

**CENTER FOR DRUG EVALUATION AND
RESEARCH AND CENTER FOR BIOLOGICS
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

125147/0

APPROVED LABELING

Vectibix™ (panitumumab)**For Intravenous Use Only****WARNING**

Dermatologic Toxicity: Dermatologic toxicities, related to Vectibix™ blockade of EGF binding and subsequent inhibition of EGFR-mediated signaling pathways, were reported in 89% of patients and were severe (NCI-CTC grade 3 and higher) in 12% of patients receiving Vectibix™ monotherapy. The clinical manifestations included, but were not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. Severe dermatologic toxicities were complicated by infection including sepsis, septic death, and abscesses requiring incisions and drainage. Withhold or discontinue Vectibix™ and monitor for inflammatory or infectious sequelae in patients with severe dermatologic toxicities (see **WARNINGS: Dermatologic, Mucosal, and Ocular Toxicity; ADVERSE REACTIONS: Dermatologic, Mucosal, and Ocular Toxicity; and DOSAGE AND ADMINISTRATION: Dose Modifications, Dermatologic Toxicity**).

Infusion Reactions: Severe infusion reactions occurred with the administration of Vectibix™ in approximately 1% of patients. Severe infusion reactions were identified by reports of anaphylactic reaction, bronchospasm, fever, chills, and hypotension (see **WARNINGS: Infusion Reactions and ADVERSE REACTIONS: Infusion Reactions**). 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: Dose Modifications, Infusion Reactions**).

3

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.

9

Vectibix™ (panitumumab) 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.

17

18 CLINICAL PHARMACOLOGY

19 Mechanism of Action

20 The EGFR is a member of a subfamily of type I receptor tyrosine kinases, including EGFR
21 (HER1, c-ErbB-1), HER2/neu, HER3, and HER4. EGFR is a transmembrane glycoprotein that is
22 constitutively expressed in many normal epithelial tissues, including the skin and hair follicle.
23 Overexpression of EGFR is also detected in many human cancers, including those of the colon
24 and rectum. Interaction of EGFR with its normal ligands (eg, EGF, transforming growth factor-
25 alpha) leads to phosphorylation and activation of a series of intracellular tyrosine kinases, which
26 in turn regulate transcription of molecules involved with cellular growth and survival, motility,
27 proliferation, and transformation.

28
29 Panitumumab binds specifically to EGFR on both normal and tumor cells, and competitively
30 inhibits the binding of ligands for EGFR. Nonclinical studies show that binding of panitumumab
31 to the EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-
32 associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased pro-
33 inflammatory cytokine and vascular growth factor production, and internalization of the EGFR.
34 In vitro assays and in vivo animal studies demonstrate that panitumumab inhibits the growth and
35 survival of selected human tumor cell lines expressing EGFR.

37 Human Pharmacokinetics

38 Vectibix™ administered as a single agent exhibits nonlinear pharmacokinetics.

39
40 Following a single-dose administration of panitumumab as a 1-hour infusion, the area under the
41 concentration-time curve (AUC) increased in a greater than dose-proportional manner and
42 clearance (CL) of panitumumab decreased from 30.6 to 4.6 mL/day/kg as the dose increased
43 from 0.75 to 9 mg/kg. However, at doses above 2 mg/kg, the AUC of panitumumab increases in
44 an approximately dose-proportional manner.

45
46 Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour
47 infusion), panitumumab concentrations reached steady-state levels by the third infusion with
48 mean (\pm SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/mL, respectively.
49 The mean (\pm SD) $AUC_{0-\tau}$ and CL were 1306 ± 374 mcg·day/mL and 4.9 ± 1.4 mL/kg/day,
50 respectively. The elimination half-life was approximately 7.5 days (range: 3.6 to 10.9 days).

52 Special Populations

53 A population pharmacokinetic analysis was performed to explore the potential effects of selected
54 covariates on Vectibix™ pharmacokinetics. Results suggest that age (21–88 years), gender, race
55 (15% nonwhite), mild-to-moderate renal dysfunction, mild-to-moderate hepatic dysfunction, and
56 EGFR membrane-staining intensity (1+, 2+, 3+) in tumor cells had no apparent impact on the
57 pharmacokinetics of panitumumab.

58
59 No formal pharmacokinetic studies of panitumumab have been conducted in patients with renal
60 or hepatic impairment.

61
62 Vectibix™ has not been studied in pediatric patients.

63

64 **CLINICAL STUDIES**

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

80

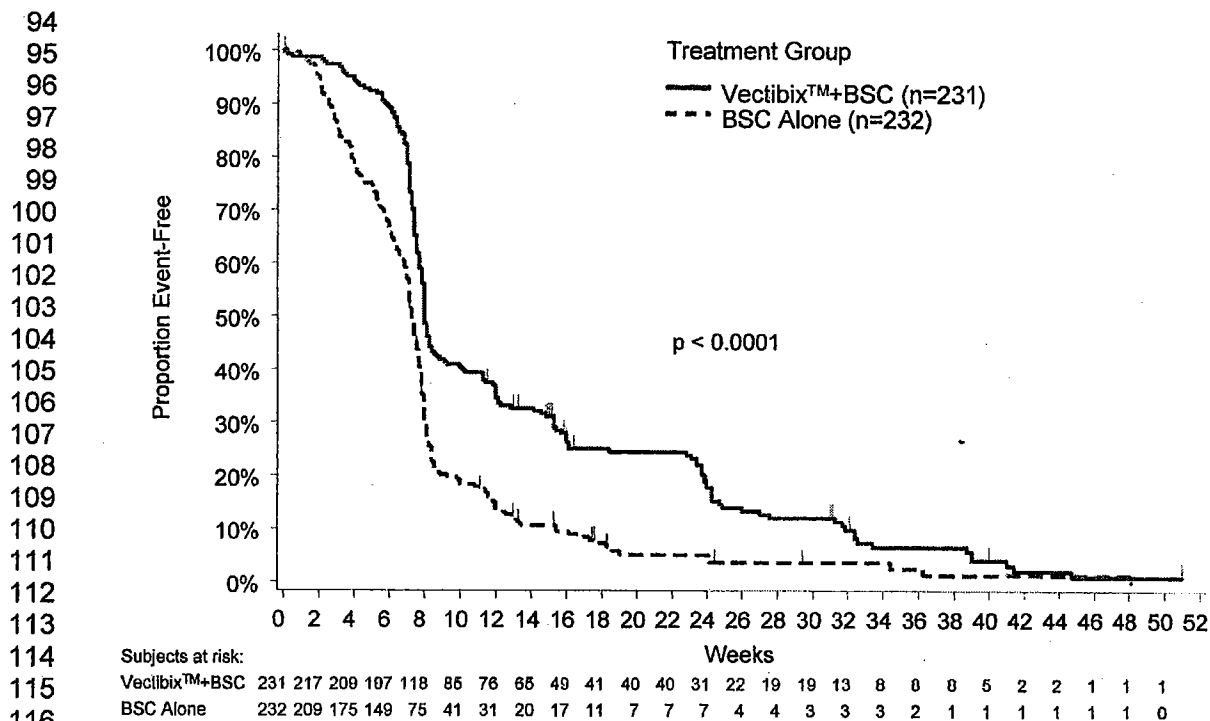
81 Among the 463 patients, 63% were male, the median age was 62 years, 40% were 65 years or
82 older, 99% were Caucasian, 86% had a baseline ECOG performance status of 0 or 1, and 67%
83 had colon cancer. The median number of prior therapies for metastatic disease was 2.4. The
84 membrane-staining intensity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

87

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

92

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



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

121
122 Of the 232 patients randomized to BSC alone, 75% of patients crossed over to receive
123 Vectibix™ following investigator determination of disease progression; the median time to cross
124 over was 8.4 weeks (0.3–26.4 weeks).

125
126 There were 19 partial responses identified by the IRC in patients randomized to Vectibix™ for
127 an overall response of 8% (95% CI: 5.0%, 12.6%). No patient in the control arm had an objective
128 response identified by the IRC. The median duration of response was 17 weeks (95% CI: 16
129 weeks, 25 weeks). There was no difference in overall survival observed between the study arms.

131 **EGFR Expression and Response**

132 Patients enrolled in the colorectal cancer clinical studies were required to have
133 immunohistochemical evidence of EGFR expression; these are the only patients studied and for
134 whom benefit has been shown (see **INDICATIONS AND USAGE** and **PRECAUTIONS: EGF**
135 **Receptor Testing**). EGFR tumor expression was determined using the Dako EGFR pharmDx®
136 test kit. Specimens were scored based on the percentage of cells expressing EGFR and staining
137 intensity (3+, 2+, and 1+). Exploratory univariate analyses assessing the relationship between
138 EGFR expression and PFS did not suggest that the PFS benefit differed as a function of EGFR
139 staining intensity or percentage of EGFR-expressing tumor cells.

140

141 INDICATIONS AND USAGE

142 Vectibix™ is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma
143 with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-
144 containing chemotherapy regimens.

145
146 The effectiveness of Vectibix™ for the treatment of EGFR-expressing, metastatic colorectal
147 carcinoma is based on progression-free survival (see **CLINICAL STUDIES**). Currently no data
148 are available that demonstrate an improvement in disease-related symptoms or increased survival
149 with Vectibix™.

150

151 CONTRAINDICATIONS

152 None known.

153

154 WARNINGS

155 Dermatologic, Mucosal, and Ocular Toxicity

156 Weekly administration of panitumumab to cynomolgus monkeys for 4 to 26 weeks resulted in
157 dermatologic findings, including dermatitis, pustule formation and exfoliative rash, and deaths
158 secondary to bacterial infection and sepsis at doses of 1.25 to 5-fold higher (on a mg/kg basis)
159 than the recommended human dose.

160

161 In the randomized, controlled clinical trial of Vectibix™, dermatologic toxicities, related to
162 Vectibix™ blockade of EGF binding and subsequent inhibition of EGFR-mediated signaling
163 pathways, were reported in 90% of patients and were severe (NCI-CTC grade 3 and higher) in
164 16% of patients with mCRC receiving Vectibix™. The clinical manifestations included, but were
165 not limited, to dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry
166 skin, and skin fissures. Subsequent to the development of severe dermatologic toxicities,
167 infectious complications, including sepsis, septic death, and abscesses requiring incisions and
168 drainage were reported. Toxicity involving gastrointestinal mucosa, the eye, and nail was also
169 reported (see **BOXED WARNING: Dermatologic Toxicity; ADVERSE REACTIONS:**
170 **Dermatologic, Mucosal, and Ocular Toxicity; and DOSAGE AND ADMINISTRATION:**
171 **Dose Modifications, *Dermatologic Toxicity***).

172

173 Infusion Reactions

174 In the randomized, controlled clinical trial of Vectibix™, 4% of patients experienced infusion
175 reactions, and in 1% reactions were graded as severe (NCI-CTC grade 3–4).

176 Across all clinical studies, severe infusion reactions occurred with the administration of
177 Vectibix™ in approximately 1% of patients. Severe infusion reactions were identified by reports
178 of anaphylactic reaction, bronchospasm, fever, chills, and hypotension (see **BOXED**
179 **WARNING: Infusion Reactions and ADVERSE REACTIONS: Infusion Reactions**).
180 Although fatal infusion reactions have not been reported with Vectibix™, fatalities have
181 occurred with other monoclonal antibody products. Stop infusion if a severe infusion reaction
182 occurs. Depending on the severity and/or persistence of the reaction, permanently discontinue

183 Vectibix™ (see **DOSAGE AND ADMINISTRATION: Dose Modifications, Infusion**
184 **Reactions**).

185

186 **Pulmonary Fibrosis**

187 Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of
188 Vectibix™. Of these two cases, one, occurring in a patient with underlying idiopathic pulmonary
189 fibrosis who received Vectibix™ in combination with chemotherapy, resulted in death from
190 worsening pulmonary fibrosis after four doses of panitumumab. The second case was
191 characterized by cough and wheezing 8 days following the initial dose, exertional dyspnea on the
192 day of the 7th-dose, and persistent symptoms and CT evidence of pulmonary fibrosis following
193 the 11th dose of panitumumab as monotherapy. An additional patient died with bilateral
194 pulmonary infiltrates of uncertain etiology with hypoxia, after 23 doses of Vectibix™ in
195 combination with chemotherapy. Following the initial fatality, patients with a history of
196 interstitial pneumonitis, pulmonary fibrosis, evidence of interstitial pneumonitis, or pulmonary
197 fibrosis were excluded from clinical studies. Therefore, the estimated risk in a general population
198 that may include such patients is uncertain. Permanently discontinue Vectibix™ therapy in
199 patients developing interstitial lung disease, pneumonitis, or lung infiltrates.

200

201

202 **Diarrhea**

203 Vectibix™ treatment can cause diarrhea (see **ADVERSE REACTIONS: Table 1**), and when
204 used in combination with irinotecan, appears to increase the incidence and severity of
205 chemotherapy-induced diarrhea. In a study of 19 patients receiving panitumumab in combination
206 with irinotecan, bolus 5-fluorouracil, and leucovorin (IFL), the incidence of NCI-CTC grade 3–4
207 diarrhea was 58% and was fatal in one patient. In a study of 24 patients receiving Vectibix™
208 plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhea was 25%.

209

210 The combination of Vectibix™ with IFL is not recommended.

211

212 **Electrolyte Depletion**

213 In the randomized, controlled clinical trial of Vectibix™, median magnesium levels decreased by
214 0.1 mmol/L in the panitumumab arm; hypomagnesemia (NCI-CTC grade 3 or 4) requiring oral
215 or IV electrolyte repletion occurred in 2% of patients. Hypomagnesemia occurred 6 weeks or
216 longer after the initiation of Vectibix™. In some patients hypomagnesemia was associated with
217 hypocalcemia. Patients' electrolytes should be periodically monitored during and for 8 weeks
218 after the completion of Vectibix™ therapy (see **PRECAUTIONS: Laboratory Tests:**
219 **Electrolyte Monitoring**).

220

221 **PRECAUTIONS**

222 **Photosensitivity**

223 It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving
224 Vectibix™ since sunlight can exacerbate any skin reactions that may occur.

225

226 EGF Receptor Testing

227 Detection of EGFR protein expression is necessary for selection of patients appropriate for
228 Vectibix™ therapy because these are the only patients studied and for whom benefit has been
229 shown (see **INDICATIONS AND USAGE** and **CLINICAL STUDIES: EGFR Expression**
230 **and Response**). Patients enrolled in the colorectal cancer clinical studies were required to have
231 immunohistochemical evidence of EGFR expression using the Dako EGFR pharmDx® test kit.
232 Assessment for EGFR expression should be performed by laboratories with demonstrated
233 proficiency in the specific technology being utilized. Improper assay performance, including use
234 of suboptimally fixed tissue, failure to utilize specific reagents, deviation from specific assay
235 instructions, and failure to include appropriate controls for assay validation, can lead to
236 unreliable results. [Refer to the package insert for the Dako EGFR pharmDx® test kit, or other
237 test kits approved by FDA, for identification of patients eligible for treatment with Vectibix™
238 and for full instructions on assay performance.]
239

240 Laboratory Tests: Electrolyte Monitoring

241 Patients should be periodically monitored for hypomagnesemia, and accompanying
242 hypocalcemia, during and for 8 weeks after the completion of Vectibix™ therapy. Institute
243 appropriate treatment, eg, oral or IV electrolyte repletion, as needed (see **WARNINGS:**
244 **Electrolyte Depletion**).
245

246 Information for Patients

247 Patients must be informed of the possible adverse effects of Vectibix™, including dermatologic
248 toxicity, infusion reactions, pulmonary fibrosis, and potential embryofetal lethality. Instruct
249 patients to report skin and ocular changes, and dyspnea to a healthcare professional. Advise
250 patients that periodic monitoring of electrolyte levels is required (see **BOXED WARNING;**
251 **WARNINGS; ADVERSE REACTIONS; PRECAUTIONS: Carcinogenesis, Mutagenesis,**
252 **and Impairment of Fertility; and PRECAUTIONS: Pregnancy Category C**).
253

254 Drug Interactions

255 No formal drug-drug interaction studies have been conducted with Vectibix™.
256

257 Carcinogenesis, Mutagenesis, and Impairment of Fertility

258 **Carcinogenesis:** No carcinogenicity data for panitumumab are available in animals or humans.
259

260 **Mutagenesis:** The mutagenic potential of panitumumab has not been evaluated in vitro or in
261 vivo.
262

263 **Impairment of Fertility:** Vectibix™ may impair fertility in women of childbearing potential.
264 Prolonged menstrual cycles and/or amenorrhea were observed in normally cycling, female
265 cynomolgus monkeys following weekly doses of panitumumab of 1.25 to 5-fold greater than the
266 recommended human dose (based on body weight). Menstrual cycle irregularities in
267 panitumumab-treated, female cynomolgus monkeys were accompanied by both a decrease and
268 delay in peak progesterone and 17β-estradiol levels. Normal menstrual cycling resumed in most
269 animals after discontinuation of panitumumab treatment. A no-effect level for menstrual cycle
270 irregularities and serum hormone levels was not identified.

271
272 The effects of Vectibix™ on male fertility have not been studied. However, no adverse effects
273 were observed microscopically in reproductive organs from male cynomolgus monkeys treated
274 for 26 weeks with panitumumab at doses of up to approximately 5-fold the recommended human
275 dose (based on body weight).
276

277 **Pregnancy Category C**

278 There are no adequate and well-controlled studies in pregnant women. However, EGFR has been
279 implicated in the control of prenatal development and may be essential for normal
280 organogenesis, proliferation, and differentiation in the developing embryo. Vectibix™ treatment
281 was associated with significant increases in embryo-lethal or abortifacient effects in pregnant
282 cynomolgus monkeys when administered weekly during the period of organogenesis (gestation
283 day [GD] 20–50), at doses approximately 1.25 to 5-fold greater than the recommended human
284 dose (by body weight). There were no fetal malformations or other evidence of teratogenesis
285 noted in the offspring. While no panitumumab was detected in serum of neonates from
286 panitumumab-treated dams, anti-panitumumab antibody titers were present in 14 of 27 offspring
287 delivered at GD 100. Therefore, while no teratogenic effects were observed in panitumumab-
288 treated monkeys, panitumumab has the potential to cause fetal harm when administered to
289 pregnant women.

290
291 Human IgG is known to cross the placental barrier; therefore, Vectibix™ may be transmitted
292 from the mother to the developing fetus. In women of childbearing potential, appropriate
293 contraceptive measures must be used during treatment with Vectibix™ and for 6 months
294 following the last dose of Vectibix™. If Vectibix™ is used during pregnancy or if the patient
295 becomes pregnant while receiving this drug, she should be apprised of the potential risk for loss
296 of the pregnancy or potential hazard to the fetus.
297

298 **Nursing Mothers**

299 Studies have not been conducted to assess the secretion of Vectibix™ in human milk. Because
300 human IgG is secreted into human milk, panitumumab might also be secreted. The potential for
301 absorption and harm to the infant after ingestion is unknown. Women must be advised to
302 discontinue nursing during treatment with Vectibix™ and for 2 months after the last dose of
303 Vectibix™.
304

305 **Pediatric Use**

306 The safety and effectiveness of Vectibix™ have not been established in pediatric patients.
307

308 **Geriatric Use**

309 Of 229 patients with mCRC who received Vectibix™ in the randomized, controlled study, 96
310 (42%) were ≥ age 65. Although the clinical study did not include a sufficient number of geriatric
311 patients to determine whether they respond differently from younger patients, there were no
312 apparent differences in safety and effectiveness of Vectibix™ between these patients and
313 younger patients.
314

315 ADVERSE REACTIONS

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

321

322 Safety data are available from 15 clinical trials in which 1467 patients received Vectibix™; of
323 these, 1293 received Vectibix™ monotherapy and 174 received Vectibix™ in combination with
324 chemotherapy. The most common adverse events observed in clinical studies of Vectibix™ (n =
325 1467) were skin rash with variable presentations, hypomagnesemia, paronychia, fatigue,
326 abdominal pain, nausea, and diarrhea. The most serious adverse events observed were pulmonary
327 fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death,
328 infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.
329 Adverse events requiring discontinuation of Vectibix™ were infusion reactions, severe skin
330 toxicity, paronychia, and pulmonary fibrosis.

331

332 The data described in Table 1 and in other sections below, except where noted, reflect exposure
333 to Vectibix™ administered as a single agent at the recommended dose and schedule (6.0 mg/kg
334 every 2 weeks) in 229 patients with mCRC in the randomized, controlled trial. The median
335 number of doses was five (range one to 26 doses), and 71% of patients received eight or fewer
336 doses. The population had a median age of 62 years (range: 27 to 82 years); 63% were male; and
337 99% were white with < 1% black, < 1% Hispanic, and 0% other.

338 **Table 1. Per-Patient Incidence of Adverse Events Occurring in $\geq 5\%$ of Patients with a Between**
 339 **Group Difference of $\geq 5\%$**

Body System	Patients Treated With Vectibix™ Plus BSC (n = 229)		BSC Alone (n = 234)	
	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				
Peripheral Edema	12	1	6	< 1
Hypomagnesemia (Lab)	39	4	2	0
Respiratory				
Cough	14	< 1	7	0
Skin/Appendages				
All Skin/Integument Toxicity	90	16	9	0
Skin	90	14	6	0
Erythema	65	5	1	0
Acneiform Dermatitis	57	7	1	0
Pruritus	57	2	2	0
Skin Exfoliation	25	2	0	0
Rash	22	1	1	0
Skin Fissures	20	1	< 1	0
Dry Skin	10	0	0	0
Acne	13	1	0	0
Nail	29	2	0	0
Paronychia	25	2	0	0
Other Nail Disorder	9	0	0	0
Hair	9	0	1	0
Growth of Eyelashes	6	0	0	0
Eye	15	< 1	2	0

*Version 2.0 of the NCI-CTC was used for grading toxicities. Skin toxicity coded based on a modification of the NCI-CTCAE, version 3.0.

340

341 **Dermatologic, Mucosal, and Ocular Toxicity**

342 In the randomized, controlled clinical trial, skin-related toxicities were reported in 90% of
 343 patients receiving Vectibix™. Skin toxicity was severe (NCI-CTC grade 3 and higher) in 16% of
 344 patients. Eye-related toxicities occurred in 15% of patients and included, but were not limited to:

345 conjunctivitis (4%), ocular hyperemia (3%), increased lacrimation (2%), and eye/eyelid irritation
346 (1%). Stomatitis (7%) and oral mucositis (6%) were reported. One patient experienced a NCI-
347 CTC grade 3 event of mucosal inflammation. The incidence of paronychia was 25% and was
348 severe in 2% of patients. Other nail disorders were observed in 9% of patients (see
349 **WARNINGS: Dermatologic, Mucosal, and Ocular Toxicity**).

350
351 Median time to the development of skin/eye-related toxicity was 14 days; the time to most severe
352 skin/eye-related toxicity was 15 days after the first dose of Vectibix™; and the median time to
353 resolution after the last dose of Vectibix™ was 84 days. Subsequent to the development of
354 severe dermatologic toxicities, infectious complications, including sepsis, septic death, and
355 abscesses requiring incisions and drainage, were reported. Severe toxicity necessitated dose
356 interruption in 11% of Vectibix™-treated patients (see **DOSAGE AND ADMINISTRATION:**
357 **Dose Modifications, Dermatologic Toxicity**).

358

359 **Infusion Reactions**

360 Infusional toxicity was defined as any event described at any time during the clinical study as
361 allergic reaction or anaphylactoid reaction, or any event occurring on the first day of dosing
362 described as allergic reaction, anaphylactoid reaction, fever, chills, or dyspnea. Vital signs and
363 temperature were measured within 30 minutes prior to initiation and upon completion of the
364 Vectibix™ infusion. The use of premedication was not standardized in the clinical trials. Thus,
365 the utility of premedication in preventing the first or subsequent episodes of infusional toxicity is
366 unknown. Of all Vectibix™-treated patients, excluding those treated with Vectibix™ in
367 combination with carboplatin and paclitaxel, 3% (43/1336) experienced infusion reactions of
368 which approximately 1% (6/1336) were severe (NCI-CTC grade 3–4). In one patient,
369 Vectibix™ was permanently discontinued for a serious infusion reaction (see **DOSAGE AND**
370 **ADMINISTRATION: Dose Modifications, Infusion Reactions**).

371

372 **Immunogenicity**

373 As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of
374 Vectibix™ has been evaluated using two different screening immunoassays for the detection of
375 anti-panitumumab antibodies: an acid dissociation bridging enzyme linked immunosorbent assay
376 (ELISA) (detecting high-affinity antibodies) and a Biacore® biosensor immunoassay (detecting
377 both high- and low-affinity antibodies). The incidence of binding antibodies to panitumumab
378 (excluding predose and transient positive patients), as detected by the acid dissociation ELISA,
379 was 2/612 (< 1%) and as detected by the Biacore® assay was 25/610 (4.1%).

380

381 For patients whose sera tested positive in screening immunoassays, an in vitro biological assay
382 was performed to detect neutralizing antibodies. Excluding predose and transient positive
383 patients, eight of the 604 patients (1.3%) with postdose samples and 1/350 (< 1%) of the patients
384 with follow-up samples tested positive for neutralizing antibodies.

385

386 There was no evidence of altered pharmacokinetic profile or toxicity profile between patients
387 who developed antibodies to panitumumab as detected by screening immunoassays and those
388 who did not.

389

390 The detection of antibody formation is dependent on the sensitivity and specificity of the assay.
391 The observed incidence of antibody positivity in an assay may be influenced by factors such as
392 sample handling, concomitant medications, and underlying disease. For these reasons,
393 comparison of antibodies to panitumumab with the incidence of antibodies to other products may
394 be misleading.
395

396 OVERDOSAGE

397 The highest per-infusion dose administered in clinical studies was 9 mg/kg administered every 3
398 weeks. There is no experience with overdosage in human clinical trials.
399

400 DOSAGE AND ADMINISTRATION

401 The recommended dose of Vectibix™ is 6 mg/kg administered over 60 minutes as an
402 intravenous infusion every 14 days. Doses higher than 1000 mg should be administered over 90
403 minutes (see **DOSAGE AND ADMINISTRATION: Preparation and Administration**).
404

405 Appropriate medical resources for the treatment of severe infusion reactions should be available
406 during Vectibix™ infusions.
407

408 Dose Modifications

409 Infusion Reactions

410 (see **ADVERSE REACTIONS: Infusion Reactions**)

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

415

416 Dermatologic Toxicity

417 (see **ADVERSE REACTIONS: Dermatologic, Mucosal, and Ocular Toxicity**)

- 418 • Withhold Vectibix™ for dermatologic toxicities that are grade 3 or higher or are
419 considered intolerable. If toxicity does not improve to \leq grade 2 within 1 month,
420 permanently discontinue Vectibix™.
- 421 • If dermatologic toxicity improves to \leq grade 2, and the patient is symptomatically
422 improved after withholding no more than two doses of Vectibix™, treatment may be
423 resumed at 50% of the original dose.
 - 424 ○ If toxicities recur, permanently discontinue Vectibix™.
 - 425 ○ If toxicities do not recur, subsequent doses of Vectibix™ may be increased by
426 increments of 25% of the original dose until the recommended dose of 6 mg/kg is
427 reached.

428

429 Preparation and Administration

430 Do not administer Vectibix™ as an IV push or bolus. Vectibix™ must be administered by an IV
431 infusion pump using a low-protein-binding 0.2 µm or 0.22 µm in-line filter.

432

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

- 434 • Parenteral drug products should be inspected visually for particulate matter and
435 discoloration prior to administration whenever solution and container permit. Although
436 Vectibix™ should be colorless, the solution may contain a small amount of visible
437 translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be
438 removed by filtration; see below). Do not shake. Vectibix™ should not be administered if
439 discoloration is observed.
- 440 • Withdraw the necessary amount of Vectibix™ for a dose of 6 mg/kg.
- 441 • Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses
442 higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection,
443 USP. Final concentration should not exceed 10 mg/mL.
- 444 • Mix diluted solution by gentle inversion. Do not shake.
- 445 • Administer using a low-protein-binding 0.2 µm or 0.22 µm in-line filter.
- 446 • Vectibix™ must be administered via infusion pump.
 - 447 ○ Flush line before and after Vectibix™ administration with 0.9% sodium chloride
448 injection, USP, to avoid mixing with other drug products or IV solutions.
449 Vectibix™ should not be mixed with, or administered as an infusion, with other
450 medicinal products. No other medications should be added to solutions
451 containing panitumumab.
 - 452 ○ Infuse over 60 minutes through a peripheral line or indwelling catheter. Doses
453 higher than 1000 mg should be infused over 90 minutes.

454

455 Stability and Storage

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

459

460 The diluted infusion solution of Vectibix™ should be used within 6 hours of preparation if
461 stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F).
462 DO NOT FREEZE.

463

464 HOW SUPPLIED

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

467

468 Vectibix™ (panitumumab) is provided as one vial per carton.

469

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

472
473 Each 10 mL single-use vial contains 200 mg of panitumumab (20 mg/mL)
474 (NDC 55513-955-01).

475
476 Each 20 mL single-use vial contains 400 mg of panitumumab (20 mg/mL)
477 (NDC 55513-956-01).

478
479 **Rx Only**

480
481 This product, its production, and/or its use may be covered by one or more US Patents, including
482 US Patent No. 6,235,883, as well as other patents or patents pending.

483
484 **AMGEN®**
485

486 **Manufactured by:**
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491
492 3XXXXXXX-v1
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