approved 9-27-2006

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***).

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™ (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.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

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 pro-inflammatory 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.

Human Pharmacokinetics

Vectibix™ administered as a single agent exhibits nonlinear pharmacokinetics.

Following a single-dose administration of panitumumab as a 1-hour infusion, 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 increases 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).

Special Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on Vectibix™ 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+, 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.

Vectibix™ has not been studied in pediatric patients.

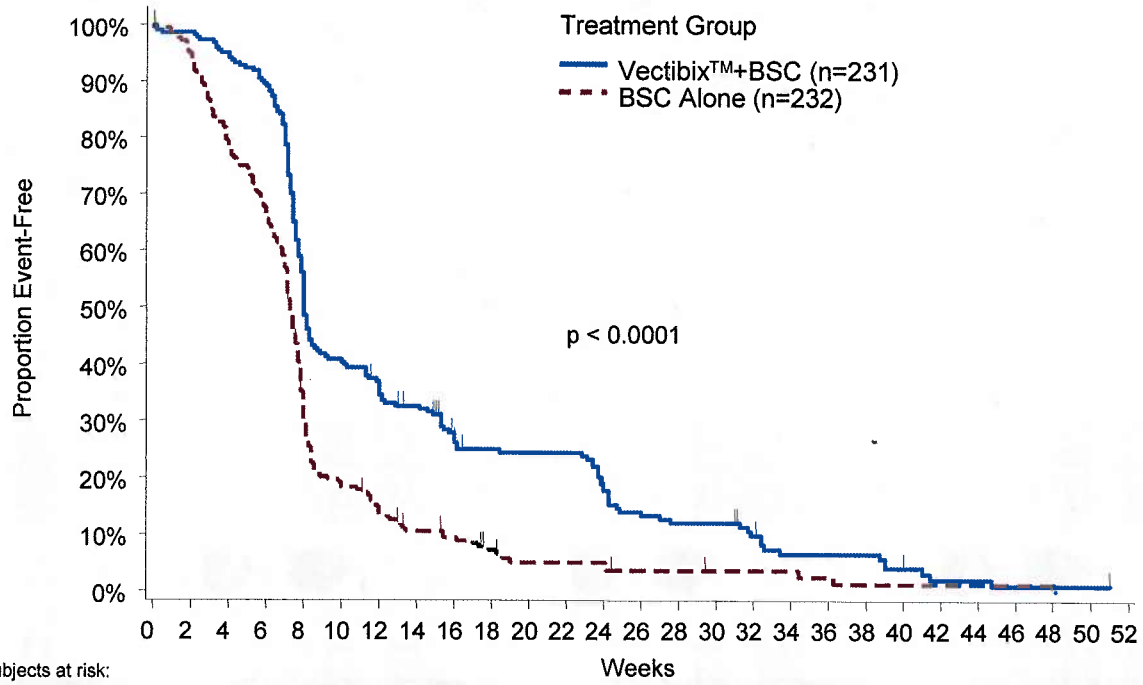
CLINICAL STUDIES

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

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

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

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



Subjects at risk:																									
Vectibix™+BSC	231	217	209	197	118	86	76	65	49	41	40	40	31	22	19	19	13	8	8	8	5	2	2	1	1	1
BSC Alone	232	209	175	149	75	41	31	20	17	11	7	7	7	4	4	3	3	3	2	1	1	1	1	1	1	0

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

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

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

EGFR Expression and Response

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None known.

WARNINGS

Dermatologic, Mucosal, and Ocular Toxicity

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 (on a mg/kg basis) than the recommended human dose.

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

Infusion Reactions

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

Across all clinical studies, severe infusion reactions occurred with the administration of Vectibix™ in approximately 1% of patients. Severe infusion reactions were identified by reports of anaphylactic reaction, bronchospasm, fever, chills, and hypotension (see **BOXED WARNING: 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***).

Pulmonary Fibrosis

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

Diarrhea

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

The combination of Vectibix™ with IFL is not recommended.

Electrolyte Depletion

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

PRECAUTIONS

Photosensitivity

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

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.

The effects of Vectibix™ 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).

Pregnancy Category C

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

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

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

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

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

	Patients Treated With Vectibix™ Plus BSC (n = 229)		BSC Alone (n = 234)	
	Grade*			
Body System	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Body as a Whole				
Fatigue	26	4	15	3
General Deterioration	11	8	4	3
Digestive				
Abdominal Pain	25	7	17	5
Nausea	23	1	16	< 1
Diarrhea	21	2	11	0
Constipation	21	3	9	1
Vomiting	19	2	12	1
Stomatitis	7	0	1	0
Mucosal Inflammation	6	< 1	1	0
Metabolic/Nutritional				
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:

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

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

Infusion Reactions

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

Immunogenicity

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

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

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

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 ≤ grade 2 within 1 month,
420 permanently discontinue Vectibix™.
421 • If dermatologic toxicity improves to ≤ 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

Preparation and Administration

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

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 whenever solution and container permit. 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. Vectibix™ should not be administered 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. Final concentration should not exceed 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Administer using a low-protein-binding 0.2 μm or 0.22 μm in-line filter.
- 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 IV solutions. Vectibix™ should not be mixed with, or administered as an infusion, with other medicinal products. No other medications should be added to solutions containing panitumumab.
    - Infuse over 60 minutes through a peripheral line or indwelling catheter. Doses higher than 1000 mg should be infused over 90 minutes.

Stability and Storage

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.

HOW SUPPLIED

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

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

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

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

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

Rx Only

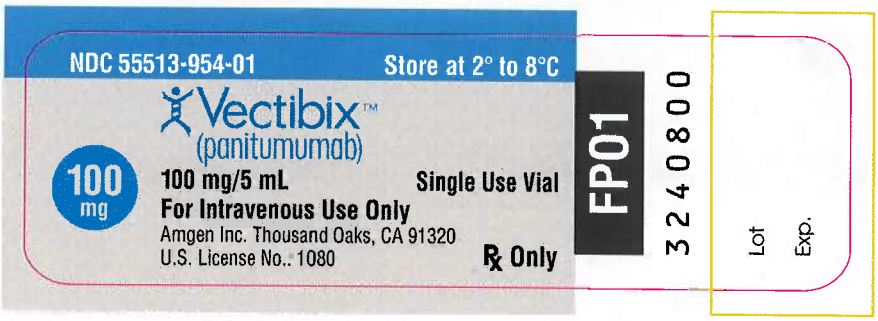
This product, its production, and/or its use may be covered by one or more US Patents, including US Patent No. 6,235,883, as well as other patents or patents pending.

AMGEN®

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
USA

3XXXXXX-v1
Issue Date: 09/28/2006

approved 9-27-2006



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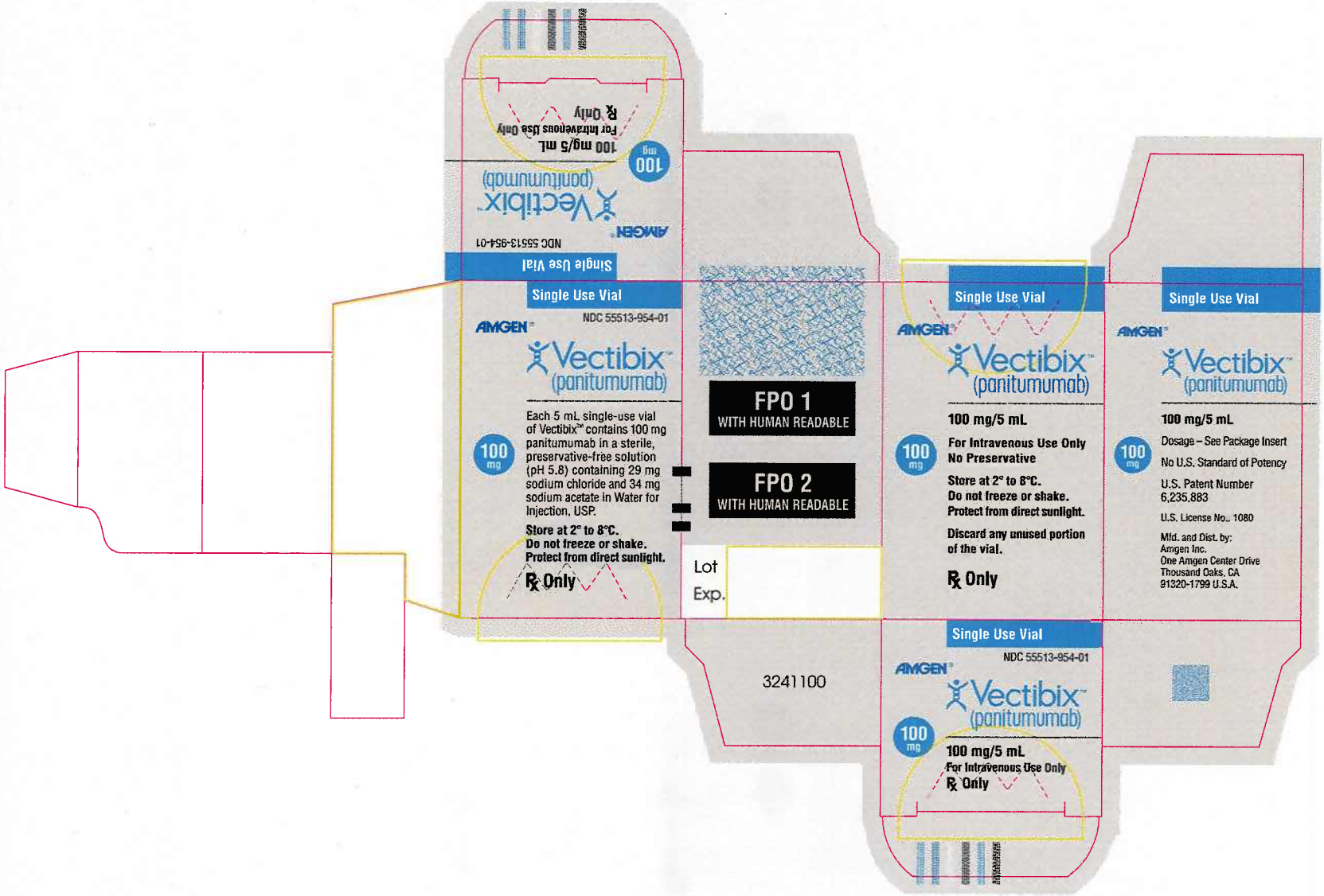
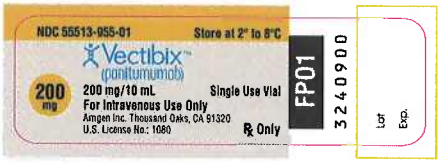
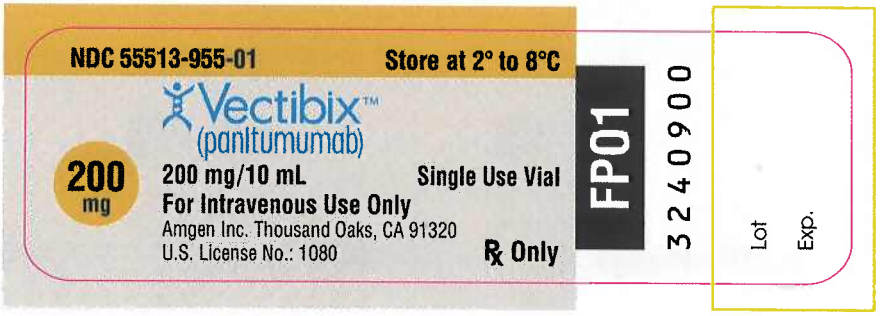

Single Use Vial
NDC 55513-954-01
AMGEN
Vectibix™
(panitumumab)
100 mg
Each 5 mL single-use vial of Vectibix™ contains 100 mg panitumumab in a sterile, preservative-free solution (pH 5.8) containing 29 mg sodium chloride and 34 mg sodium acetate in Water for Injection, USP.
Store at 2° to 8°C.
Do not freeze or shake.
Protect from direct sunlight.
℞ Only
FPO 1
WITH HUMAN READABLE
FPO 2
WITH HUMAN READABLE
Lot
Exp.
3241100
100 mg/5 mL
For Intravenous Use Only
No Preservative
Store at 2° to 8°C.
Do not freeze or shake.
Protect from direct sunlight.
Discard any unused portion of the vial.
Dosage – See Package Insert
No U.S. Standard of Potency
U.S. Patent Number 6,235,883
U.S. License No.. 1080
Mfd. and Dist. by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA
91320-1799 U.S.A.


NDC 55513-955-01
Store at 2° to 8°C
Vectibix™
(panitumumab)
200 mg
200 mg/10 mL
Single Use Vial
For Intravenous Use Only
Amgen Inc. Thousand Oaks, CA 91320
U.S. License No.: 1080
℞ Only
FP01
3240900
Lot
Exp.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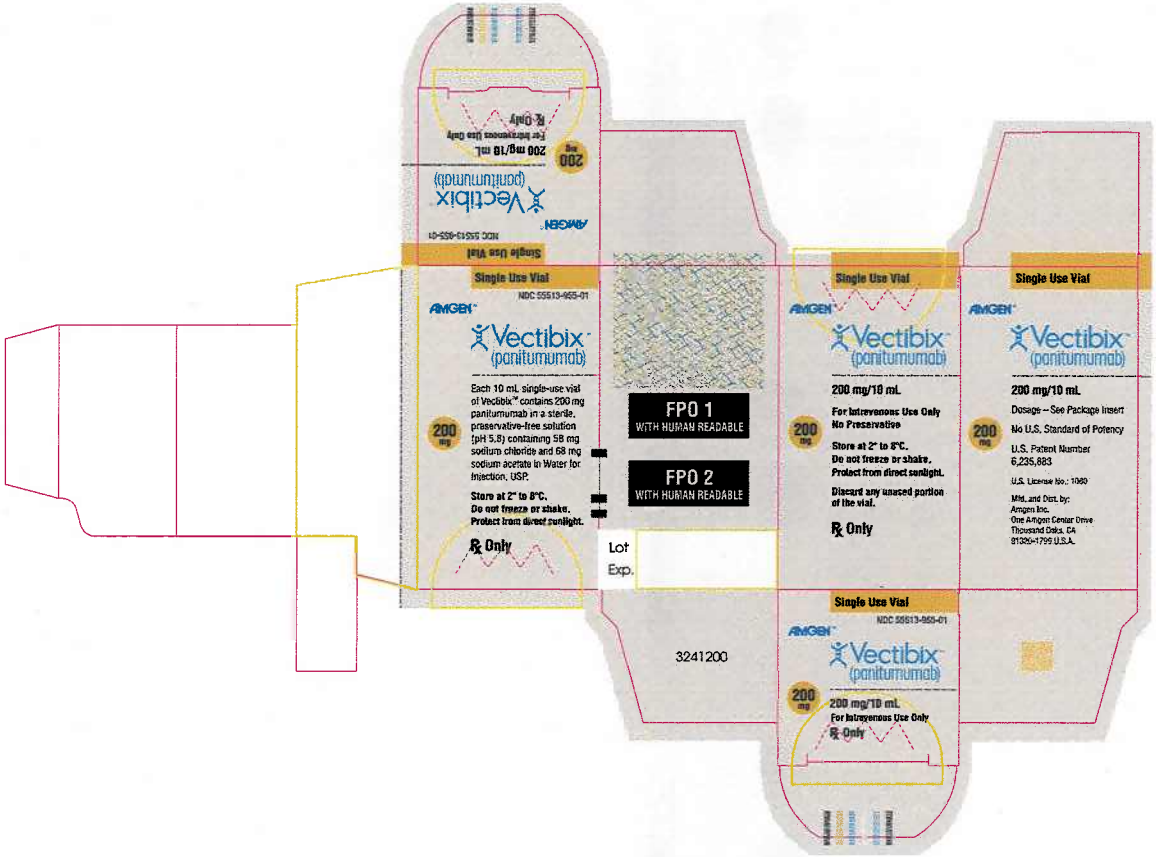

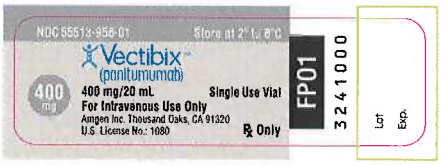
NDC 55513-956-01
Store at 2° to 8°C
Vectibix™
(panitumumab)
400 mg
400 mg/20 mL
Single Use Vial
For Intravenous Use Only
Amgen Inc. Thousand Oaks, CA 91320
U.S. License No.: 1080
℞ Only
FP01
3241000
Lot
Exp.

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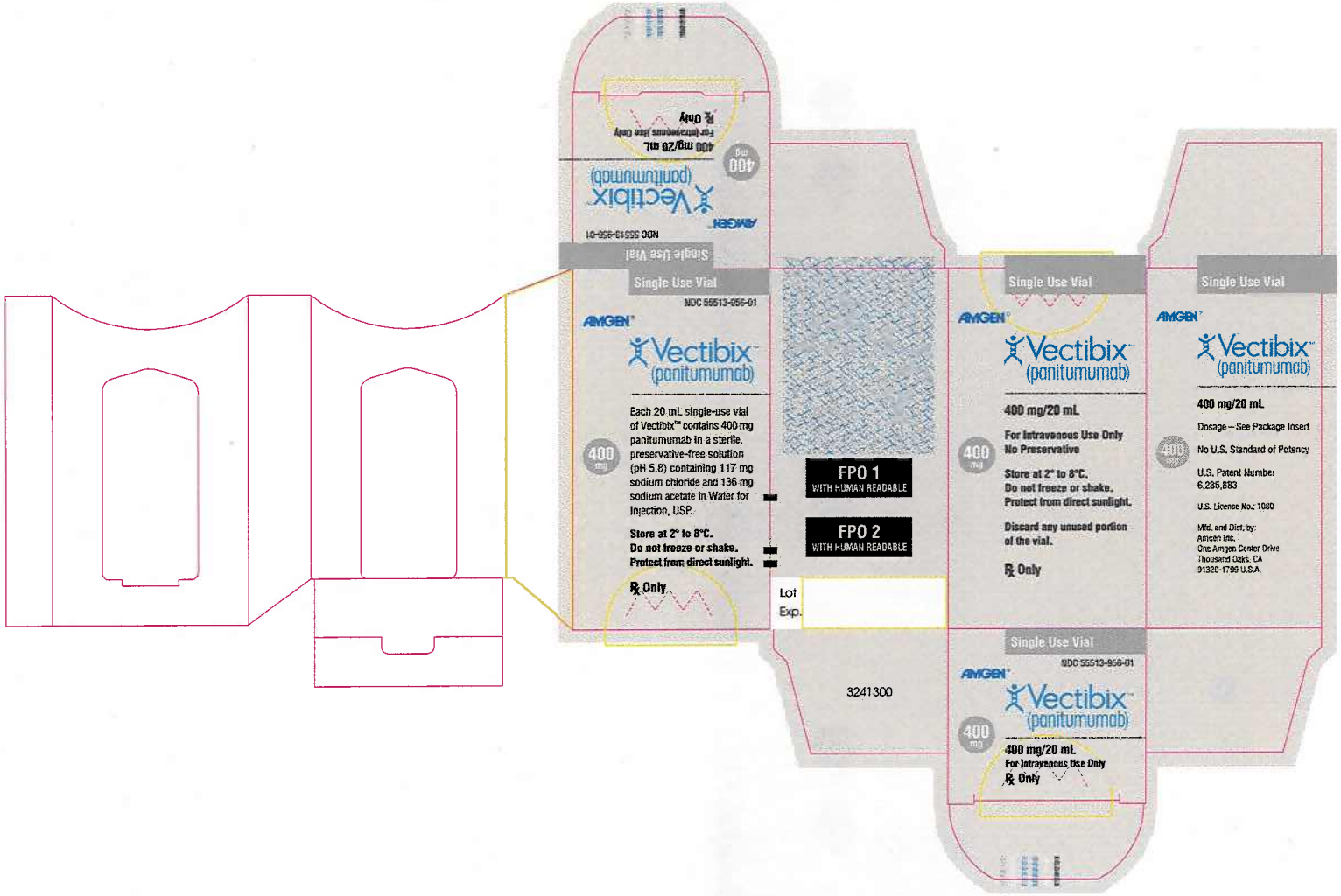
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