

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Vectibix safely and effectively. See full prescribing information for Vectibix.

Vectibix® (panitumumab)
Solution for Intravenous Infusion
Initial US Approval: 2006

WARNING: DERMATOLOGIC TOXICITY and INFUSION REACTIONS

See full prescribing information for complete boxed warning.

- Dermatologic toxicities were reported in 89% of patients and were severe in 12% of patients receiving monotherapy. (2.1, 5.1, 6.1)
- Severe infusion reactions occurred in approximately 1% of patients. Although not reported with Vectibix, fatalities have occurred with other monoclonal antibody products. (2.1, 5.2, 6.1)

RECENT MAJOR CHANGES

- Adverse Reactions: Postmarketing Experience (6.3) 02/2009
- Indications and Usage: Colorectal Cancer (1) 07/2009

INDICATIONS AND USAGE

- Vectibix is an epidermal growth factor receptor antagonist indicated as a single agent for the treatment of metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens. Approval is based on progression-free survival; no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix. (1)
- Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix is not recommended for the treatment of colorectal cancer with these mutations. (1, 12.1, 14)

DOSAGE AND ADMINISTRATION

- Administer at 6 mg/kg every 14 days as an intravenous infusion over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg). (2)
- Infusion reactions: Reduce infusion rate by 50% for mild reactions; immediately and permanently discontinue for severe reactions. (2.1)
- Dermatologic toxicities: Withhold for severe or intolerable toxicity; may resume at 50% of dose if toxicity improves. (2.1)

DOSAGE FORMS AND STRENGTHS

- Single-use vials (20 mg/mL): 100 mg/5 mL, 200 mg/10 mL, 400 mg/20 mL (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Dermatologic Toxicity: Withhold or discontinue Vectibix and monitor for inflammatory or infectious sequelae in patients with severe dermatologic toxicities. Limit sun exposure. (5.1, 5.6)
- Infusion Reactions: Stop infusion if a severe infusion reaction occurs. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix. (5.2)
- Increased Toxicity With Combination Chemotherapy: Vectibix is not indicated for use in combination with chemotherapy (5.3)
- Pulmonary Fibrosis: Discontinue Vectibix in patients developing interstitial lung disease, pneumonitis, or lung infiltrates. (5.4)
- Electrolyte Depletion/Monitoring: Monitor electrolytes during and for 8 weeks after completion of Vectibix therapy and institute appropriate treatment. (5.5)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 20\%$) are skin toxicities (ie, erythema, dermatitis acneiform, pruritus, exfoliation, rash, and fissures), paronychia, hypomagnesemia, fatigue, abdominal pain, nausea, diarrhea, and constipation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal data, may cause fetal harm. (8.1) Physicians are encouraged to enroll pregnant patients in Amgen's Pregnancy Surveillance Program by calling 1-800-772-6436 (1-800-77-AMGEN). (8.1)
- **Nursing Mothers:** Discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: [July 2009]

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FULL PRESCRIBING INFORMATION

WARNING: DERMATOLOGIC TOXICITY and INFUSION REACTIONS

Dermatologic Toxicity: Dermatologic toxicities occurred in 89% of patients and were severe (NCI-CTC grade 3 and higher) in 12% of patients receiving Vectibix monotherapy. [see *Dosage and Administration* (2.1), *Warnings and Precautions* (5.1), and *Adverse Reactions* (6.1)].

Infusion Reactions: Severe infusion reactions occurred in approximately 1% of patients. [see *Warnings and Precautions* (5.2) and *Adverse Reactions* (6.1)]. Although not reported with Vectibix, fatal infusion reactions have occurred with other monoclonal antibody products. [see *Dosage and Administration* (2.1)].

1 INDICATIONS AND USAGE

Vectibix is indicated as a single agent for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens [see *Clinical Studies* (14)].

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 Studies* (14)]. Currently, no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix.

Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix is not recommended for the treatment of colorectal cancer with these mutations [see *Clinical Studies* (14) and *Clinical Pharmacology* (12.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Dose Modifications

The recommended dose of Vectibix is 6 mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. Doses higher than 1000 mg should be administered over 90 minutes [see *Dosage and Administration* (2.2)].

Appropriate medical resources for the treatment of severe infusion reactions should be available during Vectibix infusions.

Dose Modifications for Infusion Reactions [see *Adverse Reactions* (6.1)]

- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.
- Immediately and permanently discontinue Vectibix infusion in patients experiencing severe (grade 3 or 4) infusion reactions.

Dose Modifications for Dermatologic Toxicity [see *Adverse Reactions* (6.1)]

- Withhold Vectibix for dermatologic toxicities that are grade 3 or higher or are considered intolerable. If toxicity does not improve to \leq grade 2 within 1 month, permanently discontinue Vectibix.
- If dermatologic toxicity improves to \leq grade 2, and the patient is symptomatically improved after withholding no more than two doses of Vectibix, treatment may be resumed at 50% of the original dose.
 - If toxicities recur, permanently discontinue Vectibix.

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- If toxicities do not recur, subsequent doses of Vectibix may be increased by increments of 25% of the original dose until the recommended dose of 6 mg/kg is reached.

2.2 Preparation and Administration

Do not administer Vectibix as an intravenous push or bolus.

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although Vectibix should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration; see below). Do not shake. Do not administer Vectibix if discoloration is observed.
- Withdraw the necessary amount of Vectibix for a dose of 6 mg/kg.
- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.

Administration

- Administer using a low-protein-binding 0.2 µm or 0.22 µm in-line filter.
- Vectibix must be administered via infusion pump.
 - Flush line before and after Vectibix administration with 0.9% sodium chloride injection, USP, to avoid mixing with other drug products or intravenous solutions. Do not mix Vectibix with, or administer as an infusion with, other medicinal products. Do not add other medications to solutions containing panitumumab.
 - Infuse over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. Doses higher than 1000 mg should be infused over 90 minutes.

Use the diluted infusion solution of Vectibix 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.

Discard any unused portion remaining in the vial.

3 DOSAGE FORMS AND STRENGTHS

100 mg panitumumab in 5 mL (20 mg/mL) single-use vial.
200 mg panitumumab in 10 mL (20 mg/mL) single-use vial.
400 mg panitumumab in 20 mL (20 mg/mL) single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Dermatologic Toxicity

In Study 1, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 16% of patients with mCRC receiving Vectibix. The clinical manifestations included, but were not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures.

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Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage were reported. Withhold Vectibix for severe or life-threatening dermatologic toxicity. [see *Boxed Warning, Adverse Reactions (6.1), and Dosage and Administration (2.1)*].

5.2 Infusion Reactions

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

Across all clinical studies, severe infusion reactions occurred with the administration of Vectibix in approximately 1% of patients. Severe infusion reactions included anaphylactic reactions, bronchospasm, and hypotension [see *Boxed Warning and Adverse Reactions (6.1)*]. Although fatal infusion reactions have not been reported with Vectibix, fatalities have occurred with other monoclonal antibody products. Stop infusion if a severe infusion reaction occurs. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix [see *Dosage and Administration (2.1)*].

5.3 Increased Toxicity With Combination Chemotherapy

Vectibix is not indicated for use in combination with chemotherapy. In an interim analysis of Study 2, 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 [see *Clinical Studies (14)*]. NCI-CTC grade 3–4 adverse drug reactions occurring at a higher rate in Vectibix-treated patients included rash/dermatitis acneiform (26% vs 1%), diarrhea (23% vs 12%), dehydration (16% vs 5%), primarily occurring in patients with diarrhea, hypokalemia (10% vs 4%), stomatitis/mucositis (4% vs <1%), and hypomagnesemia (4% vs 0). NCI-CTC grade 3–5 pulmonary embolism occurred at a higher rate in Vectibix-treated patients (7% vs 4%) and included fatal events in three (< 1%) Vectibix-treated patients.

As a result of the toxicities experienced, patients randomized to Vectibix, bevacizumab, and chemotherapy received a lower mean relative dose intensity of each chemotherapeutic agent (oxaliplatin, irinotecan, bolus 5-FU, and/or infusional 5-FU) over the first 24 weeks on study, compared with those randomized to bevacizumab and chemotherapy.

In a single-arm study of 19 patients receiving Vectibix in combination with IFL, the incidence of NCI-CTC grade 3–4 diarrhea was 58%; in addition, grade 5 diarrhea occurred in one patient. In a single-arm study of 24 patients receiving Vectibix plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhea was 25%.

5.4 Pulmonary Fibrosis

Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix. Following the initial fatality described below, patients with a history of interstitial pneumonitis, pulmonary fibrosis, evidence of interstitial pneumonitis, or pulmonary fibrosis were excluded from clinical studies. Therefore, the estimated risk in a general population that may include such patients is uncertain.

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One case occurred in a patient with underlying idiopathic pulmonary fibrosis who received Vectibix in combination with chemotherapy and resulted in death from worsening pulmonary fibrosis after four doses of Vectibix. The second case was characterized by cough and wheezing 8 days following the initial dose, exertional dyspnea on the day of the seventh dose, and persistent symptoms and CT evidence of pulmonary fibrosis following the 11th dose of Vectibix as monotherapy. An additional patient died with bilateral pulmonary infiltrates of uncertain etiology with hypoxia after 23 doses of Vectibix in combination with chemotherapy. Permanently discontinue Vectibix therapy in patients developing interstitial lung disease, pneumonitis, or lung infiltrates.

5.5 Electrolyte Depletion/Monitoring

In Study 1, median magnesium levels decreased by 0.1 mmol/L in the Vectibix arm; hypomagnesemia (NCI-CTC grade 3 or 4) requiring oral or intravenous electrolyte repletion occurred in 2% of patients. Hypomagnesemia occurred 6 weeks or longer after the initiation of Vectibix. In some patients, both hypomagnesemia and hypocalcemia occurred. Patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of Vectibix therapy. Institute appropriate treatment, eg, oral or intravenous electrolyte repletion, as needed.

5.6 Photosensitivity

Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving Vectibix.

5.7 EGF Receptor Testing

Detection of EGFR protein expression is necessary for selection of patients appropriate for Vectibix therapy because these are the only patients studied and for whom benefit has been shown [*see Indications and Usage (1) and Clinical Studies (14)*]. Patients with colorectal cancer enrolled in Study 1 were required to have immunohistochemical evidence of EGFR expression using the Dako EGFR pharmDx[®] test kit.

Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specific reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the package insert for the Dako EGFR pharmDx[®] test kit, or other test kits approved by FDA, for identification of patients eligible for treatment with Vectibix and for full instructions on assay performance.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Dermatologic Toxicity [*see Boxed Warning, and Warnings and Precautions (5.1)*]
- Infusion Reactions [*see Boxed Warning, and Warnings and Precautions (5.2)*]
- Increased Toxicity With Combination Chemotherapy [*see Warnings and Precautions (5.3)*]
- Pulmonary Fibrosis [*see Warnings and Precautions (5.4)*]
- Electrolyte Depletion/Monitoring [*see Warnings and Precautions (5.5)*]
- Photosensitivity [*see Warnings and Precautions (5.6)*]

The most common adverse events of Vectibix are skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea, including diarrhea resulting in dehydration.

The most serious adverse events of Vectibix are pulmonary fibrosis, pulmonary embolism, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia,

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nausea, vomiting, and constipation. Adverse reactions requiring discontinuation of Vectibix were infusion reactions, severe skin toxicity, paronychia, and pulmonary fibrosis.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

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 [see *Warnings and Precautions* (5.3)].

The data described in Table 1 and in other sections below, except where noted, reflect exposure to Vectibix administered as a single agent at the recommended dose and schedule (6 mg/kg every 2 weeks) in 229 patients with mCRC enrolled in Study 1, a randomized, controlled trial. The median number of doses was five (range: one to 26 doses), and 71% of patients received eight or fewer doses. The population had a median age of 62 years (range: 27 to 82 years), 63% were male, and 99% were white with < 1% black, < 1% Hispanic, and 0% other.

Table 1. Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients with a Between-Group Difference of ≥ 5% (Study 1)

	Patients Treated With Vectibix Plus BSC (n = 229)		Best Supportive Care (BSC) Alone (n = 234)	
	Grade*			
Body System	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Body as a Whole				
Fatigue	26	4	15	3
General Deterioration	11	8	4	3
Digestive				
Abdominal Pain	25	7	17	5
Nausea	23	1	16	< 1
Diarrhea	21	2	11	0
Constipation	21	3	9	1
Vomiting	19	2	12	1
Stomatitis	7	0	1	0
Mucosal Inflammation	6	< 1	1	0
Metabolic/Nutritional				
Hypomagnesemia (Lab)	38	4	2	0
Peripheral Edema	12	1	6	< 1
Respiratory				
Cough	14	< 1	7	0
Skin/Appendages				
All Skin/Integument Toxicity	90	16	9	0
Skin	90	14	6	0

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	Patients Treated With Vectibix Plus BSC (n = 229)		Best Supportive Care (BSC) Alone (n = 234)	
	Grade*			
Body System	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Erythema	65	5	1	0
Dermatitis Acneiform	57	7	1	0
Pruritus	57	2	2	0
Nail	29	2	0	0
Paronychia	25	2	0	0
Skin Exfoliation	25	2	0	0
Rash	22	1	1	0
Skin Fissures	20	1	< 1	0
Eye	15	< 1	2	0
Acne	13	1	0	0
Dry Skin	10	0	0	0
Other Nail Disorder	9	0	0	0
Hair	9	0	1	0
Growth of Eyelashes	6	0	0	0
*Version 2.0 of the NCI-CTC was used for grading toxicities. Skin toxicity was coded based on a modification of the NCI-CTCAE, version 3.0.				

Dermatologic, Mucosal, and Ocular Toxicity

In Study 1, dermatologic toxicities occurred in 90% of patients receiving Vectibix. Skin toxicity was severe (NCI-CTC grade 3 and higher) in 16% of patients. Ocular toxicities occurred in 15% of patients and included, but were not limited to, conjunctivitis (4%), ocular hyperemia (3%), increased lacrimation (2%), and eye/eyelid irritation (1%). Stomatitis (7%) and oral mucositis (6%) were reported. One patient experienced an NCI-CTC grade 3 event of mucosal inflammation. The incidence of paronychia was 25% and was severe in 2% of patients. Nail disorders occurred in 9% of patients [see *Warnings and Precautions (5.1)*].

Median time to the development of dermatologic, nail, or ocular toxicity was 14 days after the first dose of Vectibix; the median time to most severe skin/ocular toxicity was 15 days after the first dose of Vectibix; and the median time to resolution after the last dose of Vectibix was 84 days. Severe toxicity necessitated dose interruption in 11% of Vectibix-treated patients [see *Dosage and Administration (2.1)*].

Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage, were reported.

Infusion Reactions

Infusional toxicity was defined as any event within 24 hours of an infusion during the clinical study described as allergic reaction or anaphylactoid reaction, or any event occurring on the first day of dosing described as allergic reaction, anaphylactoid reaction, fever, chills, or dyspnea. Vital signs and temperature were measured within 30 minutes prior to initiation and upon completion of the Vectibix infusion. The use of premedication was not standardized in the clinical trials. Thus, the utility of premedication in preventing the first or subsequent episodes of infusional toxicity is unknown. Across several clinical trials of Vectibix monotherapy, 3% (43/1336) experienced infusion reactions of which approximately 1% (6/1336) were severe (NCI-CTC grade 3–4). In one

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patient, Vectibix was permanently discontinued for a serious infusion reaction [see *Dosage and Administration* (2.1)].

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of Vectibix has been evaluated using two different screening immunoassays for the detection of anti-panitumumab antibodies: an acid dissociation bridging enzyme-linked immunosorbent assay (ELISA) (detecting high-affinity antibodies) and a Biacore[®] biosensor immunoassay (detecting both high- and low-affinity antibodies). The incidence of binding antibodies to panitumumab (excluding predose and transient positive patients), as detected by the acid dissociation ELISA, was 3/613 (< 1%) and as detected by the Biacore[®] assay was 28/613 (4.6%).

For patients whose sera tested positive in screening immunoassays, an in vitro biological assay was performed to detect neutralizing antibodies. Excluding predose and transient positive patients, 10/613 patients (1.6%) with postdose samples and 3/356 (0.8%) of the patients with follow-up samples tested positive for neutralizing antibodies.

No evidence of altered pharmacokinetic profile or toxicity profile was found between patients who developed antibodies to panitumumab as detected by screening immunoassays and those who did not.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to panitumumab with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of panitumumab. Because these reactions are reported in a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Angioedema

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted with Vectibix.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no studies of Vectibix in pregnant women. Reproduction studies in cynomolgus monkeys treated with 1.25 to 5 times the recommended human dose of panitumumab resulted in significant embryoletality and abortions; however, no other evidence of teratogenesis was noted in offspring. [see *Reproductive and Developmental Toxicology* (13.3)]. Vectibix should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on animal models, EGFR is involved in prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Human IgG is known to cross the placental barrier; therefore, panitumumab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women.

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Women who become pregnant during Vectibix treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-772-6436 (1-800-77-AMGEN) to enroll.

8.3 Nursing Mothers

It is not known whether panitumumab is excreted into human milk; however, human IgG is excreted into human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from Vectibix, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If nursing is interrupted, based on the mean half-life of panitumumab, nursing should not be resumed earlier than 2 months following the last dose of Vectibix [see *Clinical Pharmacology (12.3)*].

8.4 Pediatric Use

The safety and effectiveness of Vectibix have not been established in pediatric patients. The pharmacokinetic profile of Vectibix has not been studied in pediatric patients.

8.5 Geriatric Use

Of 229 patients with mCRC who received Vectibix in Study 1, 96 (42%) were \geq age 65. Although the clinical study did not include a sufficient number of geriatric patients to determine whether they respond differently from younger patients, there were no apparent differences in safety and effectiveness of Vectibix between these patients and younger patients.

10 OVERDOSAGE

Doses up to approximately twice the recommended therapeutic dose (12 mg/kg) resulted in adverse reactions of skin toxicity, diarrhea, dehydration, and fatigue.

11 DESCRIPTION

Vectibix (panitumumab) is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Panitumumab has an approximate molecular weight of 147 kDa. Panitumumab is produced in genetically engineered mammalian (Chinese Hamster Ovary) cells.

Vectibix is a sterile, colorless, pH 5.6 to 6.0 liquid for intravenous (IV) infusion, which may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates. Each single-use 5 mL vial contains 100 mg of panitumumab, 29 mg sodium chloride, 34 mg sodium acetate, and Water for Injection, USP. Each single-use 10 mL vial contains 200 mg of panitumumab, 58 mg sodium chloride, 68 mg sodium acetate, and Water for Injection, USP. Each single-use 20 mL vial contains 400 mg of panitumumab, 117 mg sodium chloride, 136 mg sodium acetate, and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases, including EGFR, HER2, HER3, and HER4. EGFR is constitutively expressed in normal epithelial tissues, including the skin and hair follicle. EGFR is over-expressed in certain human cancers, including colon and rectum cancers. Interaction of EGFR with its normal ligands (eg, EGF, transforming growth factor-alpha) leads to

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phosphorylation and activation of a series of intracellular proteins, which in turn regulate transcription of genes involved with cellular growth and survival, motility, and proliferation. Signal transduction through the EGFR results in activation of the wild-type KRAS protein. However, in cells with activating KRAS somatic mutations, the mutant KRAS protein is continuously active and appears independent of EGFR regulation.

Panitumumab binds specifically to EGFR on both normal and tumor cells, and competitively inhibits the binding of ligands for EGFR. Nonclinical studies show that binding of panitumumab to the EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased proinflammatory cytokine and vascular growth factor production, and internalization of the EGFR. *In vitro* assays and *in vivo* animal studies demonstrate that panitumumab inhibits the growth and survival of selected human tumor cell lines expressing EGFR.

12.3 Pharmacokinetics

Panitumumab administered as a single agent exhibits nonlinear pharmacokinetics.

Following single-dose administrations of panitumumab as 1-hour infusions, 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 increased in an approximately dose-proportional manner.

Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour infusion), panitumumab concentrations reached steady-state levels by the third infusion with mean (\pm SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/mL, respectively. The mean (\pm SD) AUC_{0-tau} and CL were 1306 ± 374 mcg•day/mL and 4.9 ± 1.4 mL/kg/day, respectively. The elimination half-life was approximately 7.5 days (range: 3.6 to 10.9 days).

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics. Results suggest that age (21–88 years), gender, race (15% non-white), mild-to-moderate renal dysfunction, mild-to-moderate hepatic dysfunction, and EGFR membrane-staining intensity (1+, 2+, 3+) in tumor cells had no apparent impact on the pharmacokinetics of panitumumab.

No formal pharmacokinetic studies of panitumumab have been conducted in patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies of panitumumab have been conducted. It is not known if panitumumab can impair fertility in humans. Prolonged menstrual cycles and/or amenorrhea occurred in normally cycling, female cynomolgus monkeys treated weekly with 1.25 to 5 times the recommended human dose of panitumumab (based on body weight). Menstrual cycle irregularities in panitumumab-treated female 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. The effects of panitumumab on male fertility have not been studied. However, no adverse effects were observed microscopically in reproductive organs from male cynomolgus monkeys treated for 26 weeks with panitumumab at doses of up to approximately 5-fold the recommended human dose (based on body weight).

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13.2 Animal Toxicology and/or Pharmacology

Weekly administration of panitumumab to cynomolgus monkeys for 4 to 26 weeks resulted in dermatologic findings, including dermatitis, pustule formation and exfoliative rash, and deaths secondary to bacterial infection and sepsis at doses of 1.25 to 5-fold higher (based on body weight) than the recommended human dose.

13.3 Reproductive and Developmental Toxicology

Pregnant cynomolgus monkeys were treated weekly with panitumumab during the period of organogenesis (gestation day [GD] 20–50). 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. There were no fetal malformations or other evidence of teratogenesis noted in the offspring. However, significant increases in embryoletality and abortions occurred at doses of approximately 1.25 to 5 times the recommended human dose (based on body weight).

14 CLINICAL STUDIES

Vectibix Monotherapy

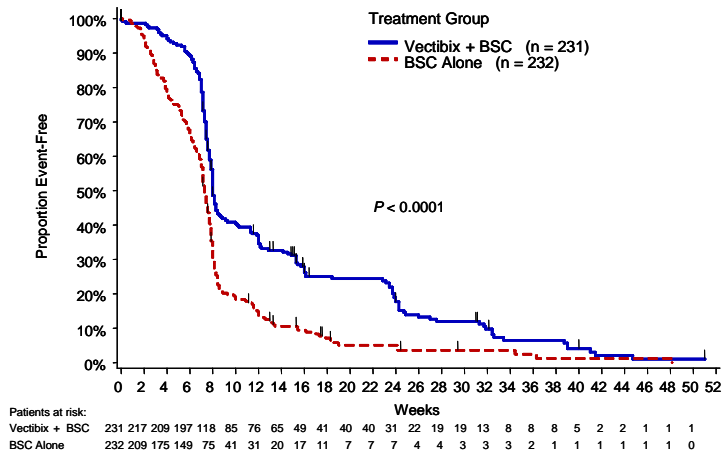
The safety and efficacy of Vectibix were studied in Study 1, an open-label, multinational, randomized, controlled trial of 463 patients with EGFR-expressing, metastatic carcinoma of the colon or rectum (mCRC). Patients were required to have progressed on or following treatment with a regimen(s) containing a fluoropyrimidine, oxaliplatin, and irinotecan; progression was confirmed by an independent review committee (IRC) for 75% of the patients. All patients were required to have EGFR expression defined as at least 1+ membrane staining in $\geq 1\%$ of tumor cells by the Dako EGFR pharmDx[®] test kit. Patients were randomized 1:1 to receive panitumumab at a dose of 6 mg/kg given once every 2 weeks plus best supportive care (BSC) (n = 231) or BSC alone (n = 232) until investigator-determined disease progression. Randomization was stratified based on ECOG performance status (0–1 vs 2) and geographic region (western Europe, eastern/central Europe, or other). Upon investigator-determined disease progression, patients in the BSC-alone arm were eligible to receive panitumumab and were followed until disease progression was confirmed by the IRC. The analyses of progression-free survival (PFS), objective response, and response duration were based on events confirmed by the IRC that was masked to treatment assignment.

Among the 463 patients, 63% were male, the median age was 62 years, 40% were 65 years or older, 99% were white, 86% had a baseline ECOG performance status of 0 or 1, and 67% had colon cancer. The median number of prior therapies for metastatic disease was 2.4. The membrane-staining intensity for EGFR was 3+ in 19%, 2+ in 51%, and 1+ in 30% of patients' tumors. The percentage of tumor cells with EGFR membrane staining in the following categories of $> 35\%$, $> 20\%$ – 35% , 10% – 20% , and 1% – $< 10\%$ was 38%, 8%, 31%, and 22%, respectively.

Based upon IRC determination of disease progression, a statistically significant prolongation in PFS was observed in patients receiving Vectibix compared to those receiving BSC alone. The mean PFS was 96 days in the Vectibix arm and 60 days in the BSC-alone arm. Results are presented in Figure 1 below.

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Figure 1. Kaplan-Meier Plot of Progression-Free Survival Time as Determined by the IRC



In a series of sensitivity analyses, including one adjusting for potential ascertainment bias, ie, assessment for progressive disease at a nonstudy specified time point, PFS was still significantly prolonged among patients receiving Vectibix as compared to patients receiving BSC alone.

Of the 232 patients randomized to BSC alone, 75% of patients crossed over to receive Vectibix following investigator determination of disease progression; the median time to cross over was 8.4 weeks (0.3–26.4 weeks). Partial responses were identified by the IRC in 19 patients randomized to Vectibix, for an overall response of 8% (95% CI: 5.0%, 12.6%). No patient in the control arm had an objective response identified by the IRC. The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks). There was no difference in overall survival between the study arms.

Vectibix in Combination With Bevacizumab and Chemotherapy

Vectibix shortened PFS, decreased survival time, and increased toxicity when given in combination with bevacizumab and chemotherapy in Study 2, a randomized, open-label, multicenter trial in the first-line treatment of metastatic colorectal cancer. Patients (n = 1053) were randomized 1:1 to Vectibix at a dose of 6 mg/kg given once every 2 weeks, in combination with bevacizumab and an oxaliplatin- or irinotecan-based 5-fluorouracil-containing chemotherapy regimen, or to bevacizumab and chemotherapy alone. Randomization was stratified by type of regimen (oxaliplatin- or irinotecan-based); 86% of patients received an oxaliplatin-based regimen and 14% received an irinotecan-based regimen.

The major study objective was comparison of PFS in the oxaliplatin stratum as determined by an independent central review. An interim analysis based on 257 PFS events in the oxaliplatin stratum demonstrated shorter PFS in patients receiving Vectibix, bevacizumab, and chemotherapy compared to those receiving bevacizumab and chemotherapy alone (median PFS were 8.8 months and 10.5 months; hazard ratio 1.44 [95% CI: 1.12, 1.85], p-value = 0.0024, Cox model with randomization factors as covariates). An unplanned analysis of overall survival after 155 deaths (both strata combined), conducted at the time of the interim analysis of PFS, yielded an adjusted hazard ratio of 1.55 [95% CI: 1.12, 2.14], comparing patients receiving Vectibix, bevacizumab, and chemotherapy (92 deaths) to those receiving bevacizumab and chemotherapy alone (63 deaths) [see *Warnings and Precautions* (5.3)].

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Lack of Efficacy of Anti-EGFR Monoclonal Antibodies in Patients With mCRC Containing KRAS Mutations

Retrospective analyses as presented in Table 2 across seven randomized clinical trials suggest that anti-EGFR-directed monoclonal antibodies are not effective for the treatment of patients with mCRC containing KRAS mutations. In these trials, patients received standard of care (ie, BSC or chemotherapy) and were randomized to receive an anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy. In all studies, investigational tests were used to detect KRAS mutations in codon 12 or 13. The percentage of study populations for which KRAS status was assessed ranged from 23% to 92% [see Clinical Pharmacology (12.1)].

Table 2. Retrospective Analyses of Treatment Effect in the Subset of Patients With mCRC Containing KRAS Mutations Enrolled in Randomized Clinical Trials

Population (n: ITT ¹)	Treatment	Number of Patients with KRAS Results (% ITT)	Number of Patients with KRAS mutant (mAb ² /control)	Effect of mAb on Endpoints: KRAS mutant ³
1 st line treatment mCRC (n = 1198)	FOLFIRI ± cetuximab	540 (45%)	105/87	PFS²: no difference OS ² : no difference ORR ² : decreased
1 st line treatment mCRC (n = 337)	FOLFOX-4 ± cetuximab	233 (69%)	52/47	ORR: decreased PFS: decreased OS: no difference
Study 2: 1 st line treatment mCRC (n = 1053)	oxaliplatin or irinotecan-based chemotherapy, bevacizumab ± Vectibix	oxaliplatin 664 (81%)	135/125	PFS: decreased OS: no difference ORR: increased
		irinotecan 201 (87%)	47/39	ORR: decreased PFS: decreased OS: decreased
1 st line treatment mCRC (n = 736)	bevacizumab, capecitabine, oxaliplatin ± cetuximab	528 (72%)	98/108	PFS: decreased OS: decreased ORR: decreased
2 nd line treatment mCRC (n = 1298)	irinotecan ± cetuximab	300 (23%)	49/59	OS: decreased PFS: no difference ORR: increased
3 rd line treatment mCRC (n = 572)	BSC ± cetuximab	394 (69%)	81/83	OS: no difference PFS: no difference ORR: increased
Study 1: 3 rd line treatment mCRC (n = 463)	BSC ± Vectibix	427 (92%)	84/100	PFS: no difference OS: no difference ORR: no difference
¹ ITT: intent-to-treat ² mAb: EGFR monoclonal antibody; PFS: progression-free-survival; ORR: overall response rate; OS: overall survival ³ Results from the primary efficacy endpoint are in bold. A given endpoint is designated as “decreased” if there was a numerically smaller result and as “increased” if there was a numerically higher result in the mAb group than in the control group.				

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16 HOW SUPPLIED/STORAGE AND HANDLING

Vectibix is supplied as a sterile, colorless, preservative-free solution containing 20 mg/mL Vectibix (panitumumab) in a single-use vial.

Vectibix is provided as one vial per carton.

Each 5 mL single-use vial contains 100 mg of panitumumab in 5 mL (20 mg/mL) (NDC 55513-954-01).

Each 10 mL single-use vial contains 200 mg of panitumumab in 10 mL (20 mg/mL) (NDC 55513-955-01).

Each 20 mL single-use vial contains 400 mg of panitumumab in 20 mL (20 mg/mL) (NDC 55513-956-01).

Store vials in the original carton under refrigeration at 2° to 8°C (36° to 46°F) until time of use. Protect from direct sunlight. **DO NOT FREEZE**. Since Vectibix does not contain preservatives, any unused portion remaining in the vial must be discarded.

The diluted infusion solution of Vectibix 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**.

17 PATIENT COUNSELING INFORMATION

Advise patients to contact a healthcare professional for any of the following:

- Skin and ocular/visual changes [*see Boxed Warning and Warnings and Precautions (5.1)*],
- Signs and symptoms of infusion reactions including fever, chills, or breathing problems [*see Boxed Warning and Warnings and Precautions (5.2)*],
- Persistent or recurrent coughing, wheezing, dyspnea, or new onset facial swelling [*see Warnings and Precautions (5.4)*, and *Adverse Reactions (6.1)*],
- Pregnancy or nursing [*see Use in Specific Populations (8.1, 8.3)*].

Advise patients of the need for:

- Periodic monitoring of electrolytes [*see Warnings and Precautions (5.5)*],
- Limitation of sun exposure (use sunscreen, wear hats) while receiving Vectibix and for 2 months after the last dose of Vectibix therapy. [*see Warnings and Precautions (5.6)*],
- Adequate contraception in both males and females while receiving Vectibix and for 6 months after the last dose of Vectibix therapy [*see Use in Specific Populations (8.1, 8.3)*].

AMGEN[®]

Vectibix[®] (panitumumab) Injection for Intravenous Use

Manufactured by:

Amgen Inc.

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Thousand Oaks, CA 91320-1799

USA

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent No. 6,235,883, as well as other patents or patents pending.

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