

PRODUCT MONOGRAPH

PrVectibix[®]
(panitumumab)

Sterile Solution for Infusion
100, 200, 400 mg (20 mg/mL)

Professed Standard

Antineoplastic

Vectibix[®], indicated as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

Manufactured by:
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Distributed by:
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Date of Authorisation:
February 26, 2010

Submission Control No: 130165

**This product has been approved under the
Notice of Compliance with Conditions (NOC/c)
policy for one or all of its indicated uses.**

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c Policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol **NOC/c**. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c Policy, the conditions associated with market authorization will be removed.

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PrVectibix[®]
(panitumumab)

PART I: HEALTH PROFESSIONAL INFORMATION

Vectibix[®], indicated as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens, has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous (IV) Infusion <i>See Dosage and Administration</i>	Sterile Concentrate for Solution for Infusion/ 100, 200, 400 mg (20mg/mL)	Not Applicable <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

Vectibix[®] (panitumumab) is a recombinant, fully human IgG2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Vectibix[®] consists of 2 gamma heavy chains and 2 kappa light chains and has an approximate molecular weight of 147 kDa. Vectibix[®] is produced in a mammalian cell line (CHO) by recombinant DNA technology.

INDICATIONS AND CLINICAL USE

NOC/c

Vectibix[®] (panitumumab) is indicated as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

The effectiveness of Vectibix[®] as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma is based on progression-free survival (see **CLINICAL TRIALS**). Currently no data are available that demonstrate an increased survival with Vectibix[®].

Pediatrics

The safety and effectiveness of Vectibix[®] in pediatric patients have not yet been established.

Geriatrics (≥ 65 years of age)

Fifty-two patients ≥ 65 years old and 71 < 65 years old in the non-mutated (wild-type) *KRAS* stratum were treated with Vectibix[®] plus best supportive care (BSC). The efficacy and qualitative safety results were similar between the geriatric patients (65 years or older) versus those patients who were younger.

CONTRAINDICATIONS

Vectibix[®] (panitumumab) is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to panitumumab or any other component of the product. For a complete listing of the components, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

NOC/c

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Dermatologic Toxicity: Dermatologic toxicities, related to Vectibix[®] (panitumumab) blockade of EGF receptor occurred in 91% (721/789) of patients and were severe (NCI-CTC grade 3 and higher) in 12% of patients receiving Vectibix[®] monotherapy. The clinical manifestations included dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. Severe dermatologic toxicities were complicated by infection, including sepsis, in rare cases leading to death, and local abscesses requiring incision and drainage. Withhold or discontinue Vectibix[®] and monitor for inflammatory or infectious sequelae in patients with severe dermatologic toxicities (see **DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment**). It is recommended that patients wear sunscreen and a hat and limit sun exposure while receiving Vectibix[®] as sunlight can exacerbate any skin reactions that may occur.

Infusion Reactions: Infusion reactions, including anaphylactic reactions, bronchospasm, fever, chills, and hypotension, have been reported in the clinical trials and post-marketing experience. Across all clinical studies, severe infusion reactions (NCI-CTC grade 3 and grade 4) occurred with the administration of Vectibix[®] in < 1% of patients. In the post-marketing setting, serious infusion reactions have been reported in < 1% of patients, very rarely with a fatal outcome (< 0.01%). Fatal reactions have also been observed in patients with a history of hypersensitivity to Vectibix[®] (see **Other Hypersensitivity Reactions**). Stop infusion if a severe or life-threatening infusion reaction occurs. Depending on the severity and/or persistence of the reaction, consider permanently discontinuing Vectibix[®] (see **DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment**).

Increased toxicity and decreased overall survival in combination with bevacizumab and chemotherapy: Vectibix[®] is not indicated for use in combination with chemotherapy with or without bevacizumab. In an interim analysis of a randomized, open-label, multicenter trial in the first-line treatment of metastatic colorectal cancer, the

addition of Vectibix[®] to the combination of bevacizumab and chemotherapy resulted in decreased overall survival and increased incidence of NCI-CTC grade 3-5 (87% vs. 72%) adverse reactions.

Gastrointestinal

Combination treatment with IFL regimen: Administration of Vectibix[®] in combination with IFL should be avoided due to an increase in grade 3-5 diarrhea.

Other Hypersensitivity Reactions

Hypersensitivity reactions have been reported, including a fatal case of angioedema that occurred more than 24 hours after the infusion. Depending on the severity (eg presence of bronchospasm, edema, angioedema, hypotension, need for parenteral medication, or anaphylaxis) and/or persistence (eg prolonged versus transient) of hypersensitivity reactions, permanently discontinue Vectibix[®] (see **CONTRAINDICATIONS AND ADVERSE REACTIONS**). Hypersensitivity reactions should be treated immediately with appropriate medical therapy consistent with the treating physician's medical judgement.

It is recommended to warn patients of the possibility of a late onset hypersensitivity reaction and instruct them to contact their physician if symptoms occur.

Carcinogenesis and Mutagenesis

No carcinogenesis or mutagenesis studies were conducted with Vectibix[®].

Respiratory

As Interstitial Lung Disease (ILD) has been observed with EGFR inhibitors, in the event of acute onset or worsening of pulmonary symptoms, Vectibix[®] treatment should be interrupted and a prompt investigation of these symptoms should occur. If pneumonitis or lung infiltrates are confirmed, Vectibix[®] should be discontinued and the patient should be treated appropriately.

In patients with a history of, or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of administration of Vectibix[®] versus the risk of pulmonary complications in these patients must be carefully considered before administration. These patients were excluded from clinical studies.

Sexual Function/Reproduction

No studies evaluating sexual function or reproduction in humans were conducted with Vectibix[®]. Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys. Vectibix[®] may impair fertility in women of childbearing potential (see **TOXICOLOGY**).

Special Populations

Pregnant Women:

There are no data from the use of Vectibix[®] in pregnant women. The potential risk for humans is unknown. However, 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 fetal harm when administered to pregnant women. Vectibix[®] should not be used in pregnant women. Studies in animals have shown reproductive toxicity (see **TOXICOLOGY**).

Human IgG is known to cross the placental barrier; therefore Vectibix[®] may be transmitted from the mother to the developing fetus. In women of childbearing potential, appropriate contraceptive measures must be used during treatment with Vectibix[®] and for 6 months following the last dose. If Vectibix[®] is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be advised of the potential risk for loss of the pregnancy and the potential hazard to the fetus (see **TOXICOLOGY**).

Nursing Women:

It is unknown whether Vectibix[®] is excreted in human breast milk. Because human IgG is secreted into human milk, Vectibix[®] may also be secreted. The potential for absorption and harm to the infant after ingestion is unknown. It is recommended that women do not breastfeed during treatment with Vectibix[®] and for 2 months after the last dose.

Pediatrics (< 18 years of age):

The safety and effectiveness of Vectibix[®] in pediatric patients have not been established.

Geriatrics (≥ 65 years of age):

Fifty-two patients ≥ 65 years old and 71 < 65 years old in the non-mutated (wild-type) *KRAS* stratum were treated with Vectibix[®] plus best supportive care (BSC). The efficacy results and qualitative safety were similar between the geriatric patients (65 years or older) versus those patients who were younger. Differences in adverse reactions between the ≥ 65 year old patients and < 65 were in the following system organ classes: eye disorders with growth of eyelashes (17% vs. 4%), ocular hyperemia (10% vs. 1%) and conjunctivitis (6% vs. 1%); gastrointestinal disorders with diarrhea (13% vs. 7%); general disorders and administrative site conditions with fatigue (8% vs. 3%) and mucosal inflammation (13% vs. 3%); skin and subcutaneous tissue disorders with dermatitis acneiform (65% vs. 56%) and nail disorders (15% vs. 7%), respectively. The incidence of adverse events leading to permanent discontinuation from Vectibix[®] plus BSC in patients ≥ 65 years (10%) was higher compared to patients < 65 years (6%).

Renal/Hepatic:

The safety and effectiveness of Vectibix[®] in patients with renal or hepatic impairment have not been established.

Acute Renal Failure:

Acute renal failure has been observed in mCRC patients treated with Vectibix[®] who develop severe diarrhea and dehydration (see **Post-Market Adverse Drug Reactions - Gastrointestinal Disorders**).

Patients should be monitored for signs and symptoms of severe diarrhea and dehydration (such as decreased urine output, dizziness, low blood pressure, rapid heartbeat) and treated immediately with appropriate medical therapy consistent with the treating physician's medical judgement. Vectibix[®] should be withheld until the patient is no longer experiencing severe diarrhea, dehydration or acute renal failure.

Monitoring and Laboratory Tests

Electrolyte Monitoring:

Progressively decreasing serum magnesium levels leading to severe hypomagnesemia have been observed in some patients. Patients should be monitored for hypomagnesemia and accompanying hypocalcemia prior to initiating Vectibix[®] treatment, and periodically during Vectibix[®] treatment and for up to 8 weeks after the completion of treatment. Magnesium repletion is recommended, as appropriate.

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

NOC/c

KRAS Testing:

Detection of non-mutated *KRAS* expression should be performed by an experienced laboratory using a validated test method.

NOC/c

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Safety data are available from 15 clinical trials in which 1467 patients received Vectibix[®]; of these, 1293 received Vectibix[®] monotherapy and 174 received Vectibix[®] in combination with chemotherapy. The most common adverse events observed in clinical studies of Vectibix[®] (n = 1467) were skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea, including diarrhea resulting in dehydration. The most serious adverse events observed were pulmonary fibrosis, pulmonary embolism, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation. Adverse events requiring discontinuation of Vectibix[®] were infusion reactions, severe skin toxicity, paronychia, and pulmonary fibrosis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reactions by *KRAS* Status Pivotal Clinical Trial

The safety profile of Vectibix[®] in patients whose tumors express *KRAS* wild-type (n = 123) was generally consistent with overall mCRC monotherapy set.

In the randomized controlled trial, all 123 patients (100%), with non-mutated (wild-type) *KRAS* status, treated with Vectibix[®] experienced adverse reactions, of which 62% reported grade 3-4 events.

The most frequently ($\geq 20\%$ patients) reported adverse reactions were erythema (71%), pruritus (69%), dermatitis acneiform (60%), paronychia (33%), fatigue (33%), anorexia (30%), abdominal pain (27%), exfoliative rash (25%), constipation (24%), diarrhea (24%), skin fissures (24%), rash (20%) and cough (20%) of which the grade 3-4 reactions included dermatitis acneiform (9%), erythema (8%), abdominal pain (7%), anorexia (6%), constipation (5%), fatigue (5%), pruritus (4%), paronychia (3%), exfoliative rash (3%), skin fissures (2%), rash (2%), and diarrhea (2%).

Adverse drug reactions by *KRAS* status reported in $\geq 1\%$ whose tumour express *KRAS* wild-type are shown in Table 1.

Table 1: Per-Patient Incidence of Adverse Events Occurring in $\geq 1\%$ of *KRAS* Wild-Type Patients (N = 123)

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 123)		BSC Alone (N = 120)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Subjects with at least one adverse event - n (%)	123 (100)	76 (62)	108 (90)	36 (30)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	10 (8)	4 (3)	5 (4)	1 (1)
Anemia	8 (7)	2 (2)	3 (3)	1 (1)
EAR AND LABYRINTH DISORDERS	3 (2)	0 (0)	1 (1)	0 (0)
Vertigo	2 (2)	0 (0)	1 (1)	0 (0)
EYE DISORDERS	29 (24)	1 (1)	4 (3)	0 (0)
Conjunctivitis	5 (4)	0 (0)	1 (1)	0 (0)
Eye irritation	2 (2)	0 (0)	0 (0)	0 (0)
Eyelid irritation	3 (2)	0 (0)	0 (0)	0 (0)
Growth of eyelashes	12 (10)	0 (0)	0 (0)	0 (0)
Lacrimation increased	5 (4)	0 (0)	1 (1)	0 (0)
Ocular hyperemia	7 (6)	0 (0)	0 (0)	0 (0)
GASTROINTESTINAL DISORDERS	87 (71)	27 (22)	64 (53)	10 (8)
Abdominal distension	5 (4)	1 (1)	3 (3)	0 (0)
Abdominal pain	33 (27)	9 (7)	21 (18)	5 (4)
Abdominal pain lower	2 (2)	1 (1)	1 (1)	0 (0)
Abdominal pain upper	11 (9)	2 (2)	12 (10)	3 (3)
Aphthous stomatitis	3 (2)	0 (0)	1 (1)	0 (0)
Ascites	6 (5)	2 (2)	2 (2)	0 (0)
Constipation	30 (24)	6 (5)	11 (9)	0 (0)
Diarrhea	30 (24)	3 (2)	13 (11)	0 (0)
Dry mouth	6 (5)	1 (1)	0 (0)	0 (0)

Table 1: Per-Patient Incidence of Adverse Events Occurring in ≥ 1% of KRAS Wild-Type Patients (N = 123), continued

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 123)		BSC Alone (N = 120)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Dyspepsia	5 (4)	0 (0)	3 (3)	0 (0)
Flatulence	4 (3)	0 (0)	2 (2)	0 (0)
Gastritis	2 (2)	0 (0)	0 (0)	0 (0)
Gastroesophageal reflux disease	2 (2)	0 (0)	1 (1)	0 (0)
Intestinal obstruction	9 (7)	4 (3)	3 (3)	1 (1)
Nausea	22 (18)	1 (1)	19 (16)	1 (1)
Proctalgia	2 (2)	1 (1)	0 (0)	0 (0)
Rectal hemorrhage	3 (2)	0 (0)	4 (3)	0 (0)
Stomatitis	9 (7)	0 (0)	2 (2)	0 (0)
Vomiting	18 (15)	4 (3)	8 (7)	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	83 (67)	24 (20)	50 (42)	15 (13)
Asthenia	18 (15)	8 (7)	12 (10)	3 (3)
Chills	4 (3)	0 (0)	1 (1)	0 (0)
Fatigue	40 (33)	6 (5)	15 (13)	4 (3)
General physical health deterioration	11 (9)	7 (6)	4 (3)	2 (2)
Mucosal inflammation	10 (8)	1 (1)	2 (2)	0 (0)
Edema	7 (6)	1 (1)	4 (3)	1 (1)
Edema peripheral	14 (11)	1 (1)	9 (8)	1 (1)
Pain	5 (4)	0 (0)	4 (3)	2 (2)
Pyrexia	22 (18)	1 (1)	14 (12)	3 (3)

Table 1: Per-Patient Incidence of Adverse Events Occurring in ≥ 1% of *KRAS* Wild-Type Patients (N = 123), continued

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 123)		BSC Alone (N = 120)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
HEPATOBIILIARY DISORDERS	20 (16)	10 (8)	13 (11)	8 (7)
Hepatic failure	2 (2)	0 (0)	2 (2)	2 (2)
Hepatic pain	1 (1)	0 (0)	3 (3)	0 (0)
Hepatomegaly	7 (6)	2 (2)	4 (3)	3 (3)
Hyperbilirubinemia	1 (1)	1 (1)	2 (2)	1 (1)
Jaundice	9 (7)	4 (3)	5 (4)	1 (1)
INFECTIONS AND INFESTATIONS	68 (55)	11 (9)	19 (16)	6 (5)
Bronchitis	3 (2)	0 (0)	3 (3)	1 (1)
Catheter related infection	2 (2)	0 (0)	0 (0)	0 (0)
Eye infection	4 (3)	0 (0)	0 (0)	0 (0)
Eyelid infection	2 (2)	0 (0)	0 (0)	0 (0)
Folliculitis	2 (2)	0 (0)	0 (0)	0 (0)
Fungal infection	2 (2)	0 (0)	0 (0)	0 (0)
Impetigo	2 (2)	0 (0)	0 (0)	0 (0)
Nasopharyngitis	7 (6)	0 (0)	0 (0)	0 (0)
Paronychia	41 (33)	4 (3)	0 (0)	0 (0)
Pharyngitis	1 (1)	0 (0)	2 (2)	0 (0)
Rash pustular	5 (4)	2 (2)	0 (0)	0 (0)
Respiratory tract infection	3 (2)	0 (0)	0 (0)	0 (0)
Septic shock	0 (0)	0 (0)	2 (2)	2 (2)
Upper respiratory tract infection	2 (2)	0 (0)	0 (0)	0 (0)

Table 1: Per-Patient Incidence of Adverse Events Occurring in ≥ 1% of *KRAS* Wild-Type Patients (N = 123), continued

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 123)		BSC Alone (N = 120)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Urinary tract infection	2 (2)	1 (1)	3 (3)	0 (0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	10 (8)	6 (5)	2 (2)	1 (1)
Procedural pain	2 (2)	2 (2)	0 (0)	0 (0)
INVESTIGATIONS	15 (12)	6 (5)	5 (4)	1 (1)
Blood bilirubin increased	2 (2)	2 (2)	1 (1)	0 (0)
Blood magnesium decreased	2 (2)	1 (1)	0 (0)	0 (0)
Blood urine present	2 (2)	1 (1)	0 (0)	0 (0)
Cardiac murmur	0 (0)	0 (0)	2 (2)	0 (0)
Weight decreased	7 (6)	1 (1)	1 (1)	0 (0)
METABOLISM AND NUTRITION DISORDERS	49 (40)	13 (11)	32 (27)	6 (5)
Anorexia	37 (30)	7 (6)	25 (21)	4 (3)
Cachexia	4 (3)	0 (0)	0 (0)	0 (0)
Decreased appetite	3 (2)	1 (1)	1 (1)	0 (0)
Dehydration	5 (4)	3 (2)	3 (3)	0 (0)
Gout	1 (1)	0 (0)	2 (2)	1 (1)
Hypocalcemia	2 (2)	0 (0)	0 (0)	0 (0)
Hypokalemia	5 (4)	1 (1)	1 (1)	0 (0)
Hypomagnesemia	2 (2)	1 (1)	0 (0)	0 (0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	38 (31)	5 (4)	27 (23)	1 (1)
Arthralgia	7 (6)	2 (2)	3 (3)	1 (1)
Back pain	16 (13)	1 (1)	6 (5)	0 (0)
Bone pain	4 (3)	1 (1)	1 (1)	0 (0)

Table 1: Per-Patient Incidence of Adverse Events Occurring in ≥ 1% of *KRAS* Wild-Type Patients (N = 123), continued

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 123)		BSC Alone (N = 120)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Groin pain	0 (0)	0 (0)	2 (2)	0 (0)
Muscle spasms	5 (4)	0 (0)	2 (2)	0 (0)
Muscular weakness	2 (2)	0 (0)	2 (2)	0 (0)
Musculoskeletal chest pain	5 (4)	0 (0)	4 (3)	0 (0)
Myalgia	2 (2)	0 (0)	1 (1)	0 (0)
Pain in extremity	6 (5)	1 (1)	4 (3)	0 (0)
Shoulder pain	4 (3)	1 (1)	5 (4)	0 (0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	25 (20)	3 (2)	21 (18)	2 (2)
Cancer pain	2 (2)	1 (1)	0 (0)	0 (0)
Colorectal cancer	7 (6)	0 (0)	4 (3)	0 (0)
Colorectal cancer metastatic	14 (11)	0 (0)	13 (11)	0 (0)
NERVOUS SYSTEM DISORDERS	25 (20)	7 (6)	19 (16)	5 (4)
Dizziness	2 (2)	0 (0)	1 (1)	0 (0)
Dysgeusia	2 (2)	0 (0)	1 (1)	0 (0)
Headache	5 (4)	1 (1)	4 (3)	0 (0)
Lethargy	2 (2)	1 (1)	0 (0)	0 (0)
Neuropathy	2 (2)	1 (1)	0 (0)	0 (0)
Paresthesia	4 (3)	0 (0)	4 (3)	1 (1)
Somnolence	0 (0)	0 (0)	3 (3)	0 (0)
PSYCHIATRIC DISORDERS	19 (15)	3 (2)	13 (11)	2 (2)
Agitation	1 (1)	1 (1)	2 (2)	1 (1)
Anxiety	4 (3)	0 (0)	3 (3)	1 (1)
Confusional state	2 (2)	1 (1)	1 (1)	1 (1)

Table 1: Per-Patient Incidence of Adverse Events Occurring in ≥ 1% of *KRAS* Wild-Type Patients (N = 123), continued

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 123)		BSC Alone (N = 120)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Depression	6 (5)	1 (1)	1 (1)	0 (0)
Insomnia	6 (5)	1 (1)	6 (5)	0 (0)
RENAL AND URINARY DISORDERS	16 (13)	6 (5)	2 (2)	0 (0)
Dysuria	3 (2)	1 (1)	0 (0)	0 (0)
Hematuria	5 (4)	1 (1)	0 (0)	0 (0)
Oliguria	2 (2)	1 (1)	0 (0)	0 (0)
Renal failure	2 (2)	2 (2)	0 (0)	0 (0)
Renal pain	2 (2)	0 (0)	0 (0)	0 (0)
Urinary retention	2 (2)	0 (0)	0 (0)	0 (0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	49 (40)	8 (7)	27 (23)	4 (3)
Cough	24 (20)	0 (0)	9 (8)	0 (0)
Dysphonia	2 (2)	0 (0)	0 (0)	0 (0)
Dyspnea	23 (19)	6 (5)	18 (15)	4 (3)
Epistaxis	6 (5)	0 (0)	0 (0)	0 (0)
Hemoptysis	2 (2)	0 (0)	0 (0)	0 (0)
Pharyngolaryngeal pain	2 (2)	0 (0)	0 (0)	0 (0)
Pleural effusion	2 (2)	0 (0)	1 (1)	1 (1)
Productive cough	2 (2)	0 (0)	1 (1)	0 (0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	112 (91)	24 (20)	10 (8)	0 (0)
Acne	21 (17)	2 (2)	0 (0)	0 (0)
Alopecia	3 (2)	0 (0)	0 (0)	0 (0)
Dermatitis acneiform	74 (60)	11 (9)	1 (1)	0 (0)
Dry skin	16 (13)	0 (0)	0 (0)	0 (0)
Ecchymosis	0 (0)	0 (0)	2 (2)	0 (0)

Table 1: Per-Patient Incidence of Adverse Events Occurring in ≥ 1% of *KRAS* Wild-Type Patients (N = 123), continued

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 123)		BSC Alone (N = 120)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Erythema	87 (71)	10 (8)	1 (1)	0 (0)
Exfoliative rash	31 (25)	4 (3)	0 (0)	0 (0)
Hair disorder	2 (2)	0 (0)	0 (0)	0 (0)
Hyperhidrosis	3 (2)	0 (0)	2 (2)	0 (0)
Intertrigo	2 (2)	0 (0)	0 (0)	0 (0)
Nail disorder	13 (11)	0 (0)	0 (0)	0 (0)
Night sweats	2 (2)	0 (0)	1 (1)	0 (0)
Onychoclasia	2 (2)	0 (0)	0 (0)	0 (0)
Onychomadesis	2 (2)	0 (0)	0 (0)	0 (0)
Pain of skin	3 (2)	0 (0)	0 (0)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	2 (2)	0 (0)	0 (0)	0 (0)
Pruritus	85 (69)	5 (4)	2 (2)	0 (0)
Rash	25 (20)	2 (2)	1 (1)	0 (0)
Rash erythematous	3 (2)	0 (0)	0 (0)	0 (0)
Rash papular	4 (3)	0 (0)	0 (0)	0 (0)
Rash pruritic	2 (2)	0 (0)	0 (0)	0 (0)
Scab	6 (5)	2 (2)	0 (0)	0 (0)
Skin exfoliation	14 (11)	2 (2)	0 (0)	0 (0)
Skin fissures	30 (24)	3 (2)	0 (0)	0 (0)
Skin toxicity	4 (3)	0 (0)	0 (0)	0 (0)
Skin ulcer	8 (7)	1 (1)	0 (0)	0 (0)
VASCULAR DISORDERS	12 (10)	4 (3)	3 (3)	0 (0)
Hypertension	6 (5)	3 (2)	2 (2)	0 (0)
Pallor	2 (2)	0 (0)	1 (1)	0 (0)

Vectibix[®] mCRC Monotherapy Set

Except where indicated, the safety data described below reflect single agent exposure to Vectibix[®] (panitumumab) in 789 patients with mCRC. Patients who received Vectibix[®] at the dose schedule of 2.5 mg/kg given weekly had a median of 8 infusions; patients who received Vectibix[®] at the dose schedule of 6 mg/kg given once every 2 weeks had a median of 4 infusions; patients who received Vectibix[®] at the dose schedule of 9 mg/kg given once every 3 weeks had a median of 4 infusions. The population had a median age of 61 and was 60% male and 90% Caucasian. The number of doses of Vectibix[®] received by patients ranged from 1 to 69 doses corresponding to 1 to 87 weeks of treatment. Thirty-four percent of patients received Vectibix[®] for 3 months and longer.

Serious adverse reactions associated with Vectibix[®] treatment included hypersensitivity occurring within 24 hours of the first dose (1%), hypomagnesemia (1%), dehydration (1%), pulmonary embolism and diarrhea (< 1%). Three percent of patients receiving Vectibix[®] discontinued treatment primarily due to adverse reactions that were predominantly skin-related.

The most commonly reported adverse reactions were dermatologic-related toxicities including, but not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures occurring in 91% of patients treated with Vectibix[®]. These toxicities are related to the pharmacological effects of Vectibix[®] and are primarily mild to moderate in nature with 13% reported as severe (\geq grade 3).

In clinical studies with Vectibix[®] as a single agent, diarrhea was reported in 13% of the patients. Most of these cases of diarrhea were mild to moderate in severity; < 2% of patients treated with Vectibix[®] had reported grade 3 or higher diarrhea.

The data described in Table 2 reflect exposure to Vectibix[®] administered as a single agent at the recommended dose and schedule (6.0 mg/kg every 2 weeks) in 229 patients randomized to the Vectibix[®] arm with mCRC in the controlled trial. The control arm consisted of 234 subjects randomized to BSC (total n = 463).

Adverse drug reactions reported in \geq 5% of Vectibix[®]-treated patients in the randomized controlled trial of 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum (mCRC) are shown in Table 2.

Table 2: Per-Patient Incidence of Adverse Events Occurring in $\geq 5\%$ of Patients with a Between Group Difference of $\geq 5\%$ (Randomized Controlled Trial N = 463)

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 229)		BSC Alone (N = 234)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Subjects with at least one adverse event - n (%)	229 (100)	128 (56)	204 (87)	67 (29)
EYE DISORDERS	36 (16)	0 (0)	7 (3)	0 (0)
Growth of eyelashes	13 (6)	0 (0)	0 (0)	0 (0)
GASTROINTESTINAL DISORDERS	159 (69)	40 (17)	117 (50)	23 (10)
Abdominal pain	58 (25)	17 (7)	40 (17)	12 (5)
Constipation	48 (21)	7 (3)	21 (9)	2 (1)
Diarrhea	49 (21)	4 (2)	26 (11)	0 (0)
Nausea	52 (23)	2 (1)	37 (16)	1 (0)
Stomatitis	15 (7)	0 (0)	2 (1)	0 (0)
Vomiting	43 (19)	5 (2)	28 (12)	2 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	143 (62)	41 (18)	104 (44)	27 (12)
Fatigue	60 (26)	10 (4)	34 (15)	7 (3)
General physical health deterioration	26 (11)	19 (8)	9 (4)	6 (3)
Mucosal inflammation	14 (6)	1 (0)	2 (1)	0 (0)
Edema peripheral	27 (12)	2 (1)	13 (6)	1 (0)

Table 2: Per-Patient Incidence of Adverse Events Occurring in $\geq 5\%$ of Patients with a Between Group Difference of $\geq 5\%$ (Randomized Controlled Trial N = 463), continued

System Organ Class Preferred Term	Panitumumab Plus BSC (N = 229)		BSC Alone (N = 234)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
INFECTIONS AND INFESTATIONS	108 (47)	14 (6)	34 (15)	7 (3)
Paronychia	57 (25)	4 (2)	0 (0)	0 (0)
METABOLISM AND NUTRITION DISORDERS	86 (38)	16 (7)	58 (25)	7 (3)
Anorexia	66 (29)	8 (3)	45 (19)	5 (2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	81 (35)	15 (7)	50 (21)	9 (4)
Cough	32 (14)	1 (0)	17 (7)	0 (0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	205 (90)	33 (14)	20 (9)	1 (0)
Acne	30 (13)	3 (1)	0 (0)	0 (0)
Dermatitis acneiform	130 (57)	17 (7)	2 (1)	0 (0)
Dry skin	22 (10)	0 (0)	0 (0)	0 (0)
Erythema	149 (65)	12 (5)	2 (1)	0 (0)
Nail disorder	21 (9)	0 (0)	0 (0)	0 (0)
Pruritus	131 (57)	5 (2)	4 (2)	0 (0)
Rash	50 (22)	2 (1)	2 (1)	0 (0)
Skin exfoliation	58 (25)	5 (2)	0 (0)	0 (0)
Skin fissures	45 (20)	2 (1)	1 (0)	0 (0)

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

The following adverse drug reactions were reported at an incidence of < 1% in clinical studies and occurring in more than 1 patient treated with Vectibix[®]:

Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism

Infections and Infestations: cellulitis

Dermatologic Toxicity and Related Disorders

Dermatologic toxicity and related disorders were observed in 91% of patients receiving Vectibix[®]. Skin rash most commonly occurred on the face, upper back and chest, but could extend to the extremities and was characterized by multiple pustular-, macular-, or papular-appearing lesions. Skin drying and fissures were common and in some cases were associated with inflammatory and infectious sequelae, including sepsis, in rare cases leading to death, and local abscesses requiring incisions and drainage (see **WARNINGS AND PRECAUTIONS**).

Paronychia, occurring in 19% of patients (1% grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers. The following were also observed in patients treated with Vectibix[®]: exfoliative rash (14%)*, acne (10%)*, rash pustular (6%)*, nail disorder (8%)*, rash papular (5%)*, skin ulcer (5%)*, conjunctivitis (3%), rash erythematous (3%)*, rash macular (3%)*, scab (3%)*, growth of eyelashes (2%), rash maculo-papular (2%)*, rash pruritic (2%)*, increased lacrimation (1%), ocular hyperemia (1%), eye infection (1%)*, eye irritation (< 1%), dry eye (< 1%), eye pruritus (< 1%), eyelid infection (< 1%)*, and eyelid irritation (< 1%)*.

* n = 1052

The median time to first symptom of dermatologic toxicity was 10 days, and the median time to resolution after the last dose of Vectibix[®] was 28 days. The subject incidence and duration of dermatologic and related disorders were correlated with Vectibix[®] exposure.

Infusion Reactions

Across all clinical studies, potential infusion reactions (occurring within 24 hours of any infusion), which may include symptoms/signs such as chills, fever or dyspnea, were reported in 3% of Vectibix[®]-treated patients, of which < 1% were severe (NCI-CTC grade 3-grade 4).

Most of the symptoms of potential infusion reactions were mild in intensity, resolved without treatment, were isolated occurrences and did not require alteration or interruption of Vectibix[®] administration.

Abnormal Hematologic and Clinical Chemistry Findings

Electrolyte Depletion

In clinical studies in which magnesium levels were collected at specified time intervals during treatment with Vectibix[®], hypomagnesemia (any grade) was observed in 39% of patients assessed (n = 649) and occurred at various time points during treatment. Grade 3 or higher hypomagnesemia was reported in 5% of these patients, most of whom proceeded to receive IV electrolyte repletion. Serious cases of hypomagnesemia occurred 6 weeks or longer after the

initiation of Vectibix[®]. In < 1% of patients, adverse reactions of hypomagnesemia were associated with adverse reactions of hypocalcemia. Patients' electrolytes should be periodically monitored prior to initiating Vectibix[®] therapy, during, and for 8 weeks after, the completion of Vectibix[®] therapy. Institute appropriate treatment, eg, oral or intravenous electrolyte repletion, as needed (see **WARNINGS AND PRECAUTIONS**).

Other Adverse Reactions

Combination with anti-tumour therapies

In a study of 19 patients with mCRC treated with Vectibix[®] in combination with the IFL regimen (bolus 5-fluorouracil, leucovorin, and irinotecan), the incidence of grade 3 or higher diarrhea was 58% (see **WARNINGS AND PRECAUTIONS**). In a study of 24 patients with mCRC treated with Vectibix[®] plus FOLFIRI (infusional 5-fluorouracil, leucovorin, and irinotecan), the incidence of grade 3 or higher diarrhea was 25%.

A randomized, open-label, multicenter study of 1,053 patients evaluated the efficacy of bevacizumab and oxaliplatin- or irinotecan-containing chemotherapeutic regimens with and without Vectibix[®] in the first-line treatment of metastatic colorectal cancer. In an interim analysis based on 947 randomized patients, shortened progression-free survival time and increased deaths were observed in the patients receiving Vectibix[®] in combination with bevacizumab and chemotherapy. A greater frequency of pulmonary embolism, infections (predominantly of dermatologic origin), diarrhea, and dehydration was also observed in the treatment arms using Vectibix[®] in combination with bevacizumab and chemotherapy. The addition of Vectibix[®] to the combination of bevacizumab and chemotherapy in first-line metastatic colorectal cancer is not indicated.

Immunogenicity

The immunogenicity of panitumumab has been evaluated using two different immunoassays (an ELISA which detects high-affinity antibodies, and a Biosensor Immunoassay which detects both high- and low-affinity antibodies). Pre-dose antibodies were detected in < 1% (5/636) and 2.5% (16/635) of patients tested by the ELISA and Biosensor Immunoassay, respectively. The overall incidence of a post-dose anti-panitumumab antibody response was low. Post-dose neutralizing antibodies were detected in 0.2% (1/447) and 1.6% (7/447) of patients tested by the ELISA and Biosensor Immunoassay, respectively. Compared with patients who did not develop antibodies, no relationship between the presence of anti-panitumumab antibodies and pharmacokinetics, efficacy and safety has been observed.

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

Post-Market Adverse Drug Reactions**Gastrointestinal Disorders**

There have been reports of severe diarrhea and dehydration in patients administered Vectibix[®]. In some cases of severe diarrhea and dehydration patients have experienced reduction in renal function. Although there appeared to be confounding factors in some of the cases, such as underlying sepsis, diabetes or hypertension, a review of these cases suggests a risk of acute renal failure (secondary to diarrhea and or dehydration), primarily in the setting of combination chemotherapy, in patients administered Vectibix[®] (see **WARNINGS AND PRECAUTIONS**).

Patients should be monitored for signs and symptoms of severe diarrhea and dehydration (such as decreased urine output, dizziness, low blood pressure, rapid heartbeat) and treated immediately with appropriate medical therapy consistent with the treating physician's medical judgement. Vectibix[®] should be withheld until the patient is no longer experiencing severe diarrhea, dehydration or acute renal failure.

Angioedema

Angioedema has been identified during post-approval use of Vectibix[®]. Because these reactions are reported in a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Infusion Reactions

In the post-marketing setting, serious infusion reactions, including anaphylaxis, have been reported in < 1% of patients, very rarely with a fatal outcome (< 0.01%).

DRUG INTERACTIONS**Overview**

No formal drug interaction studies between Vectibix[®] (panitumumab) and other drugs have been performed. No evidence of pharmacokinetic interaction has been seen in clinical studies in which Vectibix[®] was administered concurrently with paclitaxel- or irinotecan-containing chemotherapy regimens.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The Vectibix[®] (panitumumab) infusion should be prepared using appropriate aseptic technique. **Do not administer Vectibix[®] as an IV push or bolus. Vectibix[®] must be administered using an IV infusion pump and a low protein binding 0.2 µm or 0.22 µm in-line filter.**

Recommended Dose and Dosage Adjustment

The recommended dose of Vectibix[®] is 6 mg/kg of body weight given once every 2 weeks.

Infusion Reactions

Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.

Stop infusion if a severe or life-threatening infusion reaction occurs. Depending on the severity and/or persistence of the reaction, consider permanently discontinuing Vectibix[®].

Dermatological Reactions:

If a patient develops dermatologic toxicities related to Vectibix[®] that are grade 3 or higher or are considered intolerable, temporarily withhold Vectibix[®] administration until the toxicities have improved (≤ grade 2). Once improved, reinstate Vectibix[®] administration at 50% of the original dose. If toxicities do not worsen, escalate each additional dose of Vectibix[®] by 25% increments of the original dose until the recommended starting dose is reached. If toxicity does not resolve to at least grade 2 after withholding 1 or 2 doses of Vectibix[®], or if toxicity worsens or becomes intolerable at 50% of the original dose level, the use of Vectibix[®] should be permanently discontinued (see **WARNINGS AND PRECAUTIONS**).

Missed Dose

Every attempt should be made to administer Vectibix[®] within 3 days before or 3 days after the scheduled dose (except as noted in the Recommended Dose and Dosage Adjustment: Dermatological Reactions section). If this dose is missed, Vectibix[®] should be administered as soon as possible. The next dose should be given on a new schedule, relative to the day the last dose was administered (ie every 2 weeks for doses of 6 mg/kg of Vectibix[®]).

Administration

Vectibix[®] is supplied as a sterile, colourless, preservative-free solution containing 20 mg/mL panitumumab in a single-use vial. The solution may contain a small amount of visible, amorphous, panitumumab particulates. Vectibix[®] should not be shaken.

The Vectibix[®] infusion should be prepared using appropriate aseptic technique. **Do not administer Vectibix[®] as an IV push or bolus. Vectibix[®] must be administered using an IV infusion pump:**

- Withdraw the necessary amount of Vectibix[®] for a dose of 6 mg/kg as appropriate.

- Dilute in a total volume of 100 mL in 0.9% sodium chloride injection USP*. Final concentration should not exceed 10 mg/mL.
- Mix diluted solution by gentle inversion. **Do not shake.**
- **Administer using a low protein binding 0.2 µm or 0.22 µm in-line filter.**
- Infuse over approximately 60 minutes through a peripheral line or indwelling catheter*.
- Flush line before and after Vectibix[®] administration with 0.9% sodium chloride injection USP to avoid mixing with other drug products or IV solutions.

* Doses higher than 1000 mg should be diluted in 150 mL 0.9% sodium chloride injection USP and should be infused over approximately 90 minutes via infusion pump.

Vectibix[®] should not be mixed with, or administered as, an infusion with other medicinal products. No other medications should be added to solutions containing Vectibix[®], and Vectibix[®] should be diluted with 0.9% sodium chloride injection USP.

The solution may contain a small amount of visible amorphous panitumumab particulates that will be removed during infusion by a low protein binding 0.2 µm or 0.22 µm in-line filter; the filtration does not impact the quality of the administered product.

Vectibix[®] should not be administered if discolouration is observed.

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

OVERDOSAGE

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

ACTION AND CLINICAL PHARMACOLOGY

NOC/c

Mechanism of Action

Vectibix[®] (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 (including colon, lung, breast, prostate, pancreatic, and head and neck carcinomas).

Vectibix[®] binds to the ligand-binding domain of EGFR and competitively inhibits receptor autophosphorylation induced by all known EGFR ligands. Binding of Vectibix[®] to EGFR results in the internalization of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin 8 and vascular endothelial growth factor production.

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

The *KRAS* gene encodes a small, GTP-binding protein involved in signal transduction. A variety of stimuli, including that from the EGFR, activates *KRAS*, which in turn stimulates other intracellular proteins to promote cell proliferation, cell survival, and angiogenesis.

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

Pharmacokinetics

Absorption: In all clinical trials, Vectibix[®] (panitumumab) was administered as an intravenous infusion. Therefore, panitumumab is 100% bioavailable to the blood circulation.

Distribution: After intravenous infusion, serum panitumumab declined bi-exponentially and was best described by a model with 2 compartments: central and peripheral compartments. Compartmental analysis suggested that the volume of distribution approximated the plasma volume (42 mL/kg) for the central compartment and was approximately 26 mL/kg for the peripheral compartment.

Elimination (Metabolism and Excretion): Over a wide range of clinical doses examined (0.75 to 9 mg/kg), panitumumab exhibited nonlinear pharmacokinetics; the time-averaged clearance (estimated by dose divided by area under the concentration time curve, AUC) decreased with increasing dose. The elimination of panitumumab is assumed to be mediated by two pathways: (1) via the reticuloendothelial system (RES), a common pathway for endogenous immunoglobulins, and (2) via the EGF receptor (EGFR). Since panitumumab that is bound to cell-surface EGFR can be internalized and degraded, the nonlinear clearance is probably related to saturable binding of panitumumab to EGFR.

At doses > 2 mg/kg, the time-averaged clearance of panitumumab remains relatively constant, because at these higher doses the nonlinear clearance pathway is saturated and becomes relatively insignificant, leaving the overall clearance process being driven mainly by the linear pathway. When the clearance of panitumumab is relatively constant, the exposure to panitumumab (AUC) increases in a dose-proportional manner.

Pharmacokinetic steady-state is reached after 3 doses at 6 mg/kg given once every 2 weeks without a loading dose. The pharmacokinetic parameter of panitumumab at steady state is summarized in the following Table 3.

Table 3: Mean (SD) Panitumumab Pharmacokinetic Parameters at Steady State

Dose Regimen	N	C _{max} (µg/mL)	C _{min} (µg/mL)	AUC _{0-tau} (µg·day/mL)	t _{1/2} (day)	CL (mL/day/kg)
6 mg/kg Q2W	14	219 (54)	47 (19)	1431 (412)	7.5 (1.8)	4.6 (1.4)

C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; AUC_{0-tau} = area under the curve for the dosing interval; t_{1/2} = half-life during the dosing interval; CL = serum clearance.

Special Populations and Conditions

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on Vectibix[®] pharmacokinetics. Results suggest that age, gender, tumour type, race, hepatic function, renal function, chemotherapeutic agents, and EGFR membrane expression in tumour cells had no apparent impact on the pharmacokinetics of Vectibix[®].

No clinical studies have been conducted to examine the pharmacokinetics of Vectibix[®] in patients with renal impairment or hepatic impairment. No age-related differences in the pharmacokinetics of Vectibix[®] were observed in clinical studies in patients 26 to 85 years of age (see **WARNINGS AND PRECAUTIONS: Geriatrics**).

STORAGE AND STABILITY

Store vials in the original carton under refrigeration at 2° to 8°C (36° to 46°F) until time of use. Protect from light. **Do not freeze Vectibix[®] (panitumumab)**. Do not shake. Since Vectibix[®] does not contain preservatives, any unused portion remaining in the vial must be discarded.

The diluted infusion solution of panitumumab should be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). **Do not freeze the diluted infusion solution of Vectibix[®].**

SPECIAL HANDLING INSTRUCTIONS

Vectibix[®] (panitumumab) should not be shaken or frozen.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Vectibix[®] (panitumumab) is a sterile, colourless, preservative-free solution containing 20 mg/mL Vectibix[®] in a single-use vial. The quantitative composition of Vectibix[®] is:

panitumumab	20 mg/mL
sodium chloride USP	5.8 mg/mL
sodium acetate USP	6.8 mg/mL
water for injection USP	pH 5.8

Availability of Dosage Forms

Vectibix[®] is supplied as a preservative-free solution (20 mg/mL) containing 100, 200 or 400 mg of panitumumab in 5, 10 and 20 mL single-use vials, respectively. Vectibix[®] is provided in a dispensing pack containing one vial.

PrVectibix®

(panitumumab)

PART II: SCIENTIFIC INFORMATION

Vectibix®, indicated as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens, has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	panitumumab
Chemical name:	recombinant, human IgG2 anti-EGFR monoclonal antibody
Molecular mass:	Panitumumab has a total molecular weight of 147,000 daltons.
Structural formula:	Panitumumab is a recombinant, human IgG2 monoclonal antibody produced in a mammalian cell line (CHO). Panitumumab consists of 2 gamma heavy chains and 2 kappa light chains.

Product Characteristics

Vectibix® (panitumumab) is a sterile, colourless, preservative-free solution. The solution may contain a small amount of visible amorphous panitumumab particulates.

CLINICAL TRIALS

NOC/c

Study Demographics and Trial Design

Table 4: Summary of patient demographics for clinical trials in metastatic colorectal cancer

Study #	Trial design	Dosage, route of administration and duration*	Study subjects (n = number)	Mean age (Range) years	Gender (female/male)
Randomized, Controlled Trial & Extension Study					
20020408	Phase 3, open-label, randomized, Vectibix [®] plus best supportive care (BSC) vs. (BSC), 1:1	IV infusion at 6 mg/kg given once every 2 weeks	n = 463 (n = 231 Vectibix [®] plus BSC; n = 232 BSC alone)	61.2 (10.3) Vectibix [®] plus BSC 61.4 (10.8) BSC alone	85/146 Vectibix [®] plus BSC 84/148 BSC alone
20030194	Open-label, single-arm extension study of 20020408 BSC alone arm upon disease progression	IV infusion at 6 mg/kg given once every 2 weeks	n = 174	61.7 (10.3)	63/111
Single Arm Studies					
20025405	Phase 2, open-label, single arm	IV infusion at 2.5 mg/kg given once weekly	n = 148	59.0 (13.1)	65/83
20030167	Phase 2, open-label, single arm	IV infusion at 6 mg/kg given once every 2 weeks	n = 39	58.6 (10.1)	16/23
20030250	Phase 2, open-label, single arm	IV infusion at 6 mg/kg given once every 2 weeks	n = 23	65.2 (10.5)	7/16

* duration of treatment was until disease progression, intolerance or other reason (death, withdrawal, etc) for all studies.

Study Results

The efficacy of Vectibix[®] (panitumumab) in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in a randomized controlled trial (463 patients) and open-label, single-arm trials (384 patients) (see Table 4). The safety of Vectibix[®] in patients with mCRC who received at least one dose of Vectibix[®] was evaluated in 789 patients. Additional studies were performed with Vectibix[®] as a single agent in patients with other solid tumours and in combination with chemotherapy in patients with mCRC or non-small cell lung cancer.

Randomized-Controlled Trial

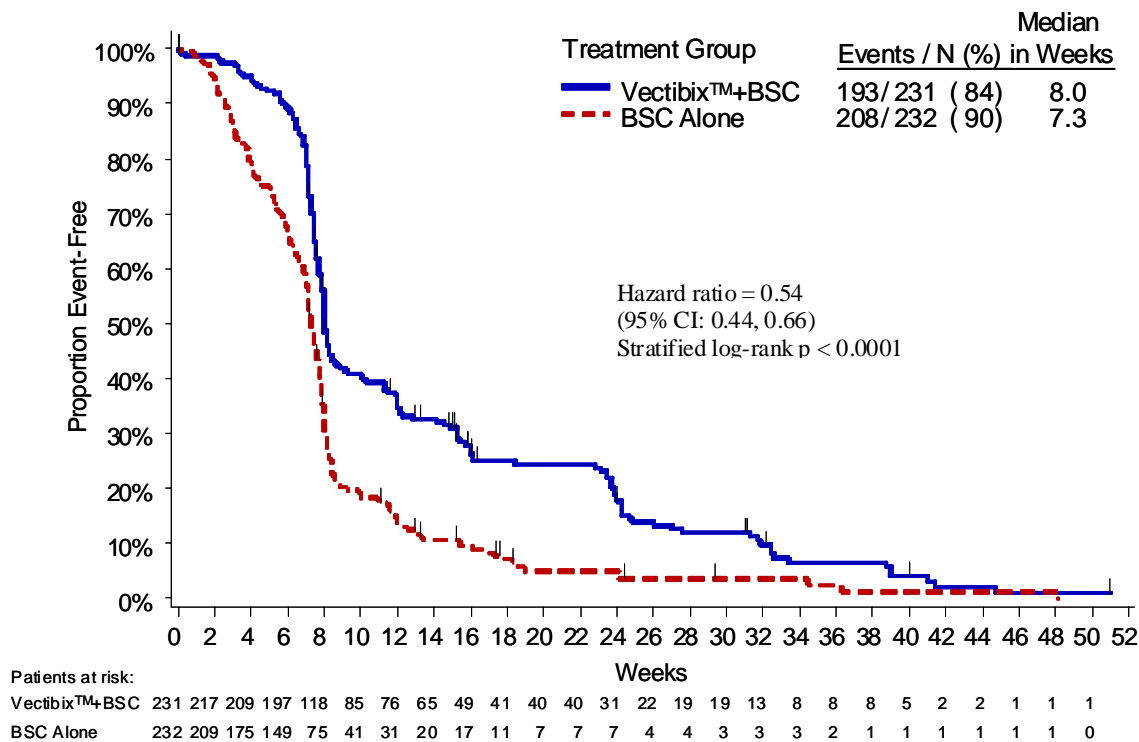
The efficacy of Vectibix[®] in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in a randomised controlled trial (463 patients) and open-label, single-arm trials (384 patients). The safety of Vectibix[®] in patients with mCRC who received at least one dose of Vectibix[®] was evaluated in 789 patients. Additional studies were performed with Vectibix[®] as a single agent in patients with other solid tumours and in combination with chemotherapy with and without bevacizumab in patients with mCRC or in combination with chemotherapy in patients with non-small cell lung cancer.

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

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

The primary endpoint was progression-free survival (PFS). The rate of disease progression or death in patients who received Vectibix[®] was reduced by 46% relative to patients that received BSC [Figure 1; Hazard Ratio = 0.54 (95% CI: 0.44-0.66), stratified log-rank $p < 0.0001$]. To correct for potential bias from unscheduled assessments, radiologic progression was assigned to the closest scheduled assessment in a sensitivity analysis; hazard ratio = 0.60 (95% CI 0.49-0.74). There was no difference seen in median PFS times as more than 50% of patients progressed in both treatment groups before the first scheduled visit. The progression-free survival rates at the first scheduled visit (week 8) were 45.5% on Vectibix[®] plus BSC and 24.6% on BSC alone, a difference of 20.9% [95% CI: 12.4, 29.4]. No difference was seen in overall survival. This may be due to patients receiving Vectibix[®] after progression among those randomized to BSC. Tumour response according to modified-RECIST criteria was determined by central review. Overall, 9.5% [95% CI: 6.1, 14.1] Vectibix[®] plus BSC patients, and 0% [95% CI: 0.0, 1.6] BSC alone patients had a confirmed objective response (partial response), with stable disease in 26% and 10% patients, respectively. Among the 176 patients who received Vectibix[®] after progression on BSC alone, the response rate (investigator assessment) was 11.4% (95% CI: 7.1, 17.0).

Figure 1: Kaplan-Meier Plot of Progression-free Survival Time (Central Assessment) (All Enrolled Analysis Set)



The progression-free rates were between 9.7% and 21.0% higher for panitumumab plus BSC between weeks 8 to 26.

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

Tumour samples obtained from the primary resection of colorectal cancer were analyzed for the presence of the seven most common activating mutations in the codon 12 and 13 (Gly12Asp, Gly12Ala, Gly12Val, Gly12Ser, Gly12Arg, Gly12Cys, and Gly13Asp) of the *KRAS* gene by using an allele-specific polymerase chain reaction. Four hundred and twenty seven (92%) patients were evaluable for *KRAS* status of which 184 had mutations. The hazard ratio for PFS was 0.45 (95% CI: 0.34-0.59) in favour of Vectibix® in the *KRAS* wild-type group (stratified log-rank p < 0.0001) and 0.99 (95% CI: 0.73-1.36) in the *KRAS* mutant group. The difference in median PFS in the *KRAS* wild-type group was 5 weeks. The progression-free survival rates at the first scheduled visit (week 8) in the *KRAS* wild-type group were 61.9% on Vectibix® plus BSC and 28.1% on BSC alone, a difference of 33.8% [95% CI: 21.9, 45.8]. To correct for potential bias from unscheduled assessments, radiologic progression was assigned to the closest scheduled assessment in a sensitivity analysis [wild type group hazard ratio = 0.49 (95% CI: 0.37-0.65) and mutant group hazard ratio = 1.07 (95% CI: 0.77-1.48)]. In these analyses, the difference in median PFS in the wild type group was 8 weeks. There was no difference in median PFS in the mutant group. The progression-free survival rates at the first scheduled visit (week 8) in the *KRAS* mutant group were 26.2% on Vectibix® plus BSC and 34.4% on BSC alone, a difference of 8.2% [95% CI: -21.9, 5.5]. There were no differences in overall survival seen in either group. In the *KRAS* wild-type group the response rate was 17% for Vectibix® and 0% for BSC. In the

KRAS mutant group there were no responses in either treatment arm. Stable disease rates in the *KRAS* wild-type group were 34% for Vectibix[®] and 12% for BSC. The stable disease rates in the *KRAS* mutant group were 12% for Vectibix[®] and 8% for BSC. Response rate (investigator assessment) in patients that crossed over to Vectibix[®] after progression on BSC alone was 22% (95% CI: 14.0, 31.9) for those with *KRAS* wild-type tumours and 0% (95% CI: 0.0, 4.3) for those with mutant *KRAS* tumours.

From the primary analysis of Patient Reported Outcomes (PRO), in the non-mutated (wild-type) *KRAS* group, a 95% confidence interval (not adjusted for multiple comparisons) for the difference in CRC symptom scores excluded more symptomatic scores for Vectibix[®] compared to BSC alone.

Figure 2: PFS by Randomized Treatment in Wild-type *KRAS* Stratum

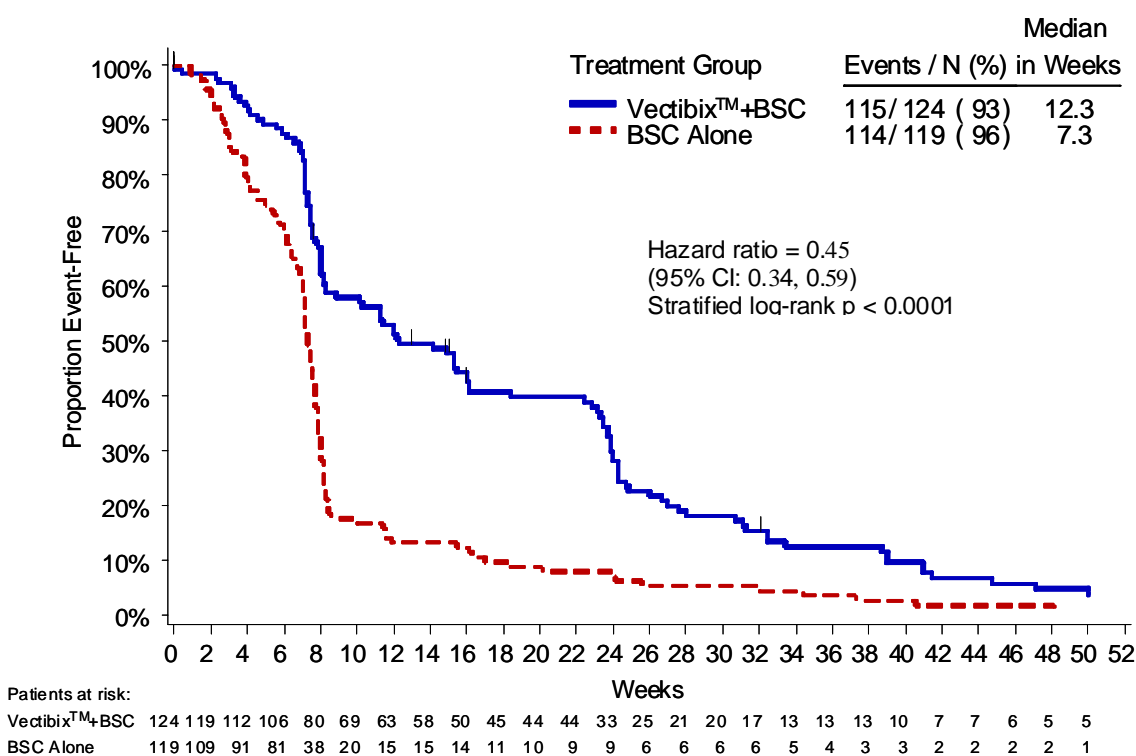
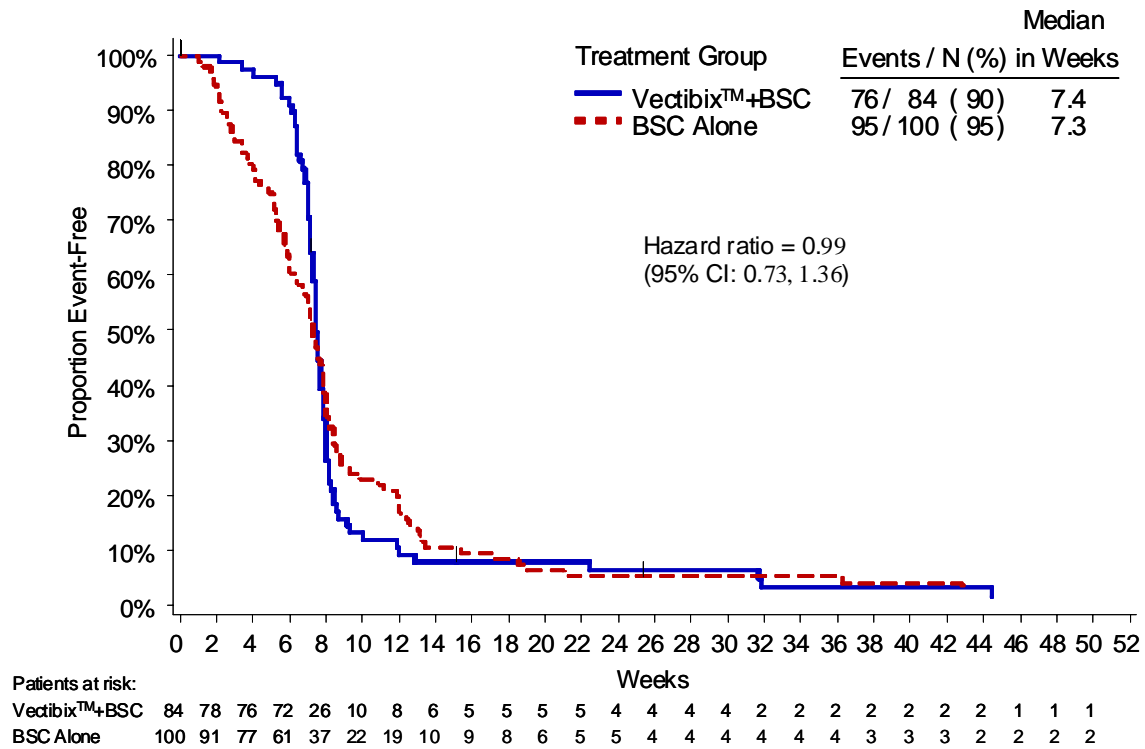


Figure 3: PFS by Randomized Treatment in Mutant *KRAS* Stratum



Retrospective analysis from Non-pivotal Clinical Studies

To further evaluate the association of *KRAS* status with the efficacy of Vectibix[®] (panitumumab) seen in pivotal Study 20020408, retrospective analysis of the efficacy and safety based on the *KRAS* status of patients from the non-pivotal clinical studies 20030167 and 20030250 was performed.

The primary objective of these retrospective analyses was to assess the effect of treatment with panitumumab on the objective response in subjects with metastatic colorectal cancer whose tumours express wild-type *KRAS* and those whose tumours express mutant *KRAS*. As was observed in Study 20020408, all of the objective responses to panitumumab in studies 20030167 and 20030250 occurred in subjects whose tumours expressed wild-type *KRAS*. No responses were seen in subjects whose tumours harboured activating *KRAS* mutations. The results of these retrospective analyses help confirm the findings in Study 20020408 and suggest that patients with tumour *KRAS* mutations are unlikely to benefit from treatment with panitumumab monotherapy.

Single-Arm Trials

Three single-arm, open-label studies evaluated the efficacy and safety of Vectibix[®] in patients with mCRC who had disease progression following 1 or more fluoropyrimidine-based regimens (with or without leucovorin) plus either irinotecan, oxaliplatin, or both (given either concurrently or sequentially) and bevacizumab. Two of these studies are ongoing with a median follow-up ranging from 12 to 15 weeks. These studies assessed the doses of 6 mg/kg given once every two weeks (n = 62) and 2.5 mg/kg given once weekly (n = 148), and explored the relationship between EGFR tumour membrane staining (≥ 10%, < 10%) and response. Across these studies,

response rate (per modified-WHO or modified-RECIST criteria) was consistent with that observed in the randomized, controlled trial (8%, 9%, and 13%) and responses were observed in patients whose tumours were negative (< 1%) for EGFR tumour membrane staining.

Other Studies

The PACCE study: In this randomised, open label, controlled clinical trial, chemotherapy (oxaliplatin or irinotecan) and bevacizumab were given with and without Vectibix[®] in the first line treatment of patients with metastatic colorectal cancer. Vectibix[®] treatment was discontinued due to a statistically significant reduction in PFS in patients receiving Vectibix[®] observed in an interim analysis. The hazard ratio for PFS was 1.44 (95% CI: 1.13, 1.85). Median PFS was 8.8 (95% CI: 8.3, 9.5) and 10.5 (95% CI 9.4, 12.0) months in the Vectibix[®] and the non- Vectibix[®] arm, respectively. There was an increase in mortality in the Vectibix[®] arm. The hazard ratio for overall survival was 1.56 (95% CI: 1.11, 2.17). Median overall survival was 18.4 (95% CI: 13.8, not estimable) in the Vectibix[®] arm and not estimable in the non- Vectibix[®] arm.

EGFR Expression and Response

Patients enrolled in clinical studies were required to have immunohistochemical evaluation of tumour EGFR expression using the DakoCytomation EGFR pharmDx™ test kit. In the randomized, controlled trial exploratory univariate analyses were conducted to assess the correlation of EGFR expression and efficacy. Efficacy results did not correlate with either presence, percentage of positive cells or the intensity of EGFR tumour expression. The utility of the test kit to guide clinical decision-making is unclear.

DETAILED PHARMACOLOGY

Vectibix[®] (panitumumab) administered as a single agent or in combination with chemotherapy exhibits non-linear pharmacokinetics. The concentration-time profile is best described by a 2-compartment pharmacokinetic model with dual linear and non-linear clearance pathways, likely mediated by the reticuloendothelial system (RES) and EGFR, respectively. Since panitumumab that is bound to cell-surface EGFR can be internalized and degraded, the non-linear clearance is probably related to saturable binding of panitumumab to EGFR. The average clearance value decreases with increasing dose and approaches the clearance value for endogenous IgG2 (1 - 4 mL/day/kg). The mean half-life values during the dosing interval are 7.5 days (SD ± 1.8) and 8.5 days (based on pharmacokinetic modeling) for the 6 mg/kg and 2.5 mg/kg doses, respectively.

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on Vectibix[®] pharmacokinetics. Results suggest that age, gender, tumour type, race, hepatic function, renal function, chemotherapeutic agents, and EGFR expression in tumour cells had no apparent impact on the pharmacokinetics of Vectibix[®]. No clinical studies have been conducted to examine the pharmacokinetics of Vectibix[®] in patients with renal impairment or hepatic impairment. No age-related differences in the pharmacokinetics of Vectibix[®] were observed in clinical studies in patients 26 to 85 years of age.

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

TOXICOLOGY

A summary of Toxicology studies is shown in Table 5.

Acute and Multiple Dose Toxicity

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 diarrhea were the major findings observed in repeat-dose toxicity studies of up to 26 weeks duration in cynomolgus monkeys who received Vectibix[®] (panitumumab) at doses up to approximately 5-fold the exposure of the recommended human dose. These findings were reversible upon termination of administration of Vectibix[®]. The skin rash and diarrhea observed in monkeys are considered related to the pharmacological action of Vectibix[®] and are consistent with the toxicities observed with other anti-EGFR inhibitors.

In the 6-month repeated-dose toxicity study, following a single-dose of Vectibix[®] (panitumumab) on Study Day 1, panitumumab exhibited dose-linear toxicokinetics within the dose range of 7.5 to 30 mg/kg of panitumumab. The mean (\pm SD) C_{max} values were 261 ± 66 , 676 ± 253 , and 1080 ± 406 $\mu\text{g/mL}$ for the 7.5, 15, and 30 mg/kg groups, respectively. The mean (\pm SD) AUC (0-7) values were 649 ± 133 , 1650 ± 440 , and 3440 ± 993 $\text{day} \cdot \mu\text{g/mL}$ for the 7.5, 15, and 30 mg/kg groups, respectively. In Week 26, for animals that did not develop monkey anti-human antibody (MAHA), a dose-proportional increase in AUC (0-7) was observed as dose increased from 7.5 mg/kg to 30 mg/kg panitumumab, with a mean \pm SD AUC (0-7) in Week 26 of 774 ± 259 , 1660 ± 266 , and 3260 ± 1300 $\text{day} \cdot \mu\text{g/mL}$ for the 7.5, 15, and 30 mg/kg groups.

NOAEL could not be identified due to mild to severe skin rash and/or diarrhea that was observed in some monkeys across all dose levels in all repeated-dose toxicity studies. This is due to the pharmacologic activity of panitumumab. Toxicities were observed within therapeutic dose level.

Mutagenicity and Oncogenic/Carcinogenic Potential

Studies to evaluate the mutagenic and carcinogenic potential of Vectibix[®] have not been performed.

Reproductive Toxicity

Vectibix[®] has been shown to be an abortifacient in cynomolgus monkeys when administered during the period of organogenesis at doses up to 5-fold the exposure of recommended human dose on a mg/kg basis.

Formal male fertility studies have not been conducted; however, microscopic evaluation of male reproductive organs from cynomolgus monkeys administered Vectibix[®] for up to 26 weeks 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 Vectibix[®] may produce secondary effects that could impact the ability of a woman to become pregnant while receiving Vectibix[®].

Prolonged menstrual cycles and/or amenorrhea were observed in normally cycling, female cynomolgus monkeys following weekly doses of panitumumab of 1.25 to 5-fold greater than the recommended human dose (based on body weight). Menstrual cycle irregularities in panitumumab-treated, female cynomolgus monkeys were accompanied by both a decrease and delay in peak progesterone and 17 β -estradiol levels. Normal menstrual cycling resumed in most animals after discontinuation of panitumumab treatment. A no-effect level for menstrual cycle irregularities and serum hormone levels was not identified. A trend of a dose-dependent decrease in the pregnancy rate was observed in monkeys.

Vectibix[®] treatment was associated with significant increases in embryo-lethal or abortifacient effects in pregnant cynomolgus monkeys when administered weekly during the period of organogenesis (gestation day [GD] 20-50), at doses approximately 1.25 to 5-fold greater than the recommended human dose (by body weight). There were no fetal malformations or other evidence of teratogenesis noted in the offspring. While no panitumumab was detected in serum of neonates from panitumumab-treated dams, anti-panitumumab antibody titers were present in 14 of 27 offspring delivered at GD 100. Therefore, while no teratogenic effects were observed in panitumumab treated monkeys, panitumumab has the potential to cause fetal harm when administered to pregnant women.

Local Tolerance

No formal local tolerance studies were conducted, however, injection sites were evaluated in repeated-dose toxicity studies, including the 6-month study. With the exception of the skin changes associated with the pharmacological action of panitumumab (erythema, thin skin, dry/flaky skin, scab formation), no other injection site changes were noted in panitumumab treated animals compared with control animals.

Table 5: Summary of Toxicology Studies

Study Type	Species	Route of Administration	Dose/Dose Regimen	Duration	Key Findings
Single-dose Toxicity^a					
Safety Pharmacology (cardiovascular, respiratory, central nervous system)	Monkey/ Cynomolgus (telemeterized)	Intravenous injection	0 (vehicle control), 7.5, 30, and 60 mg/kg	Single dose	No treatment-related effects on evaluated cardiovascular, respiratory, or central nervous system parameters were noted.
Repeated-dose Toxicity					
1-Month (4 studies) 3-Month (2 studies) 6-Month (1 study)	Monkey/ Cynomolgus	Intravenous injection	0 (vehicle), 0.3, 3, 7.5, 15, and 30 mg/kg once weekly	Up to 6 months	Principal treatment-related findings were dose-dependent skin rash and diarrhea, ranging from mild to severe. Supportive treatment such as antibiotics was necessary for some animals in order to minimize secondary infection related to skin lesions. In the 6-month study, 15 out of 36 animals (2 of 12 in 7.5 mg/kg, 7 of 12 in 15 mg/kg, and 6 of 12 in 30 mg/kg once weekly) were euthanized at unscheduled intervals during post dosing on Day 43 (Week 7) to Day 96 (Week 15) because of the severity of the skin rash and general poor condition. One animal in 15 mg/kg group died post dosing on Day 134. Both the diarrhea and skin changes were either partially or completely reversible within 4 to 8 weeks after the last panitumumab dose.

^a With the exception of the single-dose safety pharmacology study, no single-dose toxicity studies have been conducted.

Table 5: Summary of Toxicology Studies (Continued)

Study Type	Species	Route of Administration	Dose/Dose Regimen	Duration	Key Findings
Reproductive Toxicity					
Female Fertility Study	Monkey/ Cynomolgus	Intravenous injection	0, 7.5, 15, and 30 mg/kg once weekly for 2 pre-mating menstrual cycles, 1 or 2 menstrual cycles (depending on when the female became pregnant), up to gestation day 20 to 25	13 to 23 weeks (depending if the female became pregnant in the first or second mating cycle)	Prolonged menstrual cycles and/or amenorrhea and alterations in 17 β -estradiol and progesterone levels were observed in most panitumumab-treated monkeys. Normal menstrual cycling resumed in most monkeys during the dosing period or within 10 weeks after discontinuation of panitumumab treatment, suggesting that the effects on the menstrual cycle are reversible. Some panitumumab-treated monkeys did become pregnant, however, the pregnancy rate for panitumumab-treated monkeys was lower than control monkeys.
Embryo/fetal Development Study	Monkey/ Cynomolgus	Intravenous injection	0, 7.5, 15, and 30 mg/kg once weekly during the period of organogenesis (gestation days 20 to 50)	Dosing during the period of organogenesis (gestations days 20 to 50); cesarean section performed on gestation days 100 to 103	While no teratogenic effects were observed, fetal abortions or fetal deaths occurred in all panitumumab dose groups.

^aWith the exception of the single-dose safety pharmacology study, no single-dose toxicity studies have been conducted

REFERENCES

1. Amado RG, Wolf M, Peeters M, et al. Wild-Type *KRAS* is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer. *J Clin Onco.* 2008 Apr 1;26(10):1626-1634.
2. Berlin J, Posey J, Tchekmedyian S, et al. Panitumumab With Irinotecan/Leucovorin/5-Fluorouracil for First-Line Treatment of Metastatic Colorectal Cancer. *Clinical Colorectal Cancer.* 2007 Mar;6(6):427-432.
3. Foon KA, Yang XD, Weiner LM, et al. Preclinical and Clinical Evaluations of ABX-EGF, a Fully Human Anti-Epidermal Growth Factor Receptor Antibody. *Int. J. Radiation Oncology Biol. Phys.* 2004;58(3):984–990.
4. Friday BB, Adjei AA. K-ras as a Target for Cancer Therapy. *Biochimica et Biophysica Acta* 1756. 2005:127-144.
5. Hecht JR, Patnaik A, Berlin J, et al. Panitumumab Monotherapy in Patients With Previously Treated Metastatic Colorectal Cancer. *Cancer.* 2007 Sep 1;110(5):980-988.
6. Lacouture ME, Melosky BL. Cutaneous Reactions to Anticancer Agents Targeting the Epidermal Growth Factor Receptor: A Dermatology-Oncology Perspective. *Skin Therapy Letter*[®]. 2007 Jul-Aug;12(6):1-5.
7. Lofgren JA, Dhandapani S, Pennucci JJ, et al. Comparing ELISA and Surface Plasmon Resonance for Assessing Clinical Immunogenicity of Panitumumab. *J Immunol.* 2007;178:7467-7472.
8. Roskos LK, Davis CG, Schwab GM. The Clinical Pharmacology of Therapeutic Monoclonal Antibodies. *Drug Development Research* 2004;61:108-120.
9. Rowinsky EK, Schwartz GH, Gollob JA, et al. Safety, Pharmacokinetics, and Activity of ABX-EGF, a Fully Human Anti-Epidermal Growth Factor Receptor Monoclonal Antibody in Patients With Metastatic Renal Cell Cancer. *J Clin Onco.* 2004 Aug 1;22(15):3003-3015.
10. Van Cutsem E, Siena S, Humblet Y, et al. An Open-Label, Single-Arm Study Assessing Safety and Efficacy of Panitumumab in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapy. *Annals of Oncology.* 2008;19:92-98.
11. Van Cutsem E, Peeters M, Siena S, et al. Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer. *J Clin Onco.* 2007 May 1;25(13):1658-1664.
12. Yang XD, Jia XC, Corvalan JR, et al. Development of ABX-EGF, a Fully Human Anti-EGF Receptor Monoclonal Antibody, For Cancer Therapy. *Critical Reviews in Oncology/Hematology.* 2001;38:17-23.

PART III: CONSUMER INFORMATION

Vectibix[®], indicated as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens, has been authorized with conditions, pending the results of studies to verify its clinical benefit. For more information, patients are advised to contact their health care provider.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c Policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

PrVectibix[®]

(panitumumab)

This leaflet is part III of a three-part "Product Monograph" published when Vectibix[®] was authorized for sale in Canada and is designed specifically for Consumers. It provides you (or your caregiver) with information about Vectibix[®]. It does not tell you everything about Vectibix[®]. Questions about treatment with Vectibix[®] should be discussed with your doctor.

ABOUT THIS MEDICATION**What is Vectibix[®] used for?**

Vectibix[®] is used to treat epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens (medicines used to treat cancer). Metastatic colorectal cancer is cancer of the colon or rectum that has spread to other organs in the body.

What does Vectibix[®] do?

Vectibix[®] is a monoclonal antibody that recognizes and attaches to certain types of cancer cells. This may prevent the cancer cell from growing and dividing.

When Vectibix[®] should not be used.

Do not use Vectibix[®] if you are allergic (hypersensitive) to panitumumab or any of the other ingredients of Vectibix[®].

What dosage forms does Vectibix[®] come in?

Vectibix[®] is supplied as a sterile, colourless and preservative-free solution (20 mg/mL) containing 100, 200 or 400 mg of panitumumab in 5, 10 and 20 mL single-use vials, respectively. Vectibix[®] is provided in a dispensing pack containing one vial.

What is the medicinal ingredient in Vectibix[®]?

The medicinal ingredient in Vectibix[®] is panitumumab. Panitumumab is a monoclonal antibody (protein) produced by DNA technology.

What are the important nonmedicinal ingredients in Vectibix[®]?

The non-medicinal ingredients of Vectibix[®] are sodium chloride, sodium acetate and water for injection.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

Dermatologic Toxicity: Dermatologic toxicities (skin reactions) related to Vectibix[®] (panitumumab) blockade of EGFR occurred in 91% (721/789) of patients and were severe in 12% of patients receiving Vectibix[®] monotherapy (use of single medication). The signs and symptoms include: skin rash resembling acne, severe itching, redness, rash, flaking skin, minor nail infection, dry skin, and cracks in the skin. Severe skin reactions were complicated by infection, including sepsis (serious infections usually caused by bacteria), in rare cases leading to death, and local abscesses (localized infection) requiring incision and drainage. If you have severe skin reactions your doctor will monitor you for inflammation or infection and may decide to withhold or discontinue treatment with Vectibix[®]. It is recommended that patients wear sunscreen and a hat and limit sun exposure while receiving Vectibix[®] as sunlight can worsen any skin reactions that may occur.

Infusion Reactions: Infusion reactions, including anaphylactic reactions (severe allergic reactions that occur rapidly), bronchospasm (difficulty in breathing caused by tightening of airways), fever, chills, and low blood pressure, have been reported in < 1% of patients, very rarely with a fatal outcome (< 0.01%). Fatal reactions have also been observed in patients with a history of hypersensitivity to Vectibix[®]. Your doctor may stop the infusion if a severe or life-threatening infusion reaction occurs. Depending on the severity and/or persistence of the reaction, your doctor may consider permanently discontinuing Vectibix[®].

Increased Toxicity and Decreased Overall Survival In Combination With Bevacizumab and Chemotherapy: Vectibix[®] is not indicated for use in combination with

chemotherapy with or without bevacizumab. The addition of Vectibix[®] to the combination of bevacizumab and chemotherapy resulted in decreased overall survival and increased incidence of severe adverse reactions.

Gastrointestinal

Combination treatment with IFL regimen: Administration of Vectibix[®] in combination with IFL should be avoided due to an increase in severe diarrhea.

Before starting treatment with Vectibix[®], please tell your doctor or nurse if you:

- have previously had or had 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).
- are receiving the IFL regimen (5-fluorouracil, leucovorin and irinotecan) since when used with Vectibix[®], severe diarrhea has been observed.
- are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- are pregnant, think you may be pregnant, or are planning to get pregnant as Vectibix[®] has not been tested in pregnant women.

During treatment, you may experience dermatologic toxicities (skin reactions). These reactions should be monitored by your doctor to avoid and/or treat any potential infections that may develop from the skin reactions. If your symptoms worsen or become intolerable, please tell your doctor or nurse immediately.

Symptoms of hypersensitivity reactions have been observed, including difficulty breathing, sweating, swelling of the face, lips, mouth, tongue or throat (angioedema), and hives. If you think you are having a hypersensitivity reaction, stop taking Vectibix[®] and notify your doctor or emergency medical personnel immediately.

If you experience loose or watery stools which are present for a day or more, or you have diarrhea with fever, decreased urination or dizziness contact your doctor immediately.

It is not known whether Vectibix[®] is present in human milk. Do not use Vectibix[®] if you are breast-feeding.

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

INTERACTIONS WITH THIS MEDICATION

Drug interactions between Vectibix[®] and other drugs have not been studied.

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dose of Vectibix[®] is 6 mg/kg given once every two weeks (milligrams per kilogram of body weight).

A doctor experienced in the use of anti-cancer medicines will supervise your Vectibix[®] treatment. Vectibix[®] is administered intravenously (into a vein) with an infusion pump (a machine that gives a slow injection). The first treatment will be given very slowly over a period of approximately 60 minutes.

Overdose:

If an overdosage occurs, you should be monitored by your doctor and appropriate supportive treatment given.

Missed dose:

It is very important that you receive Vectibix[®] within 3 days before or 3 days after each scheduled dose (except if the dose is adjusted because of skin reactions). If you miss a dose, your doctor will administer Vectibix[®] as soon as possible and your next dose will be rescheduled relative to the day you received that last dose (every 2 weeks for a dose of 6 mg/kg of Vectibix[®]).

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most commonly reported side effects are skin reactions. If you experience any of these or other side effects, you should report these to your doctor.

Some patients experience infusion-type reactions. Symptoms of infusion-type reactions may include but are not limited to new onset facial swelling, chills, fever, dyspnea (breathing difficulties), rash (possibly including hives), low blood pressure, increased heart rate and sweating. If you notice any of these symptoms, call your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Very Common ≥ 10%	<ul style="list-style-type: none"> Diarrhea 	√	
Common > 1%, ≤ 10%	<ul style="list-style-type: none"> Reactions associated with Vectibix[®] administration such as chills, fever, and shortness of breath. 		√
	<ul style="list-style-type: none"> Severe hypomagnesemia (very low magnesium levels in the blood) may be symptomless, but when symptoms occur, they commonly include severe weakness and fatigue. Severe hypomagnesemia can be detected and/or confirmed with a blood test. 		√
Uncommon ≤ 1%	<ul style="list-style-type: none"> Dehydration 		√
	<ul style="list-style-type: none"> Pulmonary embolism (blood clot in the lung) 		√

This is not a complete list of side effects. For any unexpected effects while taking Vectibix[®], contact your doctor or pharmacist.

HOW TO STORE IT

How should Vectibix[®] be stored?

Vectibix[®] should be stored in the refrigerator at 2° to 8°C (36° to 46°F) until time of use. Protect from light. **Do not freeze Vectibix[®].** Do not shake. Since Vectibix[®] does not contain preservatives, any unused portion remaining in the vial must be discarded.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to:
Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

A copy of this document plus the full product monograph, prepared for health professionals, can be attained by contacting the sponsor, Amgen Canada Inc., at: 1-866-502-6436

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