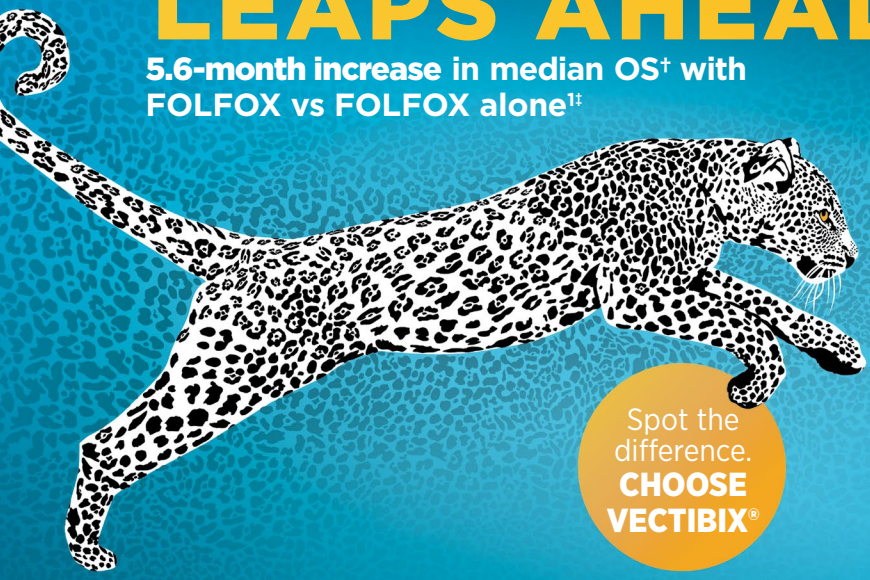
DOSING AND INFORMATION GUIDE

In patients with WT *RAS** mCRC[1]

VECTIBIX® (panitumumab)

LEAPS AHEAD

5.6-month increase in median OS† with FOLFOX vs FOLFOX alone[1‡]



Spot the difference. **CHOOSE VECTIBIX®**

‡PRIME (Vectibix® + FOLFOX vs FOLFOX alone): N = 1,183, randomized (1:1), phase 3, open-label, multicenter study of mCRC. In this post-hoc analysis, patients with WT *RAS* mCRC (n = 512) were evaluated.[1,2]

WT *RAS* mCRC (Vectibix® + FOLFOX (n = 259) vs FOLFOX (n = 253) alone)[1]:

- Median OS: 25.8 vs 20.2 months (HR = 0.77, 95% CI: 0.64–0.94)
- There were no OS or PFS benefits in Vectibix®-treated patients with *RAS* mutant mCRC

Indication

Vectibix® is indicated for the treatment of patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC):

- As first-line therapy in combination with FOLFOX.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

Limitation of Use

Vectibix® is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

Important Safety Information

BOXED 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.

*Defined as wild type in both *KRAS* and *NRAS*.[1]
†OS with updated information based on events in 82% of patients.[1]
CI = confidence interval; HR = hazard ratio; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression-free survival; PRIME = Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy; WT = wild type.

Please see full Important Safety Information, including **Boxed WARNING**, on pages 4 and 5.

Vectibix® (panitumumab)
100mg/5ml | 20mg/ml for injection

First and only FDA-approved option for WT *RAS* mCRC

Dosing and administration information for Vectibix®

Patient biomarker status and safety

Dosing & administration[1]

The recommended dose of Vectibix® is **6 mg/kg** every 14 days.[1]

No standardized premedication was required in clinical trials.[1] The utility of premedication in preventing infusional toxicity is unknown.[1]

No loading dose.[1]

Vectibix® is given by IV infusion over 60 minutes.[1]

If the first infusion is tolerated, subsequent infusions may be administered over 30 to 60 minutes.[1]

Doses of > 1,000 mg should be administered over 90 minutes.[1]

IV = intravenous.

Patient selection[1]

- Prior to initiation of treatment with Vectibix®, assess *RAS* mutational status in colorectal tumors and confirm the absence of a *RAS* mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of both *KRAS* and *NRAS*
- Information about FDA-approved tests for the detection of *RAS* mutations in patients with metastatic colorectal cancer is available at http://www.fda.gov/CompanionDiagnostics

Dermatologic toxicities[1]

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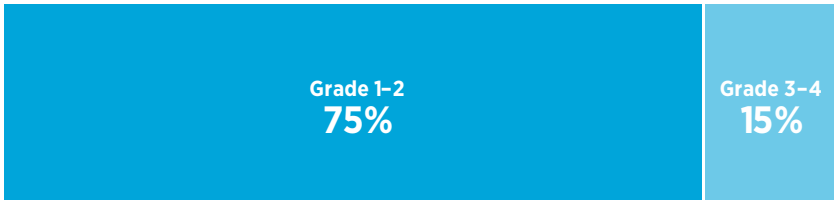

90% of patients experienced a dermatologic toxicity on Vectibix®[1]

Grades defined by NCI-CTC/CTCAE.
NCI-CTC/CTCAE = National Cancer Institute-Common Toxicity Criteria/Common Terminology Criteria for Adverse Events.

Dose Modifications for Infusion Reactions[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.
- 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[1]

- Upon first occurrence of a grade 3 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 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 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 dermatologic reaction, permanently discontinue Vectibix®.
- Permanently discontinue Vectibix® following the occurrence of a grade 4 dermatologic reaction or for a grade 3 dermatologic reaction that does not recover after withholding 1 or 2 doses.

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Vectibix® preparation

Prepare the solution for infusion, using aseptic technique, as follows[1]:

Do *not* administer Vectibix® as an intravenous push or bolus.[1]

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. Vectibix® solution is colorless and may contain a small amount of visible translucent-to-white, amorphous, proteinaceous particles. Do not use if the solution is discolored or cloudy, or if foreign matter is present.[1]

Use a 21-gauge or larger gauge (small bore) hypodermic needle to withdraw the necessary amount of Vectibix® for a dose of 6 mg/kg. Do not use needle-free devices (e.g., vial adapters) to withdraw vial contents.[1]

Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses of higher than 1,000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.[1]

Mix diluted solution by gentle inversion. Discard any unused portion of the vial.[1]

USP = United States Pharmacopeia.

Vectibix® administration

Vectibix® must be administered via infusion pump using a low-protein-binding 0.2 µm or 0.22 µm in-line filter[1]

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.[1]

Infuse doses of 1,000 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.[1]

- Administer doses of > 1,000 mg over 90 minutes[1]

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°C to 8°C (36°F to 46°F). DO NOT FREEZE.[1]

		400 mg	100 mg
Patient weight	76 kg		
Dose	6 mg/kg		
Dose calculation	6 mg/kg x 76 kg = 456 mg (22.8 mL)	(20 mL vial size)	(5 mL vial size)

Important Safety Information

- In Study 20020408, 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. Dose modifications for Vectibix® concerning dermatologic toxicity are provided in the product labeling.

Important Safety Information

- Vectibix® is not indicated for the treatment of patients with colorectal cancer that harbor somatic *RAS* mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either *KRAS* or *NRAS* and hereafter is referred to as "*RAS*."
- Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of *RAS* mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing *RAS* mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents. Additionally, in Study 20050203, 272 patients with *RAS*-mutant mCRC tumors received Vectibix® in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with *RAS*-mutant mCRC who received Vectibix® and FOLFOX versus FOLFOX alone.

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Important Safety Information

BOXED 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)].*

- In Study 20020408, 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. Dose modifications for Vectibix® concerning dermatologic toxicity are provided in the product labeling.
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- Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of *RAS* mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing *RAS* mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents. Additionally, in Study 20050203, 272 patients with *RAS*-mutant mCRC tumors received Vectibix® in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with *RAS*-mutant mCRC who received Vectibix® and FOLFOX versus FOLFOX alone.
- Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% (in Study 20080763) 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.

Important Safety Information continued on the next page.

Important Safety Information (cont'd)

Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

- In Study 20020408, 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. Fatal infusion reactions occurred in postmarketing experience. Terminate the infusion for severe infusion reactions.
- Severe diarrhea and dehydration, leading to acute renal failure and other complications, have been observed in patients treated with Vectibix® in combination with chemotherapy.
- 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.
- Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving Vectibix®.
- 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® for acute or worsening keratitis.
- 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.

Important Safety Information continued on the next page.

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Important Safety Information (cont'd)

- Vectibix® can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 months after the last dose of Vectibix®.
- In monotherapy, the most commonly reported adverse reactions (≥ 20%) in patients with Vectibix® were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.
- The most commonly reported adverse reactions (≥ 20%) with Vectibix® + FOLFOX were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin. The most common serious adverse reactions (≥ 2% difference between treatment arms) were diarrhea and dehydration.

Please see Vectibix® full Prescribing Information, including **Boxed WARNING**.

References: 1. Vectibix® (panitumumab) prescribing information, Amgen. **2.** Douillard J-Y, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4697-4705.

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