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Summary of Product Characteristics last updated on the eMC: 23/08/2012

SPC Vectibix

### Table of Contents

1. Name of the medicinal product
2. Qualitative and quantitative composition
3. Pharmaceutical form
4. Clinical particulars
  - 4.1 Therapeutic indications
  - 4.2 Posology and method of administration
  - 4.3 Contraindications
  - 4.4 Special warnings and precautions for use
  - 4.5 Interaction with other medicinal products and other forms of interaction
  - 4.6 Fertility, pregnancy and lactation
  - 4.7 Effects on ability to drive and use machines
  - 4.8 Undesirable effects
  - 4.9 Overdose
5. Pharmacological properties
  - 5.1 Pharmacodynamic properties
  - 5.2 Pharmacokinetic properties
  - 5.3 Preclinical safety data
6. Pharmaceutical particulars
  - 6.1 List of excipients
  - 6.2 Incompatibilities
  - 6.3 Shelf life
  - 6.4 Special precautions for storage
  - 6.5 Nature and contents of container
  - 6.6 Special precautions for disposal and other handling
7. Marketing authorisation holder
8. Marketing authorisation number(s)
9. Date of first authorisation/renewal of the authorisation
10. Date of revision of the text

### Document Links

- [More information about this product](#)
- [View all medicines from this company](#)
- [Print this page](#)
- [View document history](#)

### Legal Categories

POM – Prescription  
Only Medicine

### Active Ingredients/Generics

[panitumumab](#)

### 1. Name of the medicinal product

[Go to top of the page](#)

Vectibix® 20 mg/ml concentrate for solution for infusion.

### 2. Qualitative and quantitative composition

[Go to top of the page](#)

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

Excipient with known effect:

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

[Go to top of the page](#)

Concentrate for solution for infusion (sterile concentrate).

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

### 4. Clinical particulars

[Go to top of the page](#)

#### 4.1 Therapeutic indications

[Go to top of the page](#)

Vectibix is indicated for the treatment of patients with wild-type *KRAS* metastatic colorectal cancer (mCRC):

- in first-line in combination with FOLFOX
- in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
- as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

#### 4.2 Posology and method of administration

[Go to top of the page](#)

Vectibix treatment should be supervised by a physician experienced in the use of anti-cancer therapy. Evidence of wild-type *KRAS* status is required before initiating treatment with Vectibix. *KRAS* mutational status should be determined using a validated test method by an experienced laboratory.

##### Posology

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).

Modification of the dose of Vectibix may be necessary in cases of severe ( $\geq$  grade 3) dermatological reactions (see section 4.4).

##### 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. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 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.

A reduction in the rate of infusion of Vectibix may be necessary in cases of infusion-related reactions (see section 4.4).

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.

There is no clinical data to support dose adjustments in the elderly

##### Paediatric population

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

#### 4.3 Contraindications

[Go to top of the page](#)

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).

The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *KRAS* mCRC or for whom *KRAS* mCRC status is unknown.

## 4.4 Special warnings and precautions for use

[Return to the top of the page](#)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. Severe (NCI-CTC grade 3) skin reactions were reported in 34% and life-threatening (NCI-CTC grade 4) skin reactions in < 1% of patients who received Vectibix in combination with chemotherapy (n = 1536) (see section 4.8). If a patient develops dermatologic reactions that are grade 3 (CTCAE v 4.0) or higher, or that are considered intolerable, the following dose modification is recommended:

<u>Occurrence of skin symptom(s): ≥ grade 3<sup>1</sup></u>	<u>Administration of Vectibix</u>	<u>Outcome</u>	<u>Dose regulation</u>
Initial occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 100% of original dose
		Not recovered	Discontinue
At the second occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 80% of original dose
		Not recovered	Discontinue
At the third occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 60% of original dose
		Not recovered	Discontinue
At the fourth occurrence	Discontinue	-	-

<sup>1</sup> Greater than or equal to grade 3 is defined as severe or life-threatening

In clinical studies, subsequent to the development of severe dermatological reactions (including stomatitis), infectious complications including sepsis and necrotising fasciitis, 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 necrotising fasciitis), and appropriate treatment promptly initiated. Life threatening and fatal infectious complications including necrotising fasciitis and sepsis have been observed in patients treated with Vectibix. Withhold or discontinue Vectibix in the event of dermatologic toxicity with severe or life threatening inflammatory or infectious complications.

Treatment of dermatologic reactions should be based on severity and may include a moisturiser, sun screen (SPF > 15 UVA and UVB), and topical steroid cream (not stronger than 1% hydrocortisone) applied to affected areas, and/or oral antibiotics. It is also recommended that patients experiencing rash/dermatological toxicities wear sunscreen and hats and limit sun exposure as sunlight can exacerbate any skin reactions that may occur.

Proactive skin treatment including skin moisturiser, sun screen (SPF > 15 UVA and UVB), topical steroid cream (not stronger than 1% hydrocortisone) and an oral antibiotic (e.g. doxycycline) may be useful in the management of dermatologic reactions. Patients may be advised to apply moisturiser and sunscreen to face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night during treatment.

Pulmonary complications

Patients with a history of, or evidence of, interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies. Cases of interstitial lung disease (ILD), both fatal and non-fatal, have been reported, mainly from the Japanese population. 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 ILD is diagnosed, Vectibix should be permanently discontinued and the patient should be treated appropriately. In patients with a history of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with panitumumab versus the risk of pulmonary complications must be carefully considered.

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. Monitoring as above and repletion as appropriate of these electrolytes is also recommended.

Infusion related reactions

Across monotherapy and combination mCRC clinical studies (n = 2588), infusion-related reactions (occurring within 24 hours of an infusion) were reported in approximately 4% of Vectibix-treated patients, of which < 1% were severe (NCI-CTC grade 3 and grade 4).



In the post-marketing setting, serious infusion-related reactions have been reported, including rare post-marketing reports with a fatal outcome. If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion [e.g. 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 (CTCAE v 4.0 grades 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.

#### Acute renal failure

Acute renal failure has been observed in patients who develop severe diarrhoea and dehydration. Patients who experience severe diarrhoea should be instructed to consult a healthcare professional urgently.

#### 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 irinotecan, bolus 5-fluorouracil, and leucovorin (IFL) chemotherapy

Patients receiving Vectibix in combination with the IFL regimen [bolus 5-fluorouracil (500 mg/m<sup>2</sup>), leucovorin (20 mg/m<sup>2</sup>) and irinotecan (125 mg/m<sup>2</sup>)] 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 randomised, 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. 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, nausea, vomiting 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 patients 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 bevacizumab and oxaliplatin cohort, and a trend towards worse survival was observed with Vectibix in the bevacizumab and 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 patients with mutant KRAS mCRC or for whom KRAS tumour status is unknown

The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant KRAS mCRC or for whom KRAS mCRC status is unknown. In a phase 3 study (n = 1183, 656 patients with wild-type KRAS and 440 patients 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).

KRAS mutational status should be determined using a validated test method by an experienced laboratory. If Vectibix is to be used in combination with FOLFOX then it is recommended that mutational status be determined by a laboratory that participates in a KRAS European Quality Assurance program or wild-type status be confirmed in a duplicate test.

#### Ocular toxicities

Serious cases of keratitis and ulcerative keratitis have been rarely reported in the post-marketing setting. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with Vectibix should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Vectibix should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

#### Patients with ECOG 2 performance status treated with Vectibix in combination with chemotherapy

For patients with ECOG 2 performance status, assessment of benefit-risk is recommended prior to initiation of Vectibix in combination with chemotherapy for treatment of mCRC. A positive benefit-risk balance has not been documented in patients with ECOG 2 performance status (see section 5.1).

#### Elderly Patients

No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Vectibix monotherapy. However, an increased number of serious adverse events were reported in elderly patients treated with Vectibix in combination with FOLFIRI or FOLFOX chemotherapy compared to chemotherapy alone (see section 4.8).

Data from an interaction study involving Vectibix and irinotecan in patients with mCRC indicated that the pharmacokinetics of irinotecan and its active metabolite, SN-38, are not altered when the drugs are co-administered. Results from a cross-study comparison indicated that irinotecan-containing regimens (IFL or FOLFIRI) have no effect on the pharmacokinetics of panitumumab.

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).

The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *KRAS* mCRC or for whom *KRAS* mCRC status is unknown. A shortened progression-free survival and overall survival time were observed in a clinical study in patients with mutant *KRAS* tumours who received panitumumab and FOLFOX (see section 4.4 and 5.1).

#### 4.6 Fertility, pregnancy and lactation

[Go to top of the page](#)

##### 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 2 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.

Women who become pregnant during Vectibix treatment should be encouraged to enrol in Amgen's Pregnancy Surveillance programme. Contact details are provided in section 6 of the Package Leaflet – Contents of the pack and other information.

##### 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 2 months after the last dose.

Women who breast-feed during Vectibix treatment should be encouraged to enrol in Amgen's Lactation Surveillance Programme. Contact details are provided in section 6 of the Package Leaflet – Contents of the pack and other information.

##### 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

[Go to top of the page](#)

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

[Go to top of the page](#)

##### Summary of safety profile

Based on an analysis of all mCRC clinical trial patients receiving Vectibix monotherapy and in combination with chemotherapy (n = 2588), 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 25% severe (grade 3 NCI-CTC) and < 1% life threatening (grade 4 NCI-CTC). For clinical management of skin reactions, including dose modification recommendations, see section 4.4.

Very commonly reported adverse reactions occurring in ≥ 20% of patients were gastrointestinal disorders [diarrhoea (50%), nausea (41%), vomiting (27%), constipation (23%) and abdominal pain (23%)] general disorders [fatigue (37%), pyrexia (20%)]; metabolism and nutrition disorders [anorexia (27%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (45%), dermatitis acneiform (39%), pruritus (35%), erythema (30%) and dry skin (22%)].

##### Tabulated summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical studies in patients with mCRC who received panitumumab as a single agent or in combination with chemotherapy (n = 2588) and spontaneous reporting. 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)	Frequency not known*
Blood and lymphatic system disorders	Anaemia	Leukopenia			
Cardiac disorders		Tachycardia	Cyanosis		
Eye disorders	Conjunctivitis	Blepharitis Growth of eyelashes Lacrimation increased Ocular hyperaemia Dry eye Eye pruritus Eye irritation	Eyelid irritation Keratitis <sup>1</sup>	Ulcerative Keratitis <sup>1</sup>	
Gastrointestinal disorders	Diarrhoea <sup>1</sup> Nausea Vomiting Abdominal pain Stomatitis Constipation	Rectal haemorrhage Dry mouth Dyspepsia Aphthous stomatitis Cheilitis Gastrooesophageal reflux disease	Chapped lips		
General disorders and administration site conditions	Fatigue Pyrexia Asthenia Mucosal inflammation Oedema peripheral	Chest pain Pain Chills	Infusion-related reaction <sup>1</sup>		
Immune system disorders		Hypersensitivity <sup>1</sup>		Anaphylactic reaction <sup>1</sup>	
Infections and infestations	Paronychia <sup>1</sup>	Rash pustular Cellulitis <sup>1</sup> Folliculitis Localised infection	Eye infection Eyelid infection		
Investigations	Weight decreased	Blood magnesium decreased			
Metabolism and nutrition disorders	Hypokalaemia Anorexia Hypomagnesaemia	Hypocalcaemia Dehydration Hyperglycaemia Hypophosphataemia			

Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity			
Nervous system disorders		Headache Dizziness			
Psychiatric disorders	Insomnia	Anxiety			
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Epistaxis	Bronchospasm Nasal dryness		Interstitial lung disease
Skin and subcutaneous tissue disorders	Dermatitis acneiform Rash <sup>1,2</sup> Erythema Pruritus Dry skin Skin fissures Acne Alopecia	Palmar-plantar erythrodysesthesia syndrome Skin ulcer Scab Hypertrichosis Onychoclasia Nail disorder	Angioedema <sup>1</sup> Hirsutism Ingrowing nail Onycholysis	Skin Necrosis <sup>1</sup>	
Vascular disorders		Deep vein thrombosis Hypotension Hypertension Flushing			

<sup>1</sup> See section Description of selected adverse reactions below

<sup>2</sup> Rash includes common terms of skin toxicity, skin exfoliation, exfoliative rash, rash papular, rash pruritic, rash erythematous, rash generalised, rash macular, rash maculo-papular, skin lesion

<sup>\*</sup> Frequency cannot be estimated from the available data

The safety profile of Vectibix in combination with chemotherapy consisted of the reported adverse reactions of Vectibix (as a monotherapy) and the toxicities of the background chemotherapy regimen. No new toxicities or worsening of previously recognised toxicities beyond the expected additive effects were observed. Skin reactions were the most frequently occurring adverse reactions in patients receiving panitumumab in combination with chemotherapy. Other toxicities that were observed with a greater frequency relative to monotherapy included hypomagnesaemia, diarrhoea, and stomatitis. These toxicities infrequently led to discontinuation of Vectibix or of chemotherapy.

#### Description of selected adverse reactions

##### *Gastrointestinal disorders*

Diarrhoea when reported was mainly mild or moderate in severity. Severe diarrhoea (NCI-CTC grade 3 and 4) was reported in 2% of patients treated with Vectibix as a monotherapy and in 17% of patients treated with Vectibix in combination with chemotherapy.

There have been reports of acute renal failure in patients who develop diarrhoea and dehydration (see section 4.4).

##### *Infusion related reactions*

Across monotherapy and combination mCRC clinical studies (n = 2588), infusion-related reactions (occurring within 24 hours of any infusion), which may include symptoms/signs such as chills, fever or dyspnoea, were reported in approximately 4% of Vectibix-treated patients, of which < 1% were severe (NCI-CTC grade 3 and grade 4).

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.

Paronychia 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.

Across all clinical trials, skin reactions occurred in 93% of patients receiving Vectibix as monotherapy or in combination with chemotherapy (n = 2588). These events consisted predominantly of rash and dermatitis acneiform and were mostly mild to moderate in severity. Severe (NCI-CTC grade 3) skin reactions were reported in 34% and life-threatening (NCI-CTC grade 4) skin reactions in < 1% of patients who received Vectibix in combination with chemotherapy (n = 1536). Life threatening and fatal infectious complications including necrotising fasciitis and sepsis have been observed in patients treated with Vectibix (see section 4.4).

For clinical management of dermatological reactions, including dose modification recommendations, see section 4.4.

In the post-marketing setting, cases of skin necrosis have been reported.

#### Ocular toxicities

Non-serious cases of keratitis have been observed in 0.2 to 0.7% of clinical trial patients. In the post-marketing setting, serious cases of keratitis and ulcerative keratitis have been rarely reported (see section 4.4).

#### Paediatric population

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

#### Other special populations

No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Vectibix monotherapy. However, an increased number of serious adverse events were reported in elderly patients treated with Vectibix in combination with FOLFIRI (45% vs 37%) or FOLFOX (52% vs 37%) chemotherapy compared to chemotherapy alone (see Section 4.4). The most increased serious adverse events were diarrhoea in patients treated with Vectibix in combination with either FOLFOX or FOLFIRI, and dehydration and pulmonary embolism when patients were treated with Vectibix in combination with FOLFIRI.

The safety of Vectibix has not been studied in patients with renal or hepatic impairment.

#### 4.9 Overdose

[Go to top of the page](#)

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 (12 mg/kg). Adverse events observed included skin toxicity, diarrhoea, dehydration and fatigue and were consistent with the safety profile at the recommended dose.

### 5. Pharmacological properties

[Go to top of the page](#)

#### 5.1 Pharmacodynamic properties

[Go to top of the page](#)

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 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.

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 (with cross-reference to sections 4.2 and 4.8).



### Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Data on the development of anti-panitumumab antibodies has been evaluated using two different screening immunoassays for the detection of binding anti-panitumumab antibodies (an ELISA which detects high-affinity antibodies, and a Biosensor Immunoassay which detects both high and low-affinity antibodies). For patients whose sera tested positive in either screening immunoassay, an in vitro biological assay was performed to detect neutralising antibodies.

As monotherapy:

- The incidence of binding antibodies (excluding predose and transient positive patients) was < 1% as detected by the acid-dissociation ELISA and 3.8% as detected by the Biacore assay;
- The incidence of neutralising antibodies (excluding predose and transient positive patients) was < 1%;
- 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.

In combination with irinotecan- or oxaliplatin-based chemotherapy:

- The incidence of binding antibodies (excluding predose positive patients) was 1.0% as detected by the acid-dissociation ELISA and < 1% as detected by the Biacore assay;
- The incidence of neutralising antibodies (excluding predose positive patients) was < 1%;
- No evidence of an altered safety profile was found in patients who tested positive for antibodies to Vectibix.

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 assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease, therefore, comparison of the incidence of antibodies to other products may be misleading.

### Clinical efficacy as monotherapy

The efficacy of Vectibix as monotherapy 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).

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 study was retrospectively analysed by wild-type *KRAS* status versus mutant *KRAS* status. *KRAS* mutation status was determined by analysis of archived paraffin embedded tumour tissue.

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. The efficacy results from an analysis adjusting for potential bias from unscheduled assessments are shown in the table below. There was no difference in overall survival (OS) seen in either group.

	Wild-type <i>KRAS</i> population		Mutant <i>KRAS</i> population	
	Vectibix plus BSC (n = 124)	BSC (n = 119)	Vectibix plus BSC (n = 84)	BSC (n = 100)
<b>ORR n (%)</b>	17%	0%	0%	0%
Response rate (investigator assessed) <sup>a</sup> (95% CI)	22% (14, 32)		0% (0, 4)	
<b>Stable Disease</b>	34%	12%	12%	8%
<b>PFS</b>				

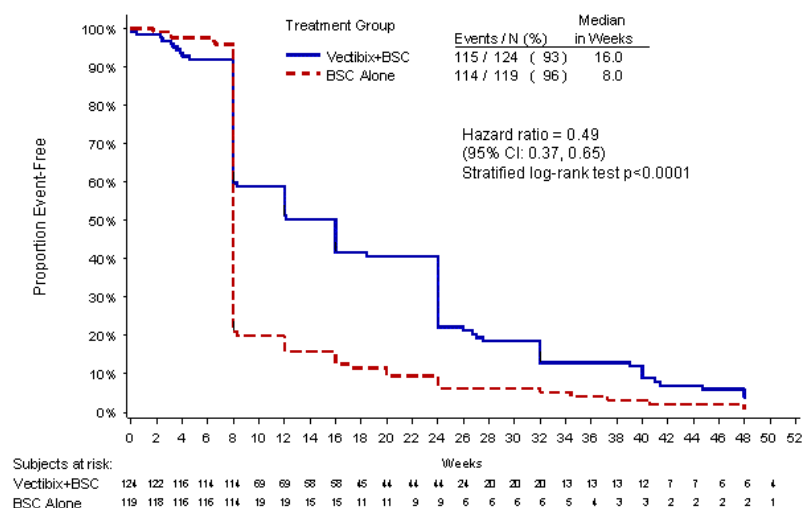
Hazard ratio (95% CI)	0.49 (0.37,0.65), p<0.0001		1.07 (0.77,1.48), p=0.6880	
Median (weeks)	16.0	8.0	8.0	8.0
Difference in median (weeks)	8.0		0.0	
Rate at week 8	60%	21%	21%	28%

CI = confidence interval

<sup>a</sup> In patients that crossed over to panitumumab after progression on BSC alone (95% CI)

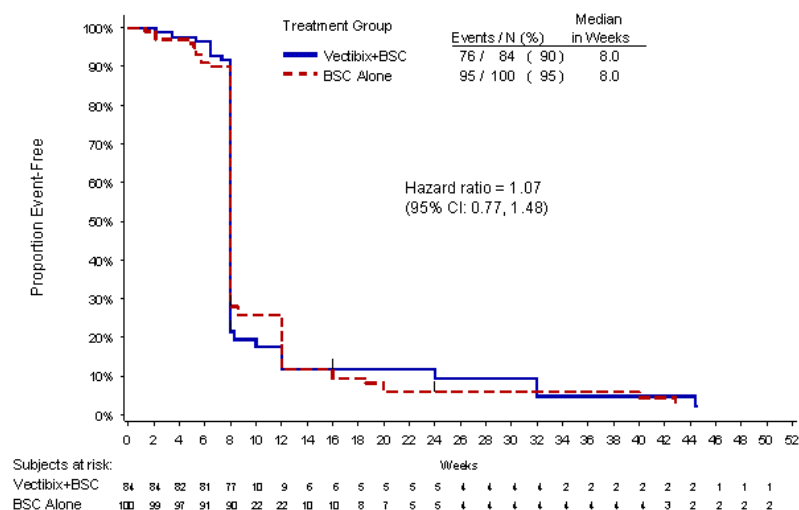
#### **PFS - Patients with mutant and wild-type KRAS**

##### **PFS - Patients with wild-type KRAS**



Unscheduled tumour assessments were moved to the nearest scheduled timepoint

##### **PFS – Patients with Mutant KRAS**



Unscheduled tumour assessments were moved to the nearest scheduled timepoint

#### **Clinical efficacy in combination with chemotherapy**

##### **First-line combination with FOLFOX**

The efficacy of Vectibix in combination with oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (FOLFOX) was evaluated in a randomised, controlled trial of 1183 patients with mCRC with the primary endpoint of progression-free survival (PFS). Other key endpoints included the overall survival (OS), objective response rate (ORR), time to response, time to progression (TTP), and duration of response. The study was prospectively analysed by tumour KRAS status which was evaluable in 93% of the patients. The efficacy results in patients with wild-type KRAS mCRC

and mutant *KRAS* mCRC are presented in the table below. Vectibix is indicated only for the treatment of wild-type *KRAS* mCRC (see sections 4.4 and 4.5).

The table below also summarises subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine) and anti-EGFR therapy. The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS treatment effect is unknown.

	First-line mCRC wild-type <i>KRAS</i> population		First-line mCRC mutant <i>KRAS</i> population	
	Vectibix plus FOLFOX	FOLFOX	Vectibix plus FOLFOX	FOLFOX
	(n = 325)	(n = 331)	(n = 221)	(n = 219)
ORR				
% (95% CI)	57% (51%, 63%)	48% (42%, 53%)	40% (33%, 47%)	41% (34%, 48%)
Odds ratio (95% CI)	1.47 (1.07, 2.04)		0.98 (0.65,1.47)	
Median duration of response (months) (95% CI)	10.9 (9.5, 13.3)	8.8 (7.7, 9.6)	7.4 (5.9, 8.3)	8.0 (6.7, 9.6)
PFS				
Median (months) (95% CI)	10.0 (9.3, 11.4)	8.6 (7.5, 9.5)	7.4 (6.9, 8.1)	9.2 (8.1, 9.9)
Difference in median (months)	1.4		-1.8	
Hazard ratio (95% CI); p-value	0.80 (0.67, 0.95); p = 0.0092		1.27 (1.04, 1.55); p = 0.0194	
Estimated rate at 12 months (95% CI)	44% (38%, 49%)	32% (27%, 38%)	24% (18%, 30%)	30% (24%, 37%)
On-treatment PFS hazard ratio (95% CI) <sup>a</sup> ; p-value	0.77 (0.63, 0.92); p = 0.0054		1.32 (1.05, 1.65); p = 0.0158	
TTP				
Median (months) (95% CI)	10.8 (9.4,12.5)	9.2 (7.7, 10.0)	7.5 (7.3, 8.9)	9.2 (8.0, 9.7)
Hazard ratio (95% CI)	0.76 (0.62, 0.92)		1.24 (0.98,1.58)	
OS				
Median (months) (95% CI)	23.9 (20.3, 27.7)	19.7 (17.6, 22.7)	15.5 (13.1, 17.6)	19.2 (16.5, 21.7)
Difference in median (months)	4.2		-3.7	
Hazard ratio (95% CI); p-value	0.88 (0.73, 1.06); p = 0.1710		1.17 (0.95, 1.45); p = 0.1444	
Estimated rate at 24 months (95% CI)	50% (44%, 55%)	41% (36%, 47%)	29% (23%, 36%)	39% (32%, 45%)
Subjects receiving chemotherapy after the protocol treatment phase – (%)	59%	65%	60%	70%

Subjects receiving anti-EGFR therapy after the protocol treatment phase - (%)	13%	25%	7%	16%
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CI = confidence interval

<sup>a</sup> Censoring death events if they occurred > 60 days after the last evaluable tumour assessment or randomization date, whichever is later.

The results of an exploratory covariate analysis according to ECOG status in subjects with wild-type *KRAS* mCRC are shown below:

	ECOG PS of 0 or 1 (n = 616)		ECOG 2 PS (n = 40)	
	Vectibix plus FOLFOX	FOLFOX	Vectibix plus FOLFOX	FOLFOX
	(n=305)	(n=311)	(n=20)	(n=20)
Median PFS (months)	10.8	8.7	4.8	7.5
Difference in median (months)	2.1		-2.7	
PFS Hazard ratio (95% CI); p-value	0.76 (0.64, 0.91); p = 0.0022		1.80 (0.88, 3.69); p = 0.1060	
Median OS (months)	25.8	20.6	7.0	11.7
Difference in median (months)	5.2		-4.7	
OS Hazard ratio (95% CI); p-value	0.84 (0.69, 1.02); p = 0.0735		1.59 (0.80, 3.16); p = 0.1850	

CI = confidence interval; PS = Performance Status

In a post-hoc analysis, the complete resection rate in wild-type *KRAS* subjects who had metastases to the liver only at baseline was 27.9% (95% CI: 17.2, 40.8) in the panitumumab plus FOLFOX arm and 17.5% (95% CI: 8.8, 29.9) in the FOLFOX alone arm.

#### Second-line combination with FOLFIRI

The efficacy of Vectibix in combination with irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) was evaluated in a randomised, controlled trial of 1186 patients with mCRC with the primary endpoints of overall survival (OS) and progression-free survival (PFS). Other key endpoints included the objective response rate (ORR), time to response, time to progression (TTP), and duration of response. The study was prospectively analysed by tumour *KRAS* status which was evaluable in 91% of the patients.

The efficacy results in patients with wild-type *KRAS* mCRC and mutant *KRAS* mCRC are presented in the table below. Eighteen (18) % (n = 115) of patients with wild-type *KRAS* mCRC had been exposed to prior bevacizumab treatment. PFS and Response Rate were similar regardless of prior bevacizumab treatment. Vectibix is indicated only for the treatment of wild-type *KRAS* mCRC (see sections 4.4 and 4.5).

The table below also summarises subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine) and anti-EGFR therapy. The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS treatment effect is unknown.

	Second-line mCRC wild-type <i>KRAS</i> population		Second-line mCRC mutant <i>KRAS</i> population	
	Vectibix plus FOLFIRI	FOLFIRI	Vectibix plus FOLFIRI	FOLFIRI
	(n = 303)	(n = 294)	(n = 238)	(n = 248)
<b>ORR</b>				
% (95% CI)	36% (31%, 42%)	10 % (7%, 14%)	13% (9%, 18%)	15% (11%, 20%)

Odds ratio (95% CI)	5.50 (3.32, 8.87)		0.93 (0.53, 1.63)	
Median duration of response (months) (95% CI)	7.6 (6.5, 9.4)	6.6 (5.7, 10.9)	5.8 (5.5, 7.4)	5.3 (4.6, 7.9)
PFS				
Median (months) (95% CI)	6.7 (5.8, 7.4)	4.9 (3.8, 5.5)	5.3 (4.2, 5.7)	5.4 (4.0, 5.6)
Difference in median (months)	1.8		-0.1	
Hazard ratio (95% CI); p-value	0.82 (0.69, 0.97); p = 0.0231		0.95 (0.78, 1.14); p = 0.5611	
Estimated rate at six months (95% CI)	54% (48%, 60%)	39% (33%, 44%)	40% (34%, 47%)	38% (32%, 44%)
On-treatment PFS hazard ratio (95% CI) <sup>a</sup> ; p-value	0.73 (0.60, 0.88); p = 0.001		0.89 (0.72, 1.10); p = 0.2951	
TTP				
Median (months) (95% CI)	7.3 (6.0, 7.5)	5.3 (3.9, 5.7)	5.5 (4.5, 5.7)	5.5 (4.8, 5.7)
Hazard ratio (95% CI)	0.72 (0.59, 0.88)		0.89 (0.71, 1.11)	
OS				
Median (months) (95% CI)	14.5 (13.0, 16.1)	12.5 (11.2, 14.2)	11.8 (10.4, 13.3)	11.1 (10.3, 12.4)
Difference in median (months)	2.0		0.7	
Hazard ratio (95% CI); p-value	0.92 (0.78, 1.10); p = 0.3660		0.93 (0.77, 1.13); p = 0.4815	
Estimated rate at 12 months (95% CI)	59% (53%, 64%)	53% (47%, 59%)	49% (42%, 55%)	45% (39%, 51%)
Estimated rate at 18 months (95% CI)	40% (34%, 45%)	33% (27%, 39%)	26% (21%, 32%)	24% (19%, 29%)
Subjects receiving chemotherapy after the protocol treatment phase – (%)	53%	50%	48%	55%
Subjects receiving anti-EGFR therapy after the protocol treatment phase - (%)	13%	34%	9%	32%

CI = confidence interval

<sup>a</sup> Censoring death events if they occurred > 60 days after the last evaluable tumour assessment or randomisation date, whichever is later.

#### First-line combination with bevacizumab and oxaliplatin or irinotecan-based chemotherapy

In a 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 patients 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 of monotherapy in patients with wild-type *KRAS* tumours which is currently supported by a retrospective analysis. Studies investigating this effect are currently ongoing. The European Medicines Agency (EMA) will review new information on the product every year and this SPC will be updated as necessary.

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Vectibix in all subsets of the paediatric population in colorectal cancer (see section 4.2 for information on paediatric use).

### 5.2 Pharmacokinetic properties

[Go to top of the page](#)

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 ( $\pm$  Standard Deviation [SD]) peak and trough concentrations of  $213 \pm 59$  and  $39 \pm 14$  mcg/ml, respectively. The mean ( $\pm$  SD) AUC<sub>0-tau</sub> and CL were  $1306 \pm 374$  mcg•day/ml and  $4.9 \pm 1.4$  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

[Go to top of the page](#)

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

[Go to top of the page](#)

### 6.1 List of excipients

[Go to top of the page](#)

Sodium chloride

Sodium acetate trihydrate

Acetic acid, glacial (for pH-adjustment)

Water for injections.

#### 6.2 Incompatibilities

[Go to top of the page](#)

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

#### 6.3 Shelf life

[Go to top of the page](#)

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

[Go to top of the page](#)

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 after dilution of the medicinal product, see section 6.3.

#### 6.5 Nature and contents of container

[Go to top of the page](#)

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

[Go to top of the page](#)

Vectibix should be diluted in 0.9% sodium chloride injection by 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 medicinal product or waste material should be disposed of in accordance with local requirements.

#### 7. Marketing authorisation holder

[Go to top of the page](#)

Amgen Europe B.V.

Minervum 7061

NL-4817 ZK Breda

The Netherlands

#### 8. Marketing authorisation number(s)

[Go to top of the page](#)

EU/1/07/423/001

EU/1/07/423/002

EU/1/07/423/003

**9. Date of first authorisation/renewal of the authorisation**[Go to top of the page](#)

Date of first authorisation: 3 December 2007

Date of last renewal: 17 March 2011

**10. Date of revision of the text**[Go to top of the page](#)

27 June 2012

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

**More information about this product**

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[Vectibix](#)

- Medicine Guides:

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