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)
Injection for intravenous infusion
Initial US Approval: 2006

WARNING: DERMATOLOGIC TOXICITY

See full prescribing information for complete boxed warning.

- **Dermatologic toxicities were reported in 90% of patients and were severe in 15% of patients receiving monotherapy. (2.3, 5.1, 6.1)**

----------RECENT MAJOR CHANGES----------

• Boxed Warning: infusion reactions	05/2014
• Indications and Usage (1)	05/2014
• Dosage and Administration (2)	05/2014
• Warnings and Precautions (5)	05~~8~~/2014

----------INDICATIONS AND USAGE----------

Vectibix is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type *KRAS* (exon 2) metastatic colorectal cancer (mCRC) as determined by an FDA-approved test for this use:

- In combination with FOLFOX for first-line treatment. (1.1, 14.2)
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy. (1.1, 14.1)
- Limitation of Use: Vectibix is not indicated for the treatment of patients with *KRAS*-mutant mCRC or for whom *KRAS* mutation status is unknown. (1.2, 2.1, 5.2, 12.1)

----------DOSAGE AND ADMINISTRATION----------

- Administer 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; terminate the infusion for severe infusion reactions. (2.3, 5.4)
- Dermatologic Toxicity: Withhold or discontinue for severe or intolerable toxicity; reduce dose for recurrent, grade 3 toxicity. (2.3, 5.1)

----------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

----------WARNINGS AND PRECAUTIONS----------

- Dermatologic and Soft Tissue Toxicity: Monitor for dermatologic and soft tissue toxicities and withhold or discontinue Vectibix for severe or life-threatening complications. Limit sun exposure. (5.1, 5.7)
- Increased tumor progression, increased mortality, or lack of benefit in patients with *KRAS*-mutant mCRC: Determine *KRAS*-mutant tumor status in an experienced laboratory using an FDA-approved test. (5.2)
- Electrolyte Depletion/Monitoring: Monitor electrolytes and institute appropriate treatment. (5.3)
- Infusion Reactions: Terminate the infusion for severe infusion reactions. (5.4)
- Pulmonary Fibrosis/Interstitial Lung Disease (ILD): Permanently discontinue Vectibix in patients developing ILD. (5.6)
- Ocular Toxicities: Monitor for keratitis or ulcerative keratitis. Interrupt or discontinue Vectibix for acute or worsening keratitis. (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 20%) of Vectibix as monotherapy are skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea. (6.1)

Most common adverse reactions (≥ 20%) in clinical trials of Vectibix in combination with FOLFOX chemotherapy are diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin. (6.1)

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: 08/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DERMATOLOGIC TOXICITY

Dermatologic Toxicity: Dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients receiving Vectibix monotherapy *[see Dosage and Administration (2.3), Warnings and Precautions (5.1), and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

Vectibix is indicated for the treatment of patients with wild-type *KRAS* (exon 2 in codons 12 or 13) metastatic colorectal cancer (mCRC) as determined by an FDA-approved test for this use:

- As first-line therapy in combination with FOLFOX *[see Clinical Studies (14.2)]*.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy *[see Clinical Studies (14.1)]*.

1.2 Limitation of Use

Vectibix is not indicated for the treatment of patients with *KRAS*-mutant mCRC or for whom *KRAS* mutation status is unknown *[see Dosage and Administration (2.1), Warnings and Precautions (5.2), and Clinical Pharmacology (12.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Prior to initiation of treatment with Vectibix, assess *KRAS* mutational status in colorectal tumors and confirm the absence of a *KRAS* mutation using an FDA-approved test *[see Warnings and Precautions (5.2)]*. Information on FDA-approved tests for the detection of *KRAS* mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dose

The recommended dose of Vectibix is 6 mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. If the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes. Administer doses higher than 1000 mg over 90 minutes *[see Dosage and Administration (2.4)]*.

Appropriate medical resources for the treatment of severe infusion reactions should be available during Vectibix infusions *[see Warnings and Precautions (5.4)]*.

2.3 Dose Modifications

Dose Modifications for Infusion Reactions *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1, 6.3)]*

- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.
- Terminate the infusion in patients experiencing severe infusion reactions. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix.

Dose Modifications for Dermatologic Toxicity *[see Boxed Warning, Warnings and Precautions (5.1), and Adverse Reactions (6.1, 6.3)]*

- Upon first occurrence of a grade 3 (NCI-CTC/CTCAE) dermatologic reaction, withhold 1 to 2 doses of Vectibix. If the reaction improves to < grade 3, reinitiate Vectibix at the original dose.
- Upon the second occurrence of a grade 3 (NCI-CTC/CTCAE) dermatologic reaction, withhold 1 to 2 doses of Vectibix. If the reaction improves to < grade 3, reinitiate Vectibix at 80% of the original dose.
- Upon the third occurrence of a grade 3 (NCI-CTC/CTCAE) dermatologic reaction, withhold 1 to 2 doses of Vectibix. If the reaction improves to < grade 3, reinitiate Vectibix at 60% of the original dose.
- Upon the fourth occurrence of a grade 3 (NCI-CTC/CTCAE) dermatologic reaction, permanently discontinue Vectibix.

Permanently discontinue Vectibix following the occurrence of a grade 4 dermatologic reaction or for a grade 3 (NCI-CTC/CTCAE) dermatologic reaction that does not recover after withholding 1 or 2 doses.

2.4 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 doses of 1000 mg or lower over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. If the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes. Administer doses higher than 1000 mg 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 and Soft Tissue Toxicity

In Study 1, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients with mCRC receiving Vectibix. The clinical manifestations included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures.

Monitor patients who develop dermatologic or soft tissue toxicities while receiving Vectibix for the development of inflammatory or infectious sequelae. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed in patients treated with Vectibix. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Vectibix. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens Johnson syndrome or toxic epidermal necrolysis). Withhold or discontinue Vectibix for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications *[see Boxed Warning and Adverse Reactions (6.1, 6.3)]*. Dose modifications for Vectibix concerning dermatologic toxicity are provided *[see Dosage and Administration (2.3)]*.

5.2 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with *KRAS*-Mutant mCRC

Determination of *KRAS* mutational status in colorectal tumors using an FDA-approved test indicated for this use is necessary for selection of patients for treatment with Vectibix. Vectibix is indicated only for the treatment of patients with *KRAS* wild-type mCRC. Vectibix is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in codons 12 and 13 (exon 2) as determined by an FDA-approved test for this use *[see Indications and Usage (1.2), Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14)]*. In Study 3, 221 patients with *KRAS*-mutant mCRC tumors receiving Vectibix in combination with FOLFOX experienced shorter overall survival (OS) compared to 219 patients receiving FOLFOX alone (HR = 1.24, 95% CI: 0.98-1.57). Perform the assessment for *KRAS* mutational status in colorectal cancer in laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results. Refer to an FDA-approved test's package insert for instructions on the identification of patients eligible for the treatment of Vectibix.

5.3 Electrolyte Depletion/Monitoring

Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% (in Study 2) of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating Vectibix treatment, periodically during Vectibix treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

5.4 Infusion Reactions

In Study 1, 4% of patients experienced infusion reactions and 1% of patients experienced severe infusion reactions (NCI-CTC grade 3-4).

Infusion reactions, manifesting as fever, chills, dyspnea, bronchospasm, and hypotension, can occur following Vectibix administration *[see Adverse Reactions (6.1, 6.3)]*. Fatal infusion reactions occurred in postmarketing experience. Terminate the infusion for severe infusion reactions *[see Dosage and Administration (2.3)]*.

5.5 Acute Renal Failure in Combination with Chemotherapy

Severe diarrhea and dehydration, leading to acute renal failure and other complications, have been observed in patients treated with Vectibix in combination with chemotherapy.

5.6 Pulmonary Fibrosis/Interstitial Lung Disease (ILD)

Fatal and nonfatal cases of interstitial lung disease (ILD) (1%) and pulmonary fibrosis have been observed in patients treated with Vectibix. Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix. In the event of acute onset or worsening of pulmonary symptoms, interrupt Vectibix therapy. Discontinue Vectibix therapy if ILD is confirmed.

In patients with a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with Vectibix versus the risk of pulmonary complications must be carefully considered.

5.7 Photosensitivity

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

5.8 Ocular Toxicities

Keratitis and ulcerative keratitis, known risk factors for corneal perforation, have been reported with Vectibix use. Monitor for evidence of keratitis or ulcerative keratitis. Interrupt or discontinue Vectibix therapy for acute or worsening keratitis.

5.9 Increased Mortality and Toxicity with Vectibix in Combination with Bevacizumab and Chemotherapy

In an interim analysis of an open-label, multicenter, randomized clinical trial in the first-line setting in patients with mCRC, the addition of Vectibix to the combination of bevacizumab and chemotherapy resulted in decreased OS and increased incidence of NCI-CTC grade 3-5 (87% vs 72%) adverse reactions. NCI-CTC grade 3-4 adverse reactions occurring at a higher rate in Vectibix-treated patients included rash/acneiform dermatitis (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 3%) 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.

6 ADVERSE REACTIONS

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

- Dermatologic and Soft Tissue Toxicity *[see Boxed Warning, Dosage and Administration (2.3), and Warnings and Precautions (5.1)]*
- Increased Tumor Progression, Increased Mortality, or Lack of Benefit in *KRAS*-Mutant mCRC *[see Indications and Usage (1.2) and Warnings and Precautions (5.2)]*
- Electrolyte Depletion/Monitoring *[see Warnings and Precautions (5.3)]*
- Infusion Reactions *[see Dosage and Administration (2.3), and Warnings and Precautions (5.4)]*
- Acute Renal Failure in Combination with Chemotherapy *[see Warnings and Precautions (5.5)]*
- Pulmonary Fibrosis/Interstitial Lung Disease (ILD) *[see Warnings and Precautions (5.6)]*
- Photosensitivity *[see Warnings and Precautions (5.7)]*
- Ocular Toxicities *[see Warnings and Precautions (5.8)]*
- Increased Mortality and Toxicity with Vectibix in combination with Bevacizumab and Chemotherapy *[see Warnings and Precautions (5.9)]*

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 presented from two clinical trials in which patients received Vectibix: Study 1, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 463) evaluating Vectibix with best supportive care (BSC) versus BSC alone in patients with EGFR-expressing mCRC and Study 3, a randomized, controlled trial (N = 1183) in patients with mCRC that evaluated Vectibix in combination with FOLFOX chemotherapy versus FOLFOX chemotherapy alone. Safety data for Study 3 are limited to 656 patients with wild-type *KRAS* mCRC.

Vectibix Monotherapy

In Study 1, the most common adverse reactions (≥ 20%) with Vectibix were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.

The most common (> 5%) serious adverse reactions in the Vectibix arm were general physical health deterioration and intestinal obstruction. The most frequently reported adverse reactions for Vectibix leading to withdrawal were general physical health deterioration (n = 2) and intestinal obstruction (n = 2).

For Study 1, the data described in Table 1 and in other sections below, except where noted, reflect exposure to Vectibix administered to patients with mCRC as a single agent at the recommended dose and schedule (6 mg/kg every 2 weeks).

Table 1: Adverse Reactions (≥ 5% Difference) Observed in Patients Treated with Vectibix Monotherapy and Best Supportive Care Compared to Best Supportive Care Alone (Study 1)

	Study 1			
	Vectibix Plus Best Supportive Care (N = 229)		Best Supportive Care (N = 234)	
SYSTEM ORGAN CLASS Preferred Term	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
EYE DISORDERS				
Growth of eyelashes	13 (6)			
GASTROINTESTINAL DISORDERS				
Nausea	52 (23)	2 (< 1)	37 (16)	1 (< 1)
Diarrhea	49 (21)	4 (2)	26 (11)	
Vomiting	43 (19)	6 (3)	28 (12)	2 (< 1)
Stomatitis	15 (7)		2 (< 1)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	60 (26)	10 (4)	34 (15)	7 (3)
Mucosal inflammation	15 (7)	1 (< 1)	2 (< 1)	
INFECTIONS AND INFESTATIONS				
Paronychia	57 (25)	4 (2)		
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS				
Dyspnea	41 (18)	12 (5)	30 (13)	8 (3)
Cough	34 (15)	1 (< 1)	17 (7)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Erythema	150 (66)	13 (6)	2 (< 1)	
Pruritus	132 (58)	6 (3)	4 (2)	
Acneiform dermatitis	131 (57)	17 (7)	2 (< 1)	
Rash	51 (22)	3 (1)	2 (< 1)	
Skin fissures	45 (20)	3 (1)	1 (< 1)	
Exfoliative rash	41 (18)	4 (2)		
Acne	31 (14)	3 (1)		
Dry skin	23 (10)			
Nail disorder	22 (10)			
Skin exfoliation	21 (9)	2 (< 1)		
Skin ulcer	13 (6)	1 (< 1)		

Adverse reactions in Study 1 that did not meet the threshold criteria for inclusion in Table 1 were conjunctivitis (4.8% vs < 1%), dry mouth (4.8% vs 0%), pyrexia (16.6% vs 13.2%), chills (3.1% vs < 1%), pustular rash (4.4% vs 0%), papular rash (1.7% vs 0%), dehydration (2.6% vs 1.7%), epistaxis (3.9% vs 0%), and pulmonary embolism (1.3% vs 0%).

In Study 1, dermatologic toxicities occurred in 90% of patients receiving Vectibix. Skin toxicity was severe (NCI-CTC grade 3 and higher) in 15% of patients. Ocular toxicities occurred in 16% of patients and included, but were not limited to, conjunctivitis (5%). 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 *[see Warnings and Precautions (5.1)]*.

In Study 1 (N = 229), median time to the development of dermatologic, nail, or ocular toxicity was 12 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 98 days. Severe toxicity necessitated dose interruption in 11% of Vectibix-treated patients *[see Dosage and Administration (2.3)]*.

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

Vectibix in Combination with FOLFOX Chemotherapy

The most commonly reported adverse reactions (≥ 20%) in patients with wild-type *KRAS* mCRC receiving Vectibix (6 mg/kg every 2 weeks) and FOLFOX therapy (N = 322) in Study 3 were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin (Table 2). Serious adverse reactions (≥ 2% difference between treatment arms) in Vectibix-treated patients with wild-type *KRAS* mCRC were diarrhea and dehydration. The commonly reported adverse reactions (≥ 1%) leading to discontinuation in patients with wild-type *KRAS* mCRC receiving Vectibix were rash, paresthesia, fatigue, diarrhea, acneiform dermatitis, and hypersensitivity. One grade 5 adverse reaction, hypokalemia, occurred in a patient who received Vectibix.

Table 2: Adverse Reactions (≥ 5% Difference) Observed in Patients with Wild-type (WT) *KRAS* Tumors Treated with Vectibix and FOLFOX Chemotherapy Compared to FOLFOX Chemotherapy Alone (Study 3)

	Vectibix Plus FOLFOX (n = 322)		FOLFOX Alone (n = 327)	
SYSTEM ORGAN CLASS Preferred Term	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
EYE DISORDERS				
Conjunctivitis	58 (18)	5 (2)	10 (3)	
GASTROINTESTINAL DISORDERS				
Diarrhea	201 (62)	59 (18)	169 (52)	29 (9)
Stomatitis	87 (27)	15 (5)	42 (13)	1 (< 1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Mucosal inflammation	82 (25)	14 (4)	53 (16)	1 (< 1)
Asthenia	79 (25)	16 (5)	62 (19)	11 (3)
INFECTIONS AND INFESTATIONS				
Paronychia	68 (21)	11 (3)		
INVESTIGATIONS				
Weight decreased	58 (18)	3 (< 1)	22 (7)	
METABOLISM AND NUTRITION DISORDERS				
Anorexia	116 (36)	14 (4)	85 (26)	6 (2)
Hypomagnesemia	96 (30)	21 (7)	26 (8)	1 (< 1)
Hypokalemia	68 (21)	32 (10)	42 (13)	15 (5)
Dehydration	26 (8)	8 (2)	10 (3)	5 (2)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS				
Epistaxis	46 (14)		30 (9)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	179 (56)	55 (17)	24 (7)	1 (< 1)
Acneiform dermatitis	104 (32)	33 (10)		
Pruritus	75 (23)	3 (< 1)	14 (4)	
Dry skin	68 (21)	5 (2)	13 (4)	
Erythema	50 (16)	7 (2)	14 (4)	
Skin fissures	50 (16)	1 (< 1)	1 (< 1)	
Alopecia	47 (15)		30 (9)	
Acne	44 (14)	10 (3)	1 (< 1)	
Nail disorder	32 (10)	4 (1)	4 (1)	
Palmar-plantar erythrodysesthesia syndrome	30 (9)	4 (1)	9 (3)	2 (< 1)

Adverse reactions that did not meet the threshold criteria for inclusion in Table 2 were abdominal pain (28% vs 23%), localized infection (3.7% vs < 1%), cellulitis (2.5% vs 0%), hypocalcemia (5.6% vs 2.1%), and deep vein thrombosis (5.3% vs 3.1%).

Infusion Reactions

Infusional toxicity manifesting as fever, chills, dyspnea, bronchospasm or hypotension was assessed within 24 hours of an infusion during the clinical study. 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 clinical trials of Vectibix monotherapy, 3% (24/725) experienced infusion reactions of which < 1% (3/725) were severe (NCI-CTC grade 3-4). In one patient, Vectibix was permanently discontinued for a serious infusion reaction *[see Dosage and Administration (2.2, 2.3)]*.

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 binding 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. For patients whose sera tested positive in screening immunoassays, an in vitro biological assay was performed to detect neutralizing antibodies.

Monotherapy: The incidence of binding anti-panitumumab antibodies (excluding preexisting and transient positive patients) was 0.4% (5/1123) as detected by the acid dissociation ELISA and 3.2% (36/1123) as detected by the Biacore® assay. The incidence of neutralizing anti-panitumumab antibodies (excluding preexisting and transient positive patients) was 0.8% (9/1123). There was no evidence of altered pharmacokinetic or safety profiles in patients who developed antibodies to Vectibix.

In combination with chemotherapy: The incidence of binding anti-panitumumab antibodies (excluding preexisting positive patients) was 0.9% (12/1297) as detected by the acid dissociation ELISA and 0.7% (9/1296) as detected by the Biacore® assay. The incidence of neutralizing anti-panitumumab antibodies (excluding preexisting positive patients) was 0.2% (2/1297). No evidence of an altered safety profile was found in patients who developed antibodies to Vectibix.

The detection 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 reactions have 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 reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Skin and subcutaneous tissue disorders*: Skin necrosis, angioedema, life threatening and fatal bullous mucocutaneous disease *[see Boxed Warning, Dosage and Administration (2.3), and Warnings and Precautions (5.1)]*
- *Immune system disorders:* Infusion reaction *[see Dosage and Administration (2.3) and Warnings and Precautions (5.4)]*
- *Eye disorders:* Keratitis/ulcerative keratitis *[see Warnings and Precautions (5.8)]*

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted between Vectibix and oxaliplatin or fluoropyrimidine.

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 embryolethality and abortions; however, no other evidence of teratogenesis was noted in offspring *[see Nonclinical 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.

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

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

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 the 737 patients who received Vectibix monotherapy in Study 1 and 2, 36% were 65 and over while 8% were 75 and over. No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Vectibix monotherapy.

Of the 322 patients in Study 3 who received Vectibix plus FOLFOX, 128 (40%) were 65 and over while 8% were 75 and over. Patients older than 65 years of age experienced an increased incidence of serious adverse events (52% vs 36%) and an increased incidence of serious diarrhea (15% vs 5%) as compared to 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 overexpressed in certain human cancers, including colon and rectum cancers. Interaction of EGFR with its normal ligands (eg, EGF, transforming growth factor-alpha) leads to 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 *KRAS*-mutant 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 (± SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/mL, respectively. The mean (± SD) $AUC_{0\text{-}tau}$ 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% nonwhite), mild-to-moderate renal dysfunction, mild-to-moderate hepatic dysfunction, and EGFR membrane-staining intensity (1+, 2+, and 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 17β-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).

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 embryolethality and abortions occurred at doses of approximately 1.25 to 5 times the recommended human dose (based on body weight).

14 CLINICAL STUDIES

14.1 Recurrent or Refractory mCRC

The safety and efficacy of Vectibix was demonstrated in Study 1, an open-label, multinational, randomized, controlled trial of 463 patients with EGFR-expressing, metastatic carcinoma of the colon or rectum, and in Study 2, an open-label, multicenter, multinational, randomized trial of 1010 patients with wild-type *KRAS* mCRC.

Study 1

Patients in Study 1 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) masked to treatment assignment for 76% of the patients. Patients were randomized (1:1) to receive panitumumab at a dose of 6 mg/kg given once every 2 weeks plus BSC (N = 231) or BSC alone (N = 232) until investigator-determined disease progression. Randomization was stratified based on Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 and 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.

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

The study results were analyzed in the wild-type *KRAS* subgroup where *KRAS* status was retrospectively determined using archived paraffin-embedded tumor tissue. *KRAS* mutation status was determined in 427 patients (92%); of these, 243 (57%) had no detectable *KRAS* mutations in either codons 12 or 13. The hazard ratio for PFS in patients with wild-type *KRAS* mCRC was 0.45 (95% CI: 0.34-0.59) favoring the panitumumab arm. The response rate was 17% for the panitumumab arm and 0% for BSC. There were no differences in OS; 77% of patients in the BSC arm received panitumumab at the time of disease progression.

Study 2

Study 2 was an open-label, multicenter, multinational, randomized (1:1) clinical trial, stratified by region (North America, Western Europe, and Australia versus rest of the world) and ECOG PS (0 and 1 vs 2) in patients with wild-type *KRAS* mCRC. A total of 1010 patients who received prior treatment with irinotecan, oxaliplatin, and a thymidylate synthase inhibitor were randomized to receive Vectibix 6 mg/kg intravenously over 60 minutes every 14 days or cetuximab 400 mg/m^2 intravenously over 120 minutes on day 1 followed by 250 mg/m^2 intravenously over 60 minutes every 7 days. The trial excluded patients with clinically significant cardiac disease and interstitial lung disease. The major efficacy analysis tested whether the OS of Vectibix was noninferior to cetuximab. Data for investigator-assessed PFS and objective response rate (ORR) were also collected. The criteria for noninferiority was for Vectibix to retain at least 50% of the OS benefit of cetuximab based on an OS hazard ratio of 0.55 from the NCIC CTG CO.17 study relative to BSC.

In Study 2, 37% of patients were women, 52% were white, 45% were Asian, and 1.3% were Hispanic or Latino. Thirty-one percent of patients were enrolled at sites in North America, Western Europe, or Australia. ECOG performance was 0 in 32% of patients, 1 in 60% of patients, and 2 in 8% of patients. Median age was 61 years. More patients (62%) had colon cancer than rectal cancer (38%). Most patients (74%) had not received prior bevacizumab.

The key efficacy analysis for Study 2 demonstrated that Vectibix was statistically significantly noninferior to cetuximab for OS.

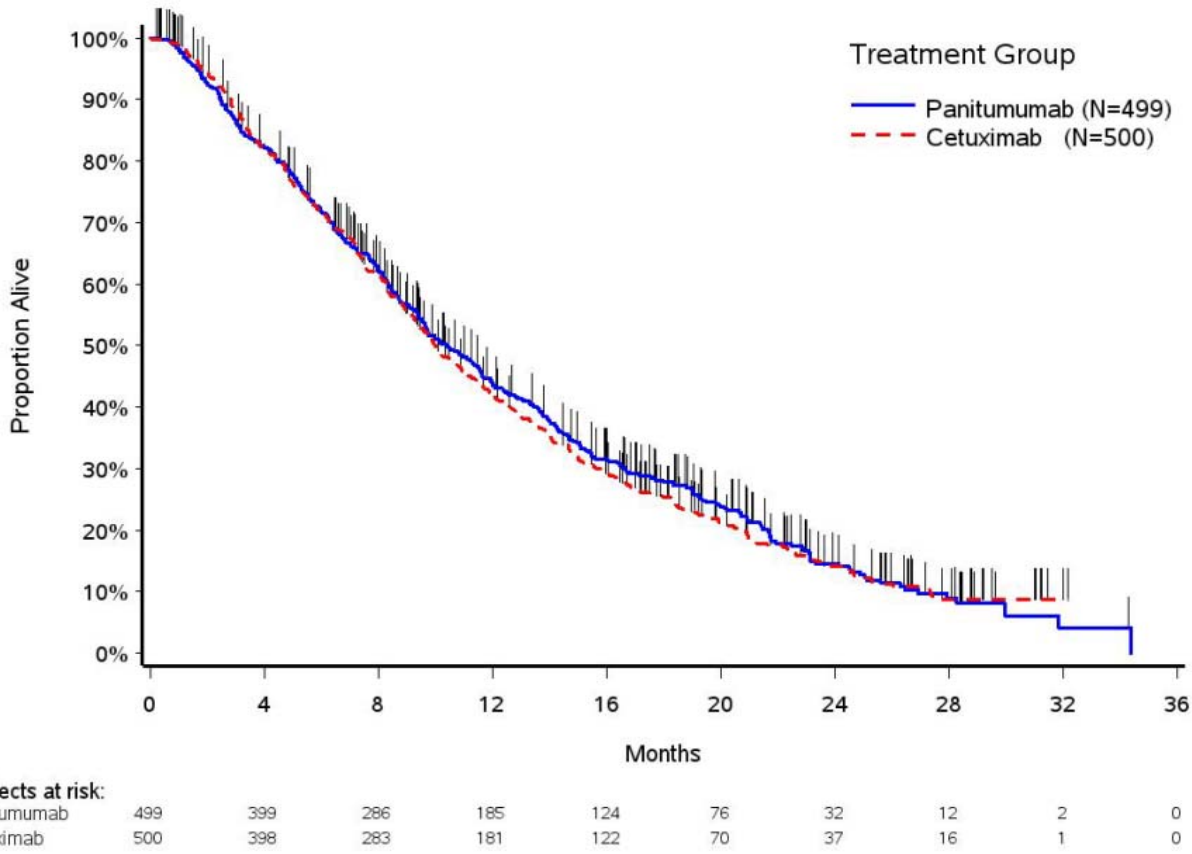
The efficacy results for Study 2 are presented in Table 3 and Figure 1.

Table 3: Results in Previously Treated Wild-type *KRAS* mCRC (Study 2)

Wild-type *KRAS* Population	**Vectibix (n = 499)[a]**	**Cetuximab (n = 500)[a]**
OS		
Number of OS events (%)	383 (76.8)	392 (78.4)
Median (months) (95% CI)	10.4 (9.4, 11.6)	10.0 (9.3, 11.0)
Hazard ratio (95% CI)	0.97 (0.84, 1.11)	
PFS		
Median (months) (95% CI)	4.1 (3.2, 4.8)	4.4 (3.2, 4.8)
Hazard ratio (95% CI)	1.00 (0.88, 1.14)	
ORR		
% (95% CI)	22% (18%, 26%)	19% (16%, 23%)

[a] Modified intent-to-treat population that included all patients who received at least one dose of therapy

Figure 1: Kaplan-Meier Plot of Overall Survival in Patients with Wild-type *KRAS* mCRC (Study 2)



14.2 First-line in Combination with FOLFOX Chemotherapy

Study 3

Study 3 was a multicenter, open-label trial that randomized (1:1) patients with mCRC who were previously untreated in the metastatic setting and who had received no prior oxaliplatin to receive Vectibix every 14 days in combination with FOLFOX or to FOLFOX alone every 14 days. Vectibix was administered at 6 mg/kg over 60 minutes prior to administration of chemotherapy. The FOLFOX regimen consisted of oxaliplatin 85 mg per m^2 IV infusion over 120 minutes and leucovorin (dl-racemic) 200 mg per m^2 intravenous infusion over 120 minutes at the same time on day 1 using a Y-line, followed on day 1 by 5-FU 400 mg per m^2 intravenous bolus. The 5FU bolus was followed by a continuous infusion of 5-FU 600 mg per m^2 over 22 hours. On day 2, patients received leucovorin 200 mg per m^2 followed by the bolus dose (400 mg per m^2) and continuous infusion of 5FU (600 mg per m^2) over 22 hours. Study 3 excluded patients with known central nervous system metastases, clinically significant cardiac disease, interstitial lung disease, or active inflammatory bowel disease. The prespecified major efficacy measure was PFS in patients (n = 656) with wild-type *KRAS* mCRC as assessed by a blinded independent central review of imaging. Other key efficacy measures included OS and ORR.

In Study 3, in the wild-type *KRAS* group, 64% of patients were men, 92% white, 2% black, and 4% Hispanic or Latino. Sixty-six percent of patients had colon cancer and 34% had rectal cancer. ECOG performance was 0 in 56% of patients, 1 in 38% of patients, and 2 in 6% of patients. Median age was 61.5 years.

The efficacy results in Study 3 in patients with wild-type *KRAS* mCRC are presented in Table 4 below.

Table 4: Results in Patients with Wild-type *KRAS* mCRC (Study 3)

	Primary Analysis	
	Vectibix plus FOLFOX	**FOLFOX Alone**
Wild-type *KRAS* population	**(n = 325)[a]**	**(n = 331)[a]**
PFS		
Median (months) (95% CI)	9.6 (9.2, 11.1)	8.0 (7.5, 9.3)
Hazard ratio (95% CI) p-value	0.80 (0.66, 0.97) p = 0.02	
ORR		
% (95% CI)	54% (48%, 59%)	47% (41%, 52%)

[a] Intent-to-treat population

KRAS-Mutant Subgroup

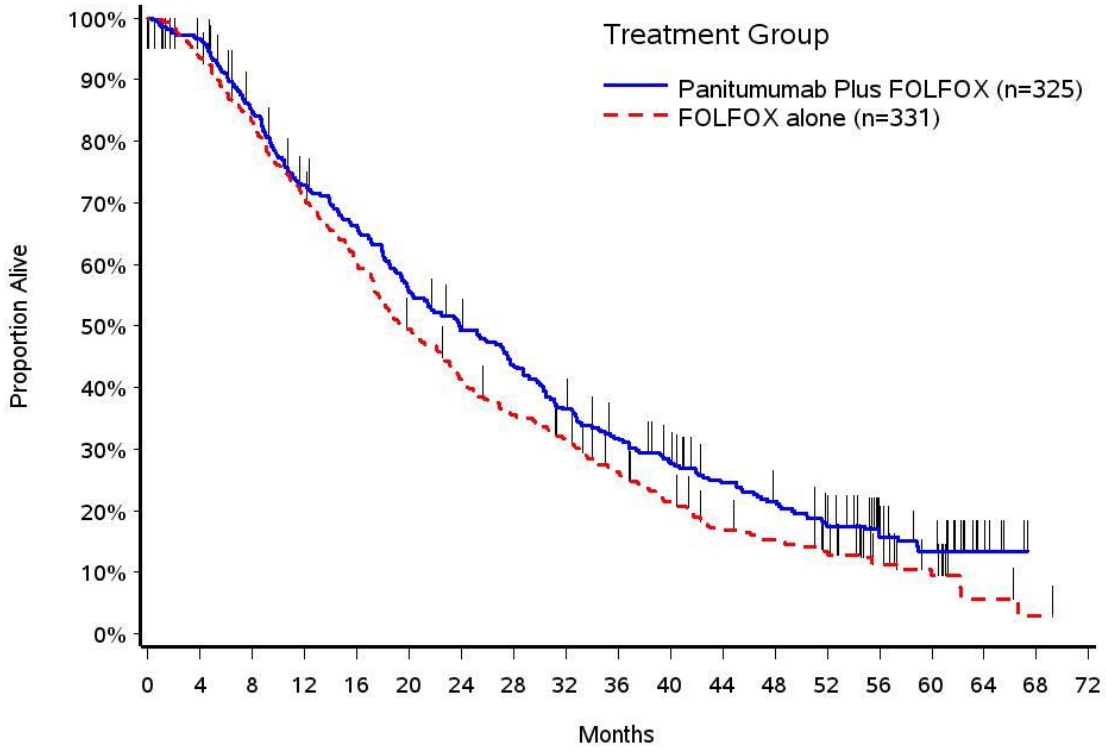
In Study 3, among patients with *KRAS*-mutant tumors, median PFS was 7.3 months (95% CI: 6.3, 8.0) among 221 patients receiving Vectibix plus FOLFOX versus 8.8 months (95% CI: 7.7, 9.4) among patients who received FOLFOX alone (HR = 1.29, 95% CI: 1.04, 1.62). Median OS was 15.5 months (95% CI: 13.1, 17.6) among patients receiving Vectibix plus FOLFOX versus 19.3 months (95% CI: 16.5, 21.8) among patients who received FOLFOX alone (HR = 1.24, 95% CI: 0.98, 1.57).

Exploratory Analysis of OS

An exploratory analysis of OS with updated information based on events in 82% of patients with wild-type *KRAS* mCRC estimated the treatment effect of Vectibix plus FOLFOX compared with FOLFOX alone on OS (Figure 2). Median OS among 325 patients with wild-type *KRAS* mCRC who received Vectibix plus FOLFOX was 23.8 months

(95% CI: 20.0, 27.7) versus 19.4 months (95% CI: 17.4, 22.6) among 331 patients who received FOLFOX alone (HR = 0.83, 95% CI: 0.70, 0.98).

Figure 2: Kaplan-Meier Plot of Overall Survival in Patients with Wild-type *KRAS* mCRC (Study 3)



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, Dosage and Administration (2.3), Warnings and Precautions (5.1, 5.8), and Adverse Reactions (6.1, 6.3)]*
- Signs and symptoms of infusion reactions, including fever, chills, or breathing problems *[see Dosage and Administration (2.3), Warnings and Precautions (5.4), and Adverse Reactions (6.1, 6.3)]*
- Diarrhea and dehydration *[see Warnings and Precautions (5.5)]*
- Persistent or recurrent coughing, wheezing, dyspnea, or new-onset facial swelling *[see Warnings and Precautions (5.6) 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 (5.3)]*
- 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 (5.7)]*
- 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®

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Patent: http://pat.amgen.com/vectibix/

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