ANNEX I

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, or 400 mg of panitumumab 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Colourless, pH 5.6 to 6.0 solution that may contain translucent to white, visible amorphous, proteinaceous panitumumab particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- in first-line in combination with FOLFOX or FOLFIRI.
- 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

Vectibix treatment should be supervised by a physician experienced in the use of anti-cancer therapy. Evidence of wild-type *RAS* (*KRAS* and *NRAS*) status is required before initiating treatment with Vectibix. Mutational status should be determined by an experienced laboratory using validated test methods for detection of *KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4) mutations.

Posology

The recommended dose of Vectibix is 6 mg/kg of bodyweight given once every two weeks.

Modification of the dose of Vectibix may be necessary in cases of severe (≥ grade 3) dermatological reactions as follows:

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

[1] Greater than or equal to grade 3 is defined as severe or life-threatening

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 relevant use of Vectibix in the paediatric population in the indication treatment of colorectal cancer.

Method of administration

Vectibix must be administered as an intravenous infusion via an infusion pump.

Prior to infusion, Vectibix should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection to a final concentration not to exceed 10 mg/mL (for preparation instructions see section 6.6).

Vectibix must be administered using a low protein binding 0.2 or 0.22 micrometre 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 1,000 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 intravenous solutions.

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

Vectibix must not be administered as an intravenous push or bolus.

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

4.3 Contraindications

Patients with a history of severe or life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (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 *RAS* mCRC or for whom *RAS* mCRC status is unknown (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Dermatologic reactions and soft tissue toxicity

Dermatologic related reactions, a pharmacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients (approximately 94%) treated with Vectibix. Severe (NCI-CTC grade 3) skin reactions were reported in 23% and life-threatening (NCI-CTC grade 4) skin reactions in < 1% of patients who received Vectibix monotherapy and in combination with chemotherapy (n = 2,224) (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, see the recommendation for dose modification in section 4.2.

In clinical studies, subsequent to the development of severe dermatologic 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 soft tissue toxicity 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. Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients treated with Vectibix in the post-marketing setting. Withhold or discontinue Vectibix in the event of dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications.

Treatment and management 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 (e.g. doxycycline). 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. 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 = 2,224), infusion-related reactions (occurring within 24 hours of an infusion) were reported in Vectibix-treated patients, including severe infusion-related reactions (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 treatment, 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.

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^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

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. 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 *RAS* mCRC or for whom *RAS* tumour status is unknown

The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown (see sections 4.3 and 5.1).

A shortened progression-free survival (PFS) and overall survival (OS) time were observed in patients with mutant *KRAS* (exon 2) tumours and additional *RAS* mutations (*KRAS* [exons 3 and 4] or *NRAS* [exons 2, 3, 4]) who received panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) versus FOLFOX alone (see section 5.1).

RAS mutational status should be determined using a validated test method by an experienced laboratory (see section 4.2). 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 *RAS* External Quality Assurance programme or wild-type status be confirmed in a duplicate test.

Ocular toxicities

Serious cases of keratitis and ulcerative keratitis, which may lead to corneal perforation, have been reported. 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.

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 reactions were reported in elderly patients treated with Vectibix in combination with FOLFIRI or FOLFOX chemotherapy compared to chemotherapy alone (see section 4.8).

Warnings for excipients

This medicinal product contains 3.45 mg sodium per mL, equivalent to 0.17% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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 medicinal products 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 *RAS* mCRC or for whom *RAS* mCRC status is unknown. A shortened progression-free survival and overall survival time were observed in a clinical study in patients with mutant *RAS* tumours who received panitumumab and FOLFOX (see sections 4.4 and 5.1).

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 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.

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.

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

Vectibix may have a minor influence on the ability to drive and use machines. 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

Summary of safety profile

Based on an analysis of all mCRC clinical trial patients receiving Vectibix monotherapy and in combination with chemotherapy (n = 2,224), the most commonly reported adverse reactions are skin reactions occurring in approximately 94% of patients. These reactions are related to the pharmacologic effects of Vectibix, and the majority are mild to moderate in nature with 23% 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 (46%), nausea (39%), vomiting (26%), constipation (23%) and abdominal pain (23%)]; general disorders [fatigue (35%), pyrexia (21%)]; metabolism and nutrition disorders [decreased appetite (30%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (47%), dermatitis acneiform (39%), pruritus (36%), erythema (33%) and dry skin (21%)].

Tabulated list 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 = 2,224) 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 (≥ 1/1,000 to < 1/100)**
Infections and infestations	Conjunctivitis Paronychia[1]	Rash pustular Cellulitis[1] Urinary tract infection Folliculitis Localised infection	Eye infection Eyelid infection
Blood and lymphatic system disorders	Anaemia	Leucopenia	
Immune system disorders		Hypersensitivity[1]	Anaphylactic reaction[2]
Metabolism and nutrition disorders	Hypokalaemia Hypomagnesaemia Decreased appetite	Hypocalcaemia Dehydration Hyperglycaemia Hypophosphataemia	
Psychiatric disorders	Insomnia	Anxiety	
Nervous system disorders		Headache Dizziness	
Eye disorders		Blepharitis Growth of eyelashes Lacrimation increased Ocular hyperaemia Dry eye Eye pruritus Eye irritation	Ulcerative keratitis[1,4] Keratitis[1] Eyelid irritation
Cardiac disorders		Tachycardia	Cyanosis
Vascular disorders		Deep vein thrombosis Hypotension Hypertension Flushing	
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Epistaxis	Interstitial lung disease[3] Bronchospasm Nasal dryness
Gastrointestinal disorders	Diarrhoea[1] Nausea Vomiting Abdominal pain Stomatitis Constipation	Rectal haemorrhage Dry mouth Dyspepsia Aphthous ulcer Cheilitis Gastro-oesophageal reflux disease	Chapped lips Dry lips

	Adverse reactions		
MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**
Skin and subcutaneous tissue disorders[1]	Dermatitis acneiform Rash Erythema Pruritus Dry skin Skin fissures Acne Alopecia	Skin ulcer Skin exfoliation Exfoliative rash Dermatitis Rash papular Rash pruritic Rash erythematous Rash generalised Rash macular Rash maculo-papular Skin lesion Skin toxicity Scab Hypertrichosis Onychoclasis Nail disorder Hyperhidrosis Palmar-plantar erythrodysaesthesia syndrome	Toxic epidermal necrolysis[1,4] Stevens-Johnson syndrome[1,4] Skin necrosis[1,4] Angioedema[1] Hirsutism Ingrowing nail Onycholysis
Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity	
General disorders and administration site conditions	Fatigue Pyrexia Asthenia Mucosal inflammation Oedema peripheral	Chest pain Pain Chills	
Injury, poisoning and procedural complications			Infusion-related reaction[1]
Investigations	Weight decreased	Blood magnesium decreased	

[1] See section "Description of selected adverse reactions" below
[2] See section 4.4 Infusion-related reactions
[3] See section 4.4 Pulmonary complications
[4] Skin necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis and ulcerative keratitis are panitumumab ADRs that were reported in the post-marketing setting. For these ADRs the maximum frequency category was estimated from the upper limit of 95% confidence interval for the point estimate based on regulatory guidelines for estimation of the frequency of adverse reactions from spontaneous reporting. The maximum frequency estimated from the upper limit of 95% confidence interval for the point estimate, i.e., 3/2,224 (or 0.13%).

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 16% 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 = 2,224), 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 5% 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 31 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.

Across all clinical trials, skin reactions occurred in approximately 94% of patients receiving Vectibix as monotherapy or in combination with chemotherapy (n = 2,224). 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 23% and life-threatening (NCI-CTC grade 4) skin reactions in < 1% of patients. 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, rare cases of skin necrosis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4) have been reported.

Ocular toxicities

Serious cases of keratitis and ulcerative keratitis, which may lead to corneal perforation, have been reported (see section 4.4).

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% versus 32%) or FOLFOX (52% versus 37%) chemotherapy compared to chemotherapy alone (see section 4.4). The most increased serious adverse events included 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 (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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FE02

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.

KRAS (Kirsten rat sarcoma 2 viral oncogene homologue) and *NRAS* (Neuroblastoma *RAS* viral oncogene homologue) are highly related members of the *RAS* oncogene family. *KRAS* and *NRAS* genes encode small, GTP-binding proteins involved in signal transduction. A variety of stimuli, including that from the EGFR activate *KRAS* and *NRAS* which in turn stimulate other intracellular proteins to promote cell proliferation, cell survival and angiogenesis.

Activating mutations in the *RAS* genes 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.

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% 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 medicinal products 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 open-label, single-arm trials (585 patients) and in two randomised controlled trials versus best supportive care (463 patients) and versus cetuximab (1,010 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.

The primary endpoint was PFS. The study was retrospectively analysed by wild-type *KRAS* (exon 2) status versus mutant *KRAS* (exon 2) status. 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 of the *KRAS* gene. 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 *KRAS* (exon 2) population		Mutant *KRAS* (exon 2) population	
	Vectibix plus BSC (n = 124)	**BSC (n = 119)**	**Vectibix plus BSC (n = 84)**	**BSC (n = 100)**
ORR n (%)	17%	0%	0%	0%
Response rate (investigator assessed)[a] (95% CI)	22% (14, 32)		0% (0, 4)	
Stable Disease	34%	12%	12%	8%
PFS				
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

CI = confidence interval

[a] In patients that crossed over to panitumumab after progression on BSC alone (95% CI)

In an exploratory analysis of banked tumour specimens from this study, 11 of 72 patients (15%) with wild-type *RAS* tumours receiving panitumumab had an objective response compared to only 1 of 95 patients (1%) with mutant *RAS* tumour status. Moreover, panitumumab treatment was associated with improved PFS compared to BSC in patients with wild-type *RAS* tumours (HR = 0.38 [95% CI: 0.27, 0.56]), but not in patients with tumours harbouring a *RAS* mutation (HR = 0.98 [95% CI: 0.73, 1.31]).

The efficacy of Vectibix was also evaluated in an open-label trial in patients with wild-type *KRAS* (exon 2) mCRC. A total of 1,010 patients refractory to chemotherapy were randomised 1:1 to receive Vectibix or cetuximab to test whether Vectibix is non-inferior to cetuximab. The primary endpoint was OS. Secondary endpoints included PFS and objective response rate (ORR).

The efficacy results for the study are presented in the table below.

Wild-type *KRAS* (exon 2) population	**Vectibix** (n = 499)	**Cetuximab** (n = 500)
OS		
Median (months) (95% CI)	10.4 (9.4, 11.6)	10.0 (9.3, 11.0)
Hazard ratio (95% CI)	0.97 (0.84, 1.11)	
PFS		
Median (months) (95% CI)	4.1 (3.2, 4.8)	4.4 (3.2, 4.8)
Hazard ratio (95% CI)	1.00 (0.88, 1.14)	
ORR		
n (%) (95% CI)	22% (18%, 26%)	20% (16%, 24%)
Odds ratio (95% CI)	1.15 (0.83, 1.58)	

Overall, the safety profile of panitumumab was similar to that of cetuximab, in particular regarding skin toxicity. However, infusion reactions were more frequent with cetuximab (13% versus 3%) but electrolyte disturbances were more frequent with panitumumab, especially hypomagnesaemia (29% versus 19%).

Clinical efficacy in combination with chemotherapy

Among patients with wild-type *RAS* mCRC, PFS, OS, and ORR were improved for subjects receiving panitumumab plus chemotherapy (FOLFOX or FOLFIRI) compared with those receiving chemotherapy alone. Patients with additional *RAS* mutations beyond *KRAS* exon 2 were unlikely to benefit from the addition of panitumumab to FOLFIRI and a detrimental effect was seen with the addition of panitumumab to FOLFOX in these patients. *BRAF* mutations in exon 15 were found to be prognostic of worse outcome. *BRAF* mutations were not predictive of the outcome for panitumumab treatment in combination with FOLFOX or FOLFIRI.

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 1,183 patients with mCRC with the primary endpoint of PFS. Other key endpoints included the OS, ORR, time to response, time to progression (TTP), and duration of response. The study was prospectively analysed by tumour *KRAS* (exon 2) status which was evaluable in 93% of the patients.

A predefined retrospective subset analysis of 641 patients of the 656 patients with wild-type *KRAS* (exon 2) mCRC was performed. Patient tumour samples with wild-type *KRAS* exon 2 (codons 12/13) status were tested for additional *RAS* mutations in *KRAS* exon 3 (codons 61) and exon 4 (codons 117/146) and *NRAS* exon 2 (codons 12/13), exon 3 (codon 61), and exon 4 (codons 117/146) and *BRAF* exon 15 (codon 600). The incidence of these additional *RAS* mutations in the wild-type *KRAS* exon 2 population was approximately 16%.

Results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC are presented in the table below.

	Vectibix plus FOLFOX (months) Median (95% CI)	**FOLFOX (months) Median (95% CI)**	**Difference (months)**	**Hazard ratio (95% CI)**
Wild-type *RAS* population				
PFS	10.1 (9.3, 12.0)	7.9 (7.2, 9.3)	2.2	0.72 (0.58, 0.90)
OS	26.0 (21.7, 30.4)	20.2 (17.7, 23.1)	5.8	0.78 (0.62, 0.99)
Mutant *RAS* population				
PFS	7.3 (6.3, 7.9)	8.7 (7.6, 9.4)	-1.4	1.31 (1.07, 1.60)
OS	15.6 (13.4, 17.9)	19.2 (16.7, 21.8)	-3.6	1.25 (1.02, 1.55)

Additional mutations in *KRAS* and *NRAS* at exon 3 (codon 59) were subsequently identified (n = 7). An exploratory analysis showed similar results to those in the previous table.

Combination with FOLFIRI

The efficacy of Vectibix in second-line in combination with irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) was evaluated in a randomised, controlled trial of 1,186 patients with mCRC with the primary endpoints of OS and PFS. Other key endpoints included the ORR, time to response, TTP, and duration of response. The study was prospectively analysed by tumour *KRAS* (exon 2) status which was evaluable in 91% of the patients.

A predefined retrospective subset analysis of 586 patients of the 597 patients with wild-type *KRAS* (exon 2) mCRC was performed, where tumour samples from these patients were tested for additional *RAS* and *BRAF* mutations as previously described. The *RAS/BRAF* ascertainment was 85% (1,014 of 1,186 randomised patients). The incidence of these additional *RAS* mutations (*KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4) in the wild-type *KRAS* (exon 2) population was approximately 19%. The incidence of *BRAF* exon 15 mutation in the wild-type *KRAS* (exon 2) population was approximately 8%. Efficacy results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC are shown in the below table.

	Vectibix plus FOLFIRI (months) Median (95% CI)	FOLFIRI (months) Median (95% CI)	Hazard ratio (95% CI)
Wild-type *RAS* population			
PFS	6.4 (5.5, 7.4)	4.6 (3.7, 5.6)	0.70 (0.54, 0.91)
OS	16.2 (14.5, 19.7)	13.9 (11.9, 16.0)	0.81 (0.63, 1.02)
Mutant *RAS* population			
PFS	4.8 (3.7, 5.5)	4.0 (3.6, 5.5)	0.86 (0.70, 1.05)
OS	11.8 (10.4, 13.1)	11.1 (10.2, 12.4)	0.91 (0.76, 1.10)

The efficacy of Vectibix in first-line in combination with FOLFIRI was evaluated in a single-arm study of 154 patients with the primary endpoint of objective response rate (ORR). Other key endpoints included the PFS, time to response, TTP, and duration of response.

A predefined retrospective subset analysis of 143 patients of the 154 patients with wild-type *KRAS* (exon 2) mCRC was performed, where tumour samples from these patients were tested for additional *RAS* mutations. The incidence of these additional *RAS* mutations (*KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4) in the wild-type *KRAS* (exon 2) population was approximately 10%.

Results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC from the primary analysis are presented in the table below.

	Panitumumab + FOLFIRI	
	Wild-type *RAS* (n = 69)	**Mutant *RAS* (n = 74)**
ORR (%) (95% CI)	59 (46, 71)	41 (30, 53)
Median PFS (months) (95% CI)	11.2 (7.6, 14.8)	7.3 (5.8, 7.5)
Median Duration of response (months) (95% CI)	13.0 (9.3, 15.7)	5.8 (3.9, 7.8)
Median TTP (months) (95% CI)	13.2 (7.8, 17.0)	7.3 (6.1, 7.6)

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 = 1,053 [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* (exon 2) 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.

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

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 (± Standard Deviation [SD]) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/mL, respectively. The mean (± SD) AUC0-tau and CL were 1,306 ± 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 injections.

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

Vial

3 years.

Diluted solution

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 – 8°C. The diluted solution must not be frozen.

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 after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with an elastomeric stopper, aluminium seal and flip-off plastic cap.
One vial contains either 100 mg of panitumumab in 5 mL, or 400 mg panitumumab in 20 mL of concentrate for solution for infusion.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Vectibix is intended for single use only. Vectibix should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection by healthcare professional using aseptic technique. Do not shake or vigorously agitate the vial. Vectibix should be inspected visually prior to administration. The solution should be colourless and may contain visible translucent-to-white, amorphous, proteinaceous particulates (which will be removed by in-line filtration). Do not administer Vectibix if its appearance is not as described above. Using only a 21-gauge or smaller diameter hypodermic needle, withdraw the necessary amount of Vectibix for a dose of 6 mg/kg. Do not use needle-free devices (e.g. vial adapters) to withdraw vial contents. Dilute in a total volume of 100 mL. The final concentration should not exceed 10 mg/mL. Doses higher than 1,000 mg should be diluted in 150 mL sodium chloride 9 mg/mL (0.9%) solution for injection (see section 4.2). The diluted solution should be mixed by gentle inversion, do not shake.

Vectibix must be administered using a low protein binding 0.2 or 0.22 micrometre in-line filter, through a peripheral line or indwelling catheter.

No incompatibilities have been observed between Vectibix and sodium chloride 9 mg/mL (0.9%) solution for injection in polyvinyl chloride bags or polyolefin bags.

Discard the vial and any liquid remaining in the vial after the single-use.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 December 2007
Date of latest renewal: 23 September 2019

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Immunex Rhode Island Corporation (ARI)
40 Technology Way
West Greenwich,
Rhode Island
02817
USA

Name and address of the manufacturers responsible for batch release

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

Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The marketing authorisation holder (MAH) shall submit PSUR for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vectibix 20 mg/mL concentrate for solution for infusion
panitumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg of panitumumab.
Each vial contains 400 mg of panitumumab.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium acetate trihydrate, acetic acid (glacial), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 mL of concentrate for solution for infusion.
20 mL of concentrate for solution for infusion.

x1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Vectibix 20 mg/ml sterile concentrate
panitumumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/5 ml
400 mg/20 ml

6. OTHER

Amgen Europe B.V.

B. PACKAGE LEAFLET

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 because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vectibix is and what it is used for

Vectibix is used in the treatment of metastatic colorectal cancer (cancer of the bowel) for adult patients with a certain type of tumour known as a "Wild-type *RAS* tumour". Vectibix is used alone or in combination with other anti-cancer medicines.

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. What you need to know before you use Vectibix

Do not use Vectibix

- if you are allergic to panitumumab or any of the other ingredients of this medicine (listed in section 6).
- 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).
- in combination with oxaliplatin-based chemotherapy, if your *RAS* test shows that you have mutant *RAS* tumour, or if your *RAS* tumour status is unknown. Please consult your doctor if you are unsure of your *RAS* tumour status.

Warnings and precautions

You may experience skin reactions or severe swelling and tissue damage, if these worsen or become intolerable please tell your doctor or nurse immediately. If you experience a severe skin reaction, your doctor may recommend an adjustment of the dose of Vectibix. If you develop a severe infection or fever as a result of skin reactions, your doctor may stop your treatment with Vectibix.

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 may ask you to use a moisturiser, sun screen (SPF > 15), topical steroid, and/or oral antibiotics which may help in the management of skin toxicities that can be associated with the use of Vectibix.

Your doctor will check your blood levels of several substances such as magnesium, calcium and potassium in your blood before you start Vectibix treatment. Your doctor will also check your blood levels of magnesium and calcium periodically during your treatment, and for up to 8 weeks after you have finished your treatment. If these levels are too low, your doctor may prescribe you appropriate supplements.

If you experience severe diarrhoea please tell your doctor or nurse since you may lose a lot of water from your body (become dehydrated) and this could damage your kidneys.

Tell your doctor if you use contact lenses and/or have a history of eye problems such as severe dry eye, inflammation of the front part of the eye (cornea) or ulcers involving the front part of the eye.

If you develop acute or worsening redness and pain in the eye, increased eye watering, blurred vision and/or sensitivity to light, please tell your doctor or nurse immediately as you may need urgent treatment (see “Possible side effects” below).

Based on your age (older than 65 years) or general health, your doctor will discuss with you your ability to tolerate taking Vectibix with your chemotherapy treatment.

Other medicines and Vectibix

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

Vectibix should not be used in combination with bevacizumab (another monoclonal antibody used in cancer of the bowel) or with a chemotherapy combination known as “IFL”.

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 unborn baby or ability to stay pregnant.

If you are a woman of child bearing potential, you should use effective methods of contraception during treatment with Vectibix and for 2 months after the last dose.

It is not recommended to breast-feed your baby during treatment with Vectibix and for 2 months after the last dose. It is important to tell your doctor if you plan to breast-feed.

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

Driving and using machines

You should speak with your doctor before driving or using machines, as some side effects may impair your ability to do so safely.

Vectibix contains sodium

This medicine contains 3.45 mg sodium (main component of cooking/table salt) in each mL unit. This is equivalent to 0.17% of the recommended maximum daily dietary intake of sodium for an adult.

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, this medicine can cause side effects, although not everybody gets them.

The most serious side effects and main side effects for Vectibix are listed below:

Infusion reactions

During or following treatment you may experience an infusion reaction. These can be mild or moderate (likely to occur in approximately 5 out of 100 people who take Vectibix), or severe (likely to occur in 1 out of 100 people who take Vectibix). Symptoms may include headache, rashes, itching or hives, flushing, swelling (face, lips, mouth, around the eyes, and throat area), rapid and irregular heartbeat, fast pulse, sweating, nausea, vomiting, dizziness, difficulty breathing or swallowing, or a decrease in blood pressure that may be severe or life-threatening and, very rarely, may lead to death. If you experience any of these symptoms, you should notify your doctor immediately. Your doctor may decide to reduce the rate of your infusion or discontinue your treatment with Vectibix.

Allergic reactions

Very rarely, serious allergic (hypersensitivity) reactions involving symptoms similar to an infusion reaction (see “Infusion reactions”) have occurred more than 24 hours after treatment and resulted in a fatal outcome. Seek medical attention immediately if you experience symptoms of an allergic reaction to Vectibix, including but not limited to difficulty breathing, chest tightness, a sensation of choking, dizziness, or fainting.

Skin reactions

Skin-related reactions are likely to occur in approximately 94 out of 100 people who take Vectibix and are usually mild to moderate. The skin rash commonly resembles acne and often involves the face, upper chest and back, but can affect any area of the body. Some rashes have been associated with redness, itching and flaking of the skin which can become severe. In some cases, it may cause infected sores requiring medical and/or surgical treatment, or cause severe skin infections that in rare cases could be fatal. In rare cases patients may experience blistering of the skin, mouth, eyes and genitals, which may indicate a severe skin reaction called “Stevens-Johnson syndrome” or blistering of the

skin, which may indicate a severe skin reaction called “toxic epidermal necrolysis”. If you experience blistering, you should notify your doctor immediately. Prolonged exposure to the sun can make the rash worse. Also, dry skin, fissures (cracks in the skin) on the fingers or toes, fingernail bed or toenail bed infection (paronychia) or inflammation has been reported. Once treatment is withheld or discontinued, the skin reactions will generally resolve. Your doctor may decide to treat the rash, adjust the dose or discontinue your treatment with Vectibix.

Other side effects include:

Very common: may affect more than 1 in 10 people
- low red blood cell numbers (anaemia); low potassium levels in the blood (hypokalaemia); low magnesium levels in the blood (hypomagnesaemia);
- eye inflammation (conjunctivitis);
- local or widespread rash which may be bumpy (with or without spots), itchy, red or flaky;
- hair loss (alopecia); mouth ulcers and cold sores (stomatitis); inflammation of the mouth (mucosal inflammation);
- diarrhoea; nausea; vomiting; abdominal pain; constipation; decreased appetite; decreased weight;
- extreme tiredness (fatigue); fever or high temperature (pyrexia); lack or loss of strength (asthenia); accumulation of fluid in the extremities (oedema peripheral);
- back pain;
- inability to sleep (insomnia);
- cough; dyspnoea (breathing difficulties).

Common: may affect up to 1 in 10 people
- low white blood numbers (leucopenia); low calcium levels in the blood (hypocalcaemia); low phosphates in the blood (hypophosphataemia); high glucose in the blood (hyperglycaemia);
- growth of eyelashes; flow of tears (lacrimation increased); redness of the eye (ocular hyperaemia); dry eye; itchy eyes (eye pruritus); eye irritation; eyelid inflammation (blepharitis);
- skin ulcer; scab; excess hair growth (hypertrichosis); redness and swelling of palms of hands or soles of feet (hand-foot syndrome); excess sweating (hyperhidrosis); skin reaction (dermatitis);
- spreading infection below the skin (cellulitis); hair follicle inflammation (folliculitis); localised infection; skin rash with pus-filled blisters (rash pustular); urinary tract infection;
- nail disorder; breaking of the nails (onychoclasis);
- dehydration;
- dry mouth; indigestion (dyspepsia); rectal bleeding (rectal haemorrhage); lip inflammation (cheilitis); heartburn (gastroesophageal reflux);
- chest pain; pain; chills; pain in the extremity; immune reaction (hypersensitivity); rapid heart rate (tachycardia);
- blood clot in the lung (pulmonary embolism) the symptoms of which may be sudden onset of shortness of breath or chest pain; nose bleed (epistaxis); blood clot in a deep vein (deep vein thrombosis); high blood pressure (hypertension); flushing;
- headache; dizziness; anxiety.

Uncommon: may affect up to 1 in 100 people
- blue colouration of the skin and mucous membranes (cyanosis);
- skin cell death (skin necrosis);
- severe skin reaction with blistering of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome);
- severe skin reaction with blistering of the skin (toxic epidermal necrolysis);
- a serious condition of ulceration of the front part of the eye (cornea) requiring urgent treatment (ulcerative keratitis);
- inflammation of the front part of the eye (cornea) (keratitis);

- eyelid irritation; chapped lips and/or dry lips; eye infection; eyelid infection; nasal dryness; loosening of the nails (onycholysis); ingrowing nail; excessive hair growth (hirsutism);
- inflammation of the lungs (interstitial lung disease).

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vectibix

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

Keep this medicine out of the sight and reach 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 this medicine 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vectibix contains

- Each mL of concentrate contains 20 mg panitumumab. Each vial contains either 100 mg of panitumumab in 5 mL, or 400 mg of panitumumab in 20 mL.
- The other ingredients are sodium chloride, sodium acetate trihydrate, acetic acid (glacial) and water for injections. See section 2 “Vectibix contains sodium”.

What Vectibix looks like and contents of the pack

Vectibix is a colourless liquid that may contain visible particles and is supplied in a glass vial. Each pack contains one vial.

Marketing Authorisation Holder and Manufacturer
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Manufacturer
Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Manufacturer
Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
s.a. Amgen n.v.
Tel/Tél: +32 (0)2 7752711

България
Амджен България ЕООД
Тел.: +359 (0)2 424 7440

Česká republika
Amgen s.r.o.
Tel: +420 221 773 500

Danmark
Amgen, filial af Amgen AB, Sverige
Tlf: +45 39617500

Deutschland
Amgen GmbH
Tel.: +49 89 1490960

Eesti
Amgen Switzerland AG Vilniaus filialas
Tel: +372 586 09553

Ελλάδα
Amgen Ελλάς Φαρμακευτικά Ε.Π.Ε.
Τηλ.: +30 210 3447000

España
Amgen S.A.
Tel: +34 93 600 18 60

France
Amgen S.A.S.
Tél: +33 (0)9 69 363 363

Lietuva
Amgen Switzerland AG Vilniaus filialas
Tel: +370 5 219 7474

Luxembourg/Luxemburg
s.a. Amgen
Belgique/Belgien
Tel/Tél: +32 (0)2 7752711

Magyarország
Amgen Kft.
Tel.: +36 1 35 44 700

Malta
Amgen S.r.l.
Italy
Tel: +39 02 6241121

Nederland
Amgen B.V.
Tel: +31 (0)76 5732500

Norge
Amgen AB
Tel: +47 23308000

Österreich
Amgen GmbH
Tel: +43 (0)1 50 217

Polska
Amgen Biotechnologia Sp. z o.o.
Tel.: +48 22 581 3000

Portugal
Amgen Biofarmacêutica, Lda.
Tel: +351 21 4220606

Hrvatska
Amgen d.o.o.
Tel: +385 (0)1 562 57 20

Ireland
Amgen Ireland Limited
Tel: +353 1 8527400

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Amgen S.r.l.
Tel: +39 02 6241121

Κύπρος
C.A. Papaellinas Ltd
Τηλ.: +357 22741 741

Latvija
Amgen Switzerland AG Rīgas filiāle
Tel: +371 257 25888

România
Amgen România SRL
Tel: +4021 527 3000

Slovenija
AMGEN zdravila d.o.o.
Tel: +386 (0)1 585 1767

Slovenská republika
Amgen Slovakia s.r.o.
Tel: +421 2 321 114 49

Suomi/Finland
Amgen AB, sivuliike Suomessa/Amgen AB, filial i Finland
Puh/Tel: +358 (0)9 54900500

Sverige
Amgen AB
Tel: +46 (0)8 6951100

United Kingdom (Northern Ireland)
Amgen Limited
Tel: +44 (0)1223 420305

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

The following information is intended for healthcare professionals only:

Vectibix is intended for single use only. Vectibix should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection by healthcare professional using aseptic technique. Do not shake or vigorously agitate the vial. Vectibix should be inspected visually prior to administration. The solution should be colourless and may contain visible translucent-to-white, amorphous, proteinaceous particulates (which will be removed by in-line filtration). Do not administer Vectibix if its appearance is not as described above. Using only a 21-gauge or smaller diameter hypodermic needle, withdraw the necessary amount of Vectibix for a dose of 6 mg/kg. Do not use needle-free devices (e.g. vial adapters) to withdraw vial contents. Dilute in a total volume of 100 mL. Doses higher than 1,000 mg should be diluted in 150 mL sodium chloride 9 mg/mL (0.9%) solution for injection. The final concentration should not exceed 10 mg/mL. The diluted solution should be mixed by gentle inversion, do not shake.

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 – 8°C. The diluted solution must not be frozen.

Discard the vial and any liquid remaining in the vial after the single-use.

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

Vectibix must be administered as an intravenous infusion via an infusion pump, using a low protein binding 0.2 or 0.22 micrometre in-line filter, through a peripheral line or indwelling catheter. The recommended infusion time is approximately 60 minutes. Doses higher than 1,000 mg should be infused over approximately 90 minutes.

No incompatibilities have been observed between Vectibix and sodium chloride 9 mg/mL (0.9%) solution for injection in polyvinyl chloride bags or polyolefin bags.