results suggest that age (21-88), gender, race, hepatic function, renal function, chemotherapeutic agents, and EGFR membrane staining intensity (1+, 2+, 3+) in tumour cells had no apparent impact on the pharmacokinetics of panitumumab.

No clinical studies have been conducted to examine the pharmacokinetics of panitumumab in patients with renal or hepatic impairment.

5.3 Preclinical safety data

Adverse reactions seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Skin rash and diarrhoea were the major findings observed in repeat-dose toxicity studies of up to 26 weeks duration in cynomolgus monkeys. These findings were observed at doses approximately equivalent to the recommended human dose and were reversible upon termination of administration of panitumumab. The skin rash and diarrhoea observed in monkeys are considered related to the pharmacological action of panitumumab and are consistent with the toxicities observed with other anti-EGFR inhibitors.

Studies to evaluate the mutagenic and carcinogenic potential of panitumumab have not been performed.

Animal studies are insufficient with respect to embryo-foetal development since foetal panitumumab exposure levels were not examined. Panitumumab has been shown to cause foetal abortions and/or foetal deaths in cynomolgus monkeys when administered during the period of organogenesis at doses approximately equivalent to the recommended human dose.

Formal male fertility studies have not been conducted; however, microscopic evaluation of male reproductive organs from repeat-dose toxicity studies in cynomolgus monkeys at doses up to approximately 5-fold the human dose on a mg/kg basis, revealed no differences compared to control male monkeys. Fertility studies conducted in female cynomolgus monkeys showed that panitumumab may produce prolonged menstrual cycle and/or amenorrhea and reduced pregnancy rate which occurred at all doses evaluated.

No pre- and post-natal development animal studies have been conducted with panitumumab. All patients should be advised regarding the potential risk of panitumumab on pre- and post-natal development prior to initiation of Vectibix therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium acetate trihydrate
Acetic acid, glacial (for pH-adjustment)
Water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

Vectibix does not contain any antimicrobial preservative or bacteriostatic agent. The product should be used immediately after dilution. If not used immediately, in-use storage times and

conditions prior to use are the responsibility of the user and should be no longer than 24 hours at 2°C to 8°C. Do not freeze diluted solution.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-use vial (type I glass) with an elastomeric stopper, aluminium seal and flip-off plastic cap.
One vial contains: 100 mg of panitumumab in 5 ml, 200 mg panitumumab in 10 ml, or 400 mg panitumumab in 20 ml of concentrate for solution for infusion.

Pack of 1 vial containing 5 ml.
Pack of 1 vial containing 10 ml.
Pack of 1 vial containing 20 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vectibix should be diluted in 0.9% sodium chloride injection by a healthcare professional using aseptic technique. Do not shake or vigorously agitate the vial. Do not administer Vectibix if discolouration is observed. Withdraw the necessary amount of Vectibix for a dose of 6 mg/kg. Dilute in a total volume of 100 ml. The final concentration should not exceed 10 mg/ml. Doses higher than 1000 mg should be diluted in 150 ml 0.9% sodium chloride injection (see section 4.2). The diluted solution should be mixed by gentle inversion, do not shake.

No incompatibilities have been observed between Vectibix and 0.9% sodium chloride injection in polyvinyl chloride bags or polyolefin bags.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/423/001
EU/1/07/423/002
EU/1/07/423/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:3 December 2007
Date of last renewal: 15 March 2010

10. DATE OF REVISION OF THE TEXT

15 March 2010

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.emea.europa.eu/

PACKAGE LEAFLET: INFORMATION FOR THE USER

Vectibix 20 mg/ml concentrate for solution for infusion
panitumumab

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT VECTIBIX IS AND WHAT IT IS USED FOR

Vectibix is used in the treatment of metastatic colorectal carcinoma (cancer of the bowel) after failure of chemotherapy (medicines used to treat cancer) treatment.

Vectibix is for use in adults 18 years and over.

Vectibix contains the active substance panitumumab, which belongs to a group of medicines called monoclonal antibodies. Monoclonal antibodies are proteins, which specifically recognise and attach (bind) to other unique proteins in the body.

Panitumumab recognises and binds specifically to a protein known as epidermal growth factor receptor (EGFR), which is found on the surface of some cancer cells. When growth factors (other body proteins) attach to the EGFR, the cancer cell is stimulated to grow and divide. Panitumumab binds onto the EGFR and prevents the cancer cell from receiving the messages it needs for growth and division.

2. BEFORE YOU USE VECTIBIX

Do not use Vectibix

- If you have ever had a severe or life threatening allergic (hypersensitivity) reaction to panitumumab or any of the other ingredients of Vectibix.
- if you have previously had or have evidence of interstitial pneumonitis (swelling of the lungs causing coughing and difficulty breathing) or pulmonary fibrosis (scarring and thickening in the lungs with shortness of breath).

Take special care with Vectibix

Your doctor will check your blood levels of several substances such as magnesium, and other electrolyte levels such as calcium and potassium in your blood before you start Vectibix treatment. If these levels are too low, your doctor may prescribe you appropriate supplements.

During treatment with Vectibix

You may experience dermatologic toxicities (skin reactions), if these worsen or become intolerable please tell your doctor or nurse immediately.

It is recommended that you limit sun exposure whilst receiving Vectibix and if you are experiencing skin reactions as sunlight can worsen these. Wear sunscreen and a hat if you are going to be exposed to sunlight.

Your doctor will ask you to come in for tests to monitor hypomagnesaemia (low magnesium levels in the blood) and hypocalcaemia (low calcium levels in the blood) periodically during your treatment, and for up to 8 weeks after you have finished your treatment.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Vectibix has not been tested in pregnant women. It is important to tell your doctor if you are pregnant; think you may be pregnant; or plan to get pregnant. Vectibix could affect your ability to stay pregnant.

If you are a woman of child bearing potential, you should use suitable methods of contraception during treatment with Vectibix and for 6 months after the last dose.

Do not breast-feed your baby during treatment with Vectibix and for 3 months after the last dose.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. You should speak with your doctor before driving or using machines, as some side effects may impair your ability to do so safely.

3. HOW TO USE VECTIBIX

Vectibix will be administered in a healthcare facility under the supervision of a doctor experienced in the use of anti-cancer medicines.

Vectibix is administered intravenously (into a vein) with an infusion pump (a device that gives a slow injection).

The recommended dose of Vectibix is 6 mg/kg (milligrams per kilogram of body weight) given once every two weeks. The treatment will usually be given over a period of approximately 60 minutes.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Vectibix can cause side effects, although not everybody gets them.

Very common side effects (seen in more than 1 in 10 people who take Vectibix) were:

- Acne-like rash; acne; pruritus (itching); erythema (redness of skin); rash; skin exfoliation (flaking skin); dry skin; skin fissures (cracks in the skin); exfoliating rash (flaking rash)
- diarrhoea; nausea; vomiting; abdominal pain; constipation;
- stomatitis (chapped lips, mouth ulcers and cold sores);
- fatigue (extreme tiredness);
- pyrexia (fever or high temperature);
- paronychia (nail infection);
- cough; dyspnoea (breathing difficulties).

Common side effects (seen in more than 1, but less than 10 in 100 people taking Vectibix) were:

- infusion type reactions which may include signs and symptoms such as abdominal pain, back pain, breathing difficulties, chest pain, flushing, rapid heart rate; hypotension (low blood pressure); hypertension (high blood pressure); vomiting; chills; new onset of facial swelling and/or swelling of the mouth; and/or pyrexia (fever or high temperature));
- hand-foot syndrome (redness and swelling of palms of hands or soles of feet);
- onycholysis (loosening of the nails); nail disorder;
- rash pustular (skin rash with pus-filled blisters);
- eye infection; eyelid infection;
- cellulitis (spreading infection below the skin);
- hypomagnesaemia (low magnesium levels in the blood);
- hypocalcaemia (low calcium levels in the blood);
- hypokalaemia (low potassium levels in the blood);
- dehydration;
- nasal dryness; epistaxis (nose bleed);
- headache; dizziness;
- rash papular (bumpy rash); rash pruritic (itchy rash); rash erythematous (red skin rash); rash macular (spotty rash); rash maculo-papular (rash with bumps and spots); skin ulcer; scab;
- conjunctivitis (eye inflammation); growth of eyelashes and lacrimation increased (flow of tears); ocular hyperaemia (redness of the eye); dry eye; eye pruritus (itchy eyes); eyelid irritation; eye irritation;
- pulmonary embolism (blood clot in the lung);
- mucosal inflammation (inflammation of the mouth); dry mouth;
- onycholysis (breaking of the nails);
- hypertrichosis (excess hair growth); alopecia (hair loss);

Uncommon side effects (seen in less than 1 in 100, but more than 1 in 1000 people taking Vectibix) were:

- bronchospasm (constriction of the airways);
- anaphylactic reactions (severe allergic reaction);
- flushing; hypotension (low blood pressure); hypertension (high blood pressure);
- cyanosis (blue coloration of the skin and mucous membranes).

Rare side effects (seen in less than 1 in 1000, but more than 1 in 10,000 people taking Vectibix) were:

- angioedema (swelling of the mouth, face and throat causing difficulty in breathing).

Infusion-type reactions, which may include signs and symptoms such as chills, new onset of facial swelling, breathing difficulties, vomiting and/or fever or pyrexia (high temperature) may appear several hours or days after an infusion. If any of these side effects gets serious**,** please tell your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Important information about some of the ingredients of Vectibix

This medicinal product contains 0.150 mmol sodium (which is 3.45 mg sodium) per ml of concentrate. To be taken into consideration by patients on a controlled sodium diet.

5. HOW TO STORE VECTIBIX

Vectibix will be stored in the healthcare facility where it is used.

Keep out of the reach and sight of children.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

Do not use Vectibix after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Vectibix contains

The active substance is panitumumab 20 mg/ml.
The other ingredients of Vectibix are sodium chloride, sodium acetate trihydrate, acetic acid (glacial) and water for injections.

What Vectibix looks like and contents of the pack

Vectibix is a colourless liquid that may contain visible particles and is supplied in a vial. Each pack contains one vial of either 5 ml, 10 ml or 20 ml of concentrate.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
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This leaflet was last approved in March 2010.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.emea.europa.eu/

This medicine has been given "conditional approval".
This means that there is more evidence to come about this medicine.
The European Medicines Agency (EMA) will review new information on the medicine every year and this leaflet will be updated as necessary.

The following information is intended for medical or healthcare professionals only:

Vectibix should be diluted in 0.9% sodium chloride injection by a healthcare professional using aseptic technique. Do not shake or vigorously agitate the vial. Do not administer Vectibix if discolouration is observed. Withdraw the necessary amount of Vectibix for a dose of 6 mg/kg. Dilute in a total volume of 100 ml. Doses higher than 1000 mg should be diluted in 150 ml 0.9% sodium chloride injection. The final concentration should not exceed 10 mg/ml. The diluted solution should be mixed by gentle inversion, do not shake.

The infusion line should be flushed with sodium chloride solution before and after Vectibix administration to avoid mixing with other medicinal products or IV solutions.

Vectibix must be administered as an intravenous 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.

No incompatibilities have been observed between Vectibix and 0.9% sodium chloride injection in polyvinyl chloride bags or polyolefin bags.