PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 20 mg panitumumab.

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

When prepared according to the instructions given in Special precautions for disposal and other handling, the final VECTIBIX® 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.

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.

Colourless, pH 5.6 to 6.0 liquid that may contain, translucent to white, amorphous, proteinaceous 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 in patients who have failed treatment with oxaliplatin, fluoropyrimidine, and irinotecan-containing chemotherapy regimens.

4.2. Posology and method of administration

VECTIBIX® treatment should be supervised by a medical practitioner 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 body weight 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	-	-

Occurrence of skin symptom(s): ≥ grade 3[1]	Administration of VECTIBIX®	Outcome	Dose regulation
[1] Greater than or equal to grade 3 is defined as severe or life-threatening			

Special populations

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

Paediatric population

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

Elderly

Dose adjustment is not required in the elderly.

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).

Method of Administration

VECTIBIX® must be administered using a low protein binding 0,2 µm or 0,22 µm 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 Special precautions for disposal and other handling).

The infusion line should be flushed with 0,9 % sodium chloride solution for injection 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 VECTIBIX® before administration, see Special precautions for disposal and other handling.

4.3. Contraindications

Patients with a history of life-threatening hypersensitivity to the active substance or to any of the excipients (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).

VECTIBIX® is contraindicated in pregnancy and lactation (see section 4.6).

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 is 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. Stop or discontinue VECTIBIX® for dermatologic toxicity 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 > 50 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. Onset or worsening pulmonary symptoms, VECTIBIX® treatment should be interrupted. In the event of acute 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 VECTIBIX® 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 of these electrolytes is also recommended, as appropriate.

Infusion-related reactions

In the setting of infusion-related reactions occurring within 24 hours of infusion, adverse reactions including abdominal pain, anaphylactic reactions, angioedema, back pain, bronchospasm, cardiorespiratory arrest, chest pain, chills, cyanosis, dyspnoea, flushing, hypertension, hypotension, pyrexia, tachycardia and vomiting have been reported in clinical trials and in the post-marketing setting.

Across 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 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 section 4.3 and section 4.8).

In patients experiencing a mild or moderate (CTCAE v 4,0 grade 1 and 2) infusion-related reaction the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.

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

Patients should be informed of the possibility of a late onset reaction and instructed to contact their medical practitioner 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 with bevacizumab containing chemotherapy (see in combination with section 4.4 and section 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 section 4.3).

A shortened PFS and 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 VECTIBIX® 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).

Ocular toxicities

Serious cases of keratitis, ulcerative keratitis and corneal perforation have been 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.

Immunogenicity

There is potential for immunogenicity with VECTIBIX®. 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 3,3 % as detected by the Biacore assay;

- The incidence of neutralising antibodies (excluding predose and transient positive patients) was < 1 %.

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®.

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 medications and other forms of interaction

In monotherapy, there are no known interactions.

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 section 4.4 and section 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 PFS and OS time were observed in a clinical study in patients with mutant *RAS* tumours who received panitumumab and FOLFOX (see section 4.4 and section 5.1).

4.6. Fertility, pregnancy and lactation

Pregnancy

VECTIBIX® is contraindicated in pregnancy and lactation. There are no adequate data from the use of VECTIBIX® in pregnant women. Studies in animals have shown reproductive toxicity.

Women of childbearing potential

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.

Breastfeeding

VECTIBIX® is contraindicated in lactation. Women should not breast feed during treatment with VECTIBIX® and for 2 months after the last dose. (see section 4.3).

Fertility

Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys. VECTIBIX® may impact the ability of a woman to become pregnant.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. 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 summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical studies in patients with mCRC who received VECTIBIX® 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.

MedDRA system organ class	**Very** Common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1 000 to < 1/100)	**Not known** (cannot be estimated from the available data)
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	Leukopenia		
Immune system disorders		Hypersensitivity[1]	Anaphylactic reaction[2]	
Metabolism and nutrition disorders	Hypokalaemia Hypomagnesaemia Decreased appetite	Hypocalcaemia Dehydration Hyperglycaemia Hypophosphatemia		
Psychiatric disorders	Insomnia	Anxiety		
		Headache		

Nervous system disorders		Dizziness		
Eye disorders		Blepharitis Growth of eyelashes Lacrimation increased Ocular hyperaemia Dry eye Eye pruritus Eye irritation	Keratitis[1] Eyelid irritation	Ulcerative keratitis[1,4] Corneal perforation[1,4,5]
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 Gastroesophageal Reflux Disease	Chapped lips Dry lips	
	Dermatitis acneiform	Skin ulcer	Angioedema[1]	Toxic epidermal necrolysis[4]

Skin and subcutaneous tissue disorders[1]	Rash Erythema Pruritus Dry skin Skin fissures Acne Alopecia	Skin exfoliation Exfoliative rash Dermatitis Rash papular Rash pruritic Rash Erythematous Rash generalised Rash macular Rash maculopapular Skin lesion Skin toxicity Scab Hypertrichosis Onychoclasis Nail disorder Hyperhidrosis Palmar plantar Erythrodysaesthesia syndrome	Hirsutism Ingrowing nail Onycholysis	Stevens-Johnson syndrome[4] Skin necrosis[4]
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		
			Infusion-related reaction[1]	

Injury, poisoning and procedural complications				
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] Corneal perforation, skin necrosis, Stevens-Johnson syndrome, toxic Epidermal Necrolysis and ulcerative keratitis are panitumumab ADRs that were reported in the post-marketing setting with not known frequency.

[5] Corneal perforation includes keratorrhexis and corneal perforation.

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 VECTIBIX® 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 section 4.3 and section 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, cases of skin necrosis, Stevens- Johnson syndrome and toxic epidermal necrolysis (see section 4.4) have been reported.

Ocular toxicities

Serious cases of keratitis, ulcerative keratitis and 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Alternatively, suspected adverse events can be reported to:

Amgen South Africa (Pty) Ltd.

Tel: +27 (0)11 100 5300

Email: safety-south-africa@amgen.com

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. Treatment is palliative and supportive.

5. Pharmacological Properties

5.1. Pharmacodynamic properties

A 30.1 Biologicals – Antibodies.

Mechanism of action

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds with high affinity and specificity to the human epidermal growth factor receptor (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 (see sections 4.2 and 4.8).

Immunogenicity

There is potential for immunogenicity with VECTIBIX®. 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 3,3 % as detected by the Biacore assay;
- The incidence of neutralising antibodies (excluding predose and transient positive patients) was < 1 %.

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®.

5.2. Pharmacokinetic properties

Panitumumab 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), 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride

Sodium acetate trihydrate

Acetic acid, glacial (for pH-adjustment)

Water for injection.

6.2 Incompatibilities

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

6.3. Shelf-life

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 between 2 and 8 °C.

Do not freeze.

Store in the original carton in order to protect from light.

Keep out of the reach of children.

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 between 2 and 8 °C. Do not freeze diluted solution.

6.5. Nature and contents of container

Single-use vial (type I glass) with an elastomeric grey stopper, aluminium seal and white flip-off plastic cap.

One vial contains either 100 mg of panitumumab in 5 ml, 200 mg panitumumab in 10 ml, or 400 mg panitumumab in 20 ml of concentrate for solution for infusion.

Pack of 1 vial containing 5 ml.

Pack of 1 vial containing 10 ml.

Pack of 1 vial containing 20 ml.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

VECTIBIX® is intended for single-use only (see section 6.5).

VECTIBIX® should be diluted in 0,9 % sodium chloride 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 0,9 % sodium chloride solution for 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 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. HOLDER OF CERTIFICATE OF REGISTRATION

Amgen South Africa (Pty) Ltd.
Building D, Ballyoaks Office Park, 35 Ballyclare Drive
Bryanston Ext. 7,
2021
South Africa

8. REGISTRATION NUMBER(S)

VECTIBIX® 5 ml: 44/30.1/0110
VECTIBIX® 10 ml: 44/30.1/0111
VECTIBIX® 20 ml: 44/30.1/0112

9. DATE OF FIRST AUTHORIZATION

Date of Registration: 29 July 2016

10. DATE OF REVISION OF TEXT

Updated: 20 December 2021