
NAME OF THE MEDICINE

Vectibix® is the Amgen Inc. trademark for panitumumab (rch).

DESCRIPTION

Panitumumab is presented as a concentrate for solution for infusion, supplied in a single-use Type 1 glass vial with elastomeric rubber stopper and aluminium seal with flip-off plastic cap.

Panitumumab is a fully human IgG2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Panitumumab is produced using recombinant DNA technology in genetically engineered mammalian (CHO) cells. It consists of 2 gamma heavy chains and 2 kappa light chains, and has a molecular weight of approximately 147 kilodaltons.

Vectibix is a sterile, colourless solution for intravenous (IV) infusion, which may contain visible translucent to white, amorphous, proteinaceous panitumumab particles. Vectibix is formulated with panitumumab at a concentration of 20 mg/mL in a preservative-free solution containing 50 mM sodium acetate, 100 mM sodium chloride, and Water for Injections.

PHARMACOLOGY

Mechanism of Action

Panitumumab binds with high affinity to the ligand binding domain of human EGFR and competitively inhibits receptor autophosphorylation induced by EGFR ligands (EGF, transforming growth factor-alpha, betacellulin, HB-EGF, epiregulin, and amphiregulin). EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1/c-ErbB-1), HER2, HER3, and HER4. EGFR promotes cell proliferation in 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. Binding of panitumumab to EGFR results in the internalisation of the receptor, inhibition of cell proliferation, and decreased interleukin 8 and vascular endothelial growth factor production.

In vitro assays and in vivo animal studies have shown that panitumumab inhibits the proliferation of some tumour cells expressing EGFR. No anti-tumour effects of panitumumab were observed in human tumour xenografts lacking EGFR expression.

The Kirsten rat sarcoma 2 viral oncogene homologue (*KRAS*) gene encodes a small, GTP-binding protein involved in signal transduction. A variety of stimuli, including that from the EGFR, activates *KRAS* which in turn stimulates other intracellular proteins to promote cell proliferation, cell survival and angiogenesis.

Activating mutations in the *KRAS* gene occur frequently in a variety of human tumours and have been implicated in both oncogenesis and tumour progression.

Pharmacokinetics

Panitumumab administered as a single agent or in combination with chemotherapy exhibits nonlinear pharmacokinetics. The concentration-time profile is best described by a 2-compartment (central and peripheral) pharmacokinetic model with dual linear and nonlinear clearance pathways likely mediated by the reticuloendothelial system and EGFR, respectively. Since panitumumab that is bound to cell-surface EGFR can be internalised and degraded, the nonlinear clearance is probably related to saturable binding of panitumumab to EGFR. The average clearance value decreases with increasing dose and approaches the clearance value for endogenous IgG2 (1-4 mL/day/kg). Steady-state is obtained after 3 doses at 6 mg/kg given once every 2 weeks. At steady-state, mean minimum serum concentration was 47 µg/mL (SD ± 19), mean maximum serum concentration was 219 µg/mL (SD ± 54), and mean area under the concentration time curve (AUC) was 1431 µg·day/mL (SD ± 412) dose. The mean half-life value during the dosing interval was 7.5 days (SD ± 1.8). Compartmental analysis suggested that the volume of distribution approximated the plasma volume (42 mL/kg) for the central compartment and was approximately 26 mL/kg for the peripheral compartment.

Special Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics. Results suggest that age, gender, tumour type, race, hepatic function, renal function, chemotherapeutic agents, and EGFR expression in tumour cells had no apparent impact on the pharmacokinetics of panitumumab.

Renal and Hepatic Insufficiency

No clinical studies have been conducted to examine the pharmacokinetics of panitumumab in patients with renal impairment or hepatic impairment.

Geriatric Patients

No age-related differences in the pharmacokinetics of panitumumab were observed in clinical studies in patients 26 to 85 years of age (see PRECAUTIONS: Use in the Elderly).

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of panitumumab has been evaluated using two different screening immunoassays for the detection of binding anti-panitumumab antibodies (an ELISA which detects high-affinity antibodies, and a Biacore® Biosensor Immunoassay which detects both high- and low-affinity antibodies). For patients whose sera tested positive in either screening immunoassay, an in vitro biological assay was performed to detect neutralising antibodies.

Vectibix monotherapy:

- The incidence of binding antibodies (excluding predose and transient positive patients) was < 1% as detected by the acid-dissociation ELISA and 3.8% as detected by the Biacore assay;

- The incidence of neutralising antibodies (excluding predose and transient positive patients) was < 1%;
- Compared with patients who did not develop antibodies, no relationship between the presence of anti-panitumumab antibodies and pharmacokinetics, efficacy and safety has been observed.

In combination with irinotecan- or oxaliplatin-based chemotherapy:

- The incidence of binding antibodies (excluding predose positive patients) was 1.0% as detected by the acid-dissociation ELISA and < 1% as detected by the Biacore assay;
- The incidence of neutralising antibodies (excluding predose positive patients) was < 1%;
- No evidence of an altered safety profile was found in patients who tested positive for antibodies to panitumumab.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. The observed incidence of 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, therefore comparison of the incidence of antibodies to other products may be misleading.

CLINICAL TRIALS

Vectibix Monotherapy

The efficacy of panitumumab as monotherapy in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in a Phase 3 randomised, controlled trial (463 patients) and Phase 2 open-label, single-arm trials (384 patients).

Randomised, Controlled Trial

A multinational Phase 3, randomised, controlled trial was conducted in 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum after confirmed failure of fluoropyrimidine, oxaliplatin and irinotecan-containing regimens, as assessed by a blinded Independent Review Committee (IRC). Patients were required to have tumours with at least 1+ membrane staining intensity for EGFR by the DAKO EGFR pharmDx® test kit in ≥ 10% of evaluated tumour cells in the original protocol (n = 99) or ≥ 1% of evaluated tumour cells in an amendment (n = 364) (see CLINICAL TRIALS: EGFR Expression and Response). Patients were randomised 1:1 to receive panitumumab at a dose of 6 mg/kg given once every two weeks plus best supportive care (BSC; not including chemotherapy agents) or BSC alone (231 panitumumab plus BSC, 232 BSC alone). Premedication for the prevention of potential infusion reactions was not mandated by protocol. Patients were treated until disease progression or unacceptable toxicity. The IRC assessed tumour response to panitumumab per modified-RECIST criteria. Upon disease progression (as determined by the investigator), BSC-alone patients were eligible to cross over and receive panitumumab at a dose of 6 mg/kg given once every two weeks.

Of the 463 randomised patients, 294 (63%) were men. The median age was 62 years (range 27-to 83 years), and the majority was Caucasian (457, 99%). Three hundred and ninety-six of 463 (86%) patients had a baseline ECOG (Eastern Cooperative Oncology Group) Performance Status of 0 or 1. Three hundred and ten of 463 (67%) patients had colon cancer and 153/463 (33%) had rectal cancer. Of the 232 patients randomised to BSC alone, 174 (75%) went on to receive panitumumab after a median treatment interval of 7.0 weeks (95% CI: 6.6, 7.3).

The efficacy of panitumumab was evaluated in all randomised patients using an intent-to-treat analysis, with a primary endpoint of progression-free survival (PFS) and secondary endpoints including response rate and overall survival (OS). For the primary endpoint of PFS, the analysis was based on IRC review of all patients. In patients who received panitumumab, the rate of disease progression or death was reduced by 46% relative to patients who received BSC alone (Hazard Ratio [HR] = 0.54 [95% CI: 0.44, 0.66], $p < 0.001$).

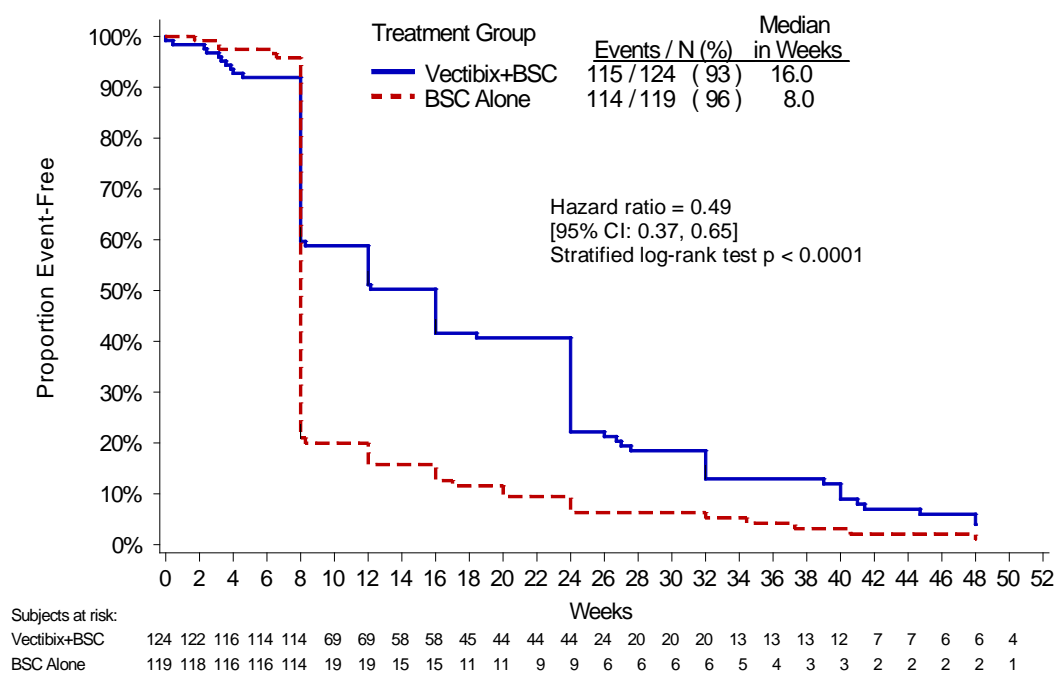
The relationship between clinical efficacy and *KRAS* mutational status was evaluated in tumour tissue in a prospectively defined analysis of the randomised controlled trial described above.

Tumour samples obtained from the primary resection of colorectal cancer were analysed for the presence of the seven most common activating mutations in codons 12 and 13 (Gly12Asp, Gly12Ala, Gly12Val, Gly12Ser, Gly12Arg, Gly12Cys, and Gly13Asp) of the *KRAS* gene by using an allele-specific polymerase chain reaction. Four hundred and twenty-seven (92%) patients were evaluable for *KRAS* status of which 184 had mutations.

The HR for PFS was 0.45 [95% CI: 0.34-0.59] in patients with wild-type *KRAS* mCRC and 0.99 [95% CI: 0.73-1.36] in patients with mutant *KRAS* mCRC. In an analysis adjusting for potential bias from unscheduled assessments, the hazard ratio for PFS was 0.49 [95% CI: 0.37-0.65] in favour of panitumumab in the wild-type *KRAS* mCRC group and 1.07 [95% CI: 0.77-1.48] in the mutant *KRAS* mCRC group. For patients randomised to panitumumab, the objective response rate (central review) in patients with wild-type versus mutant *KRAS* mCRC was 17% versus 0%. Stable disease was seen in 34% versus 12% in patients with wild-type versus mutant *KRAS* mCRC in the panitumumab arm and 12% versus 8% in the BSC arm. No treatment difference in OS according to *KRAS* mutation status was observed. Results are presented in Figure 1

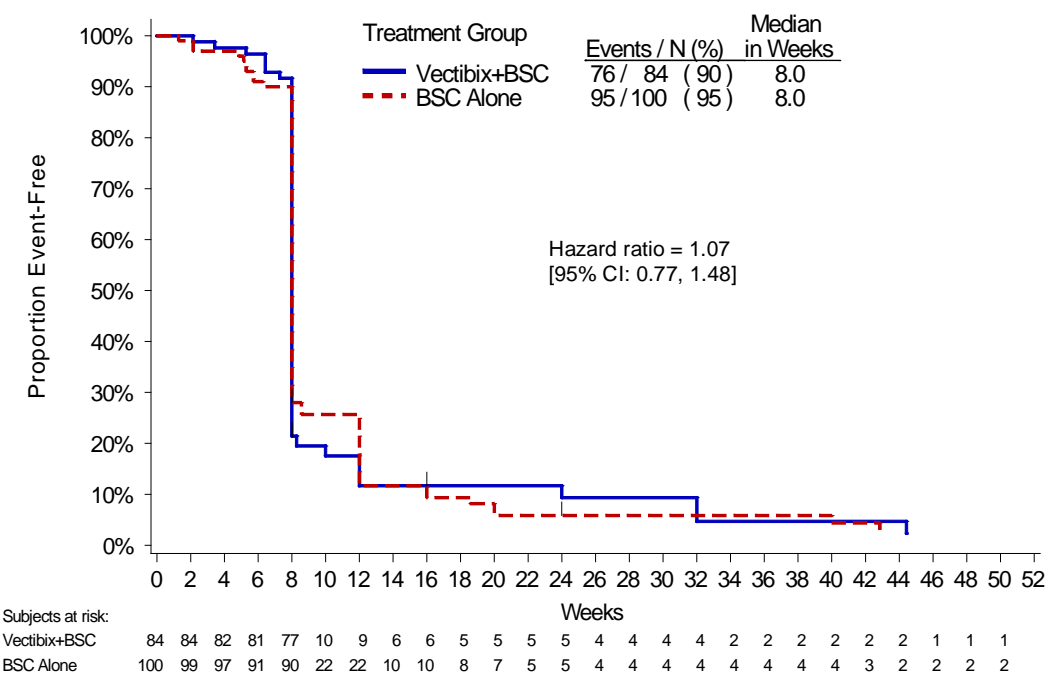
Figure 1. PFS – Patients with mutant and wild-type KRAS mCRC

Wild-type KRAS



Unscheduled tumour assessments were moved to the nearest scheduled time-point

Mutant KRAS



Unscheduled tumour assessments were moved to the nearest scheduled time-point

EGFR Expression and Response

Patients enrolled in the monotherapy mCRC clinical studies were required to undergo immunohistochemical evaluation of tumour sample EGFR expression using the DAKO EGFR pharmDx® test kit. Specimens were scored based on the percentage of tumour cells with membrane expressing EGFR, the highest membrane staining intensity (none, weak [1+], moderate [2+], strong [3+]), and complete or incomplete staining pattern. In the randomised, controlled trial exploratory univariate analyses were conducted to assess the correlation of EGFR expression and efficacy. Efficacy results did not correlate with either presence, percentage of positive cells or the intensity of EGFR expression as measured by the DAKO EGFR pharmDx® test kit. The utility of the test kit to guide clinical decision-making is unclear.

Vectibix in Combination with Chemotherapy*

First-line combination with FOLFOX

The efficacy of Vectibix in combination with oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (FOLFOX) was evaluated in a randomised, controlled trial of 1183 patients with mCRC with the primary endpoint of PFS. Other key endpoints included overall survival (OS), objective response rate (ORR), time to progression (TTP), and duration of response.

In patients with wild-type *KRAS* mCRC (n = 656) the estimated median PFS was 9.6 months (95% CI: 9.2, 11.1) in the panitumumab plus FOLFOX arm and 8.0 months (95% CI: 7.5, 9.3) in the FOLFOX alone arm, an absolute difference of 1.6 months. PFS was significantly improved in the panitumumab plus FOLFOX arm compared to the FOLFOX alone arm (p-value = 0.023). The estimated hazard ratio was 0.798 (95% CI: 0.656, 0.971) favouring the panitumumab plus FOLFOX arm. The estimated PFS rate (95% CI) at twelve (12) months was 45% (39%, 51%) in the panitumumab plus FOLFOX arm and 33% (28%, 39%) in the FOLFOX alone arm.

The estimated median OS was 23.9 months (95% CI: 20.3, 28.3) in the panitumumab plus FOLFOX arm and 19.7 months (95% CI: 17.6, 22.6) in the FOLFOX alone arm, an absolute difference of 4.2 months. The difference did not achieve statistical significance (p = 0.0723). The hazard ratio was 0.825 (95% CI: 0.669, 1.018), favouring the panitumumab plus FOLFOX arm. The estimated OS rate (95% CI) at twenty-four (24) months was 49% (43%, 55%) in the panitumumab plus FOLFOX arm and 40% (35%, 46%) in the FOLFOX alone arm.

Subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine) was given to 173 (53%) patients in the panitumumab plus FOLFOX arm and 205 (62%) patients in the FOLFOX alone arm. Subsequent anti-EGFR therapy was received by 26 (8%) patients in the panitumumab plus FOLFOX arm and 59 (18%) patients in the FOLFOX alone arm. The median time to subsequent chemotherapy was 10.5 months in the panitumumab plus FOLFOX arm and 9.7 months in the FOLFOX alone arm. The median time to anti-EGFR

therapy was 17.9 months (panitumumab plus FOLFOX) and 10.8 months (FOLFOX alone). The role of subsequent anti-EGFR therapy or chemotherapy on the estimated OS treatment effect is unknown.

In an exploratory covariate analysis of patients with an ECOG 2 performance status (n = 40), shorter median OS was observed in the panitumumab plus FOLFOX arm (7.0 months) than in the FOLFOX alone arm (11.7 months) [HR (95% CI): 1.834 (0.896, 3.753); p = 0.0937]. In patients with an ECOG performance status of 0 or 1 (n = 616), the median OS was 25.8 months in the panitumumab plus FOLFOX arm and 20.7 months in the FOLFOX alone arm [HR (95% CI): 0.767(0.616; 0.955); p = 0.0176].

Table 1. Study 20050203: Efficacy Results by Baseline ECOG Performance Status in Subjects with Wild-type KRAS

	ECOG 0/1 Status		ECOG 2 Status	
	Panitumumab + FOLFOX n = 305	FOLFOX Alone n = 311	Panitumumab + FOLFOX n = 20	FOLFOX Alone n = 20
PFS Hazard Ratio (95% CI); p-value	0.74 (0.60, 0.91); p = 0.003		2.30 (1.08, 4.89); p = 0.027	
Median PFS (months)	10.4	8.0	4.8	7.6
OS Hazard Ratio (95% CI); p-value	0.77 (0.62, 0.96); p = 0.018		1.83 (0.90, 3.75); p = 0.094	
Median OS (months)	25.8	20.7	7.0	11.7
Objective Response Rate ^a	58%	48%	20%	45%

^a Of patients with measurable disease

In patients with mutant *KRAS* mCRC (n = 440), the PFS was inferior (p = 0.0227) in patients receiving panitumumab in combination with FOLFOX (7.3 months; [95% CI: 6.3, 8.0]) than those patients receiving FOLFOX alone (8.8 months; [95% CI: 7.7, 9.4]). The estimated median OS was shorter in patients receiving panitumumab in combination with FOLFOX (15.5 months; [95% CI: 13.1, 17.6]) compared with those receiving FOLFOX alone (19.3 months; [95% CI: 16.5, 21.8]) (see CONTRAINDICATIONS).

Second-line combination with FOLFIRI

The efficacy of Vectibix in combination with irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) was evaluated in a randomised, controlled trial of 1186 patients with the co-primary endpoints of OS and PFS. Other key endpoints included the ORR, TTP, and duration of response.

In patients with wild-type *KRAS* mCRC (n = 597) a statistically significant difference in PFS in favour of panitumumab was demonstrated (p = 0.0036). The estimated median PFS times were 5.9 months (95% CI: 5.5, 6.7) in the panitumumab plus FOLFIRI arm and 3.9 months (95% CI: 3.7, 5.3) in the FOLFIRI alone arm, an absolute difference of 2.0 months. The hazard ratio was 0.732 (95% CI: 0.593, 0.903), favouring the panitumumab plus FOLFIRI arm. The estimated PFS rate (95% CI) at six (6) months was 56% (49%, 62%) in the panitumumab plus FOLFIRI arm and 41% (34%, 47%) in the FOLFIRI alone arm.

The estimated median OS was 14.5 months (95% CI: 13.0, 16.0) in the panitumumab plus FOLFIRI arm and 12.5 months (95% CI: 11.2, 14.2) in the FOLFIRI alone arm, an absolute difference of 2.0 months. The OS difference did not achieve statistical significance (p = 0.1154). The hazard ratio was 0.854 (95% CI: 0.702, 1.039), favouring the panitumumab plus FOLFIRI arm. The estimated OS rate (95% CI) at twelve (12) months was 59% (53%, 64%) in the panitumumab plus FOLFIRI arm and 53% (47%, 59%) in the FOLFIRI alone arm. The estimated OS rate (95% CI) at eighteen (18) months was 40% (35%, 46%) in the panitumumab plus FOLFIRI arm and 33% (27%, 39%) in the FOLFIRI alone arm.

Subsequent chemotherapy (irinotecan, oxaliplatin, or fluoropyrimidine) was given to 142 (47%) patients in the panitumumab plus FOLFIRI arm and 142 (48%) patients in the FOLFIRI alone arm. Subsequent anti-EGFR therapy was received by 31 (10%) patients in the panitumumab plus FOLFIRI arm and 90 (31%) patients in the FOLFIRI alone arm. The median time to subsequent chemotherapy was 9.9 months in the panitumumab plus FOLFIRI arm and 7.6 months in the FOLFIRI alone arm. The median time to anti-EGFR therapy was 11.8 months (panitumumab plus FOLFIRI) and 7.6 months (FOLFIRI alone). The role of subsequent chemotherapy or anti-EGFR therapy on the estimated OS treatment effect is unknown.

Although in an exploratory covariate analysis of patients, longer median OS was observed in the panitumumab plus FOLFIRI arm than in the FOLFIRI alone arm regardless of ECOG performance status, the efficacy gains with the combination were smaller in patients with an ECOG performance status 2 (0.9 months for ECOG 2 vs. 1.9 months for ECOG 0 or 1).

Table 2. Study 20050181: Efficacy Results by Performance Status in Subjects with Wild-type *KRAS*

	ECOG 0/1		ECOG 2	
	Panitumumab + FOLFIRI n = 291	FOLFIRI Alone n = 278	Panitumumab + FOLFIRI n = 12	FOLFIRI Alone n = 16
PFS Hazard Ratio (95% CI); p-value	0.72 (0.58, 0.89); p = 0.002		1.16 (0.45, 2.98); p = 0.753	
Median PFS (months)	5.9	3.9	3.1	2.8
OS Hazard Ratio (95% CI); p-value	0.84 (0.69, 1.03); p = 0.089		1.14 (0.51, 2.52); p = 0.755	
Median OS (months)	14.7	12.8	5.7	4.8
Objective Response Rate ^a	36%	10%	9%	13%

^a Of patients with measurable disease

In combination with irinotecan-based chemotherapy, 18% (n = 115) of panitumumab patients had been exposed to prior bevacizumab treatment. PFS and Response Rate were similar to those who did not receive prior bevacizumab.

In patients with mutant *KRAS* (n = 486), no significant difference in PFS [HR (95% CI): 0.85 (0.68, 1.06)] and OS [HR (95% CI): 0.94 (0.76, 1.15)] was observed between treatment arms.

INDICATIONS

Vectibix is indicated for the treatment of patients with wild-type *KRAS* metastatic colorectal cancer (mCRC)

- as first line therapy in combination with FOLFOX. Efficacy is influenced by patient performance status (see CLINICAL TRIALS; PRECAUTIONS).*
- as second line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). Efficacy may be influenced by patient performance status (see CLINICAL TRIALS).*
- as monotherapy in patients after the failure of standard chemotherapy.

CONTRAINDICATIONS

Vectibix is contraindicated in patients with a history of life-threatening hypersensitivity reactions to panitumumab, or any components of the product.

The combination of Vectibix with oxaliplatin-based chemotherapy is contraindicated in patients with mutant *KRAS* mCRC or for whom *KRAS* mCRC status is unknown.*

PRECAUTIONS

Combination with Oxaliplatin-based Chemotherapy in Patients with Mutant *KRAS* mCRC or for whom *KRAS* Tumour Status is Unknown*

Panitumumab should not be administered in combination with oxaliplatin-containing chemotherapy to patients with mutant *KRAS* mCRC or for whom *KRAS* mCRC status is unknown. In a phase 3 study (N = 1183; with wild-type (n = 656) and mutant (n = 440) *KRAS* mCRC) evaluating panitumumab in combination with infusional 5-FU, leucovorin, and oxaliplatin (FOLFOX) compared to FOLFOX alone as first-line therapy for mCRC, a significant shortening of PFS was observed in patients with mutant *KRAS* mCRC who received panitumumab and FOLFOX (n = 221) versus FOLFOX alone (n = 219). A trend toward shortened OS time was also observed in the mutant *KRAS* mCRC population.

Patients with ECOG 2 Performance Status Treated with Vectibix in Combination with Chemotherapy*

In a phase 3 study (N = 1,183; 656 patients with wild-type *KRAS* and 440 patients with mutant *KRAS* mCRC) evaluating panitumumab in combination with infusional 5-FU, leucovorin, and oxaliplatin (FOLFOX) compared to FOLFOX alone as first-line therapy, patients with ECOG 2 performance status (n = 40) were observed to have increased toxicity and significant shortening of PFS relative to ECOG 0 or 1 performance status (n = 616). For patients with ECOG 2 performance status, assessment of risk-benefit is recommended prior to initiation of Vectibix in combination with chemotherapy for treatment of mCRC.

Dermatologic Toxicity and Related Disorders

Dermatologic related reactions, a pharmacological effect observed with EGFR inhibitors, were reported in 93% of patients with mCRC receiving panitumumab in monotherapy mCRC clinical trials (N = 1,052). Patients developing dermatologic toxicities while receiving panitumumab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment promptly initiated. Life threatening and fatal infectious complications including events of necrotising fasciitis and/or sepsis have been observed in patients treated with panitumumab.*

In cases of severe dermatologic toxicities, dose modifications of panitumumab should be instituted (see DOSAGE AND ADMINISTRATION). In cases of dermatologic toxicity with severe or life threatening inflammatory or infectious complications, panitumumab should be withheld or discontinued.*

It is recommended that patients wear sunscreen and a hat and limit sun exposure while receiving panitumumab as sunlight can exacerbate any skin reactions that may occur.

Infusion Reactions

Infusion reactions, including anaphylactic reactions, bronchospasm, and hypotension, have been reported in the clinical trials and post-marketing experience.

Across the monotherapy mCRC clinical studies (n = 1,052), severe infusion reactions (NCI-CTC grade 3 and 4) occurred with the administration of panitumumab in 0.5% of patients.

In the (pooled) irinotecan-based chemotherapy with panitumumab (n = 951) and the irinotecan-based chemotherapy alone (n = 594) settings, severe infusion reactions (NCI-CTC grade 3 and grade 4) occurred in 0.1% and 0.2% of patients, respectively. In the oxaliplatin-based chemotherapy with panitumumab (n = 585) and the oxaliplatin-based chemotherapy alone (n = 584) settings, severe infusion reactions (NCI-CTC grade 3 and grade 4) occurred in 2.4% of patients in both treatment arms.*

In the postmarketing setting, serious infusion reactions have also been reported in < 1% of patients, very rarely with a fatal outcome (< 0.01%).*

Infusion should be stopped if a severe or life-threatening infusion reaction occurs. Depending on the severity and/or persistence of the reaction, administration of panitumumab should be permanently discontinued.

Other Hypersensitivity Reactions

Hypersensitivity reactions have been reported, including a fatal case of angioedema that occurred more than 24 hours after the infusion. Depending on the severity and/or persistence of hypersensitivity reactions, administration of panitumumab should be permanently discontinued (see CONTRAINDICATIONS and ADVERSE EFFECTS.)

Pulmonary Toxicity

Cases of fatal and non-fatal* interstitial lung disease (ILD) have been observed in patients treated with EGFR inhibitors, including panitumumab. In the event of acute onset or worsening of pulmonary symptoms, panitumumab therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, panitumumab should be permanently discontinued and the patient should be treated appropriately.

Patients with a history or evidence of interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies. The benefits of administration of panitumumab versus the risk of pulmonary complications must be carefully considered.

Venous Thromboembolism

In the pivotal, randomised controlled trial, panitumumab treatment was associated with an increased risk of venous thrombotic events (e.g. deep venous thrombosis, pulmonary embolism). Venous thrombotic events occurred in 5.2% (12/231) of patients receiving panitumumab plus BSC compared with 0.4% (1/232) receiving BSC alone. Patients should be monitored for the development of such events.

Combination with Irinotecan, Bolus 5-fluorouracil, and Leucovorin (IFL)

Chemotherapy

In a single-arm study (N = 19) patients receiving panitumumab in combination with the IFL regimen (bolus 5-fluorouracil, leucovorin, and irinotecan) experienced a high incidence of severe diarrhoea (58%). Because electrolyte depletion may be exacerbated by severe diarrhoea, administration of panitumumab in combination with IFL should be avoided.

Combination with Bevacizumab and Chemotherapy Regimens for the Treatment of Metastatic Colorectal Cancer*

A randomised, open-label, multicentre study of 1,053 patients evaluated the efficacy of bevacizumab and oxaliplatin- or irinotecan-containing chemotherapy regimens with and without panitumumab in the first-line treatment of metastatic colorectal cancer.

Across both chemotherapy treatment groups, more toxicity was seen in the panitumumab group, manifesting as a greater incidence of grade 3 and higher adverse events, a greater incidence of serious adverse events, and more overall deaths relative to the control group. Similar safety trends were seen for the oxaliplatin and irinotecan treatment groups separately.

Serious adverse events were experienced by 59% in the panitumumab group versus 37% in the control group, with higher incidences in the panitumumab group of dehydration, diarrhoea, pulmonary embolism, nausea, and vomiting. Serious infections overall displayed a treatment difference (15% versus 9%); however, no one specific type of infection occurred at a high frequency. Nineteen percent of patients receiving panitumumab experienced a serious event that was considered related to panitumumab, the most common of which were diarrhoea, dehydration, and vomiting.

This study did not demonstrate an improvement in PFS (the primary endpoint) by the addition of panitumumab to bevacizumab and oxaliplatin-based chemotherapy. The addition of panitumumab to the combination of bevacizumab and chemotherapy in the treatment of metastatic colorectal cancer is not indicated.

Acute Renal Failure

Acute renal failure has been observed in patients who develop severe diarrhoea and dehydration.

Ocular Toxicities

Serious cases of keratitis and/or ulcerative keratitis have been reported very rarely in the postmarketing setting. Patients developing ocular toxicities while receiving panitumumab should be monitored for evidence of keratitis or ulcerative keratitis.*

Information for Patients

Patients must be informed of the possible adverse effects of panitumumab, including dermatologic reactions, and instructed to report these, or any other adverse effects, to the prescribing physician (see ADVERSE-EFFECTS).

It is recommended that patients wear sunscreen and a hat and limit sun exposure while receiving panitumumab as sunlight can exacerbate any skin reactions that may occur.

Management of Skin Toxicities*

Proactive skin treatment including skin moisturiser, sun screen (SPF > 15 UVA and UVB), topical steroid cream (\leq 1% hydrocortisone) and an oral antibiotic (e.g. doxycycline) may be useful in the management of skin toxicities. Consider advising patients to apply moisturiser and sunscreen to the face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night.

Treatment of skin reactions should be based on severity and may include a moisturiser, sun screen (SPF > 15 UVA and UVB), and topical steroid cream (\leq 1% hydrocortisone) applied to the affected areas, and/or oral antibiotics.

Laboratory Tests

Electrolyte Disturbances/Monitoring

Progressively decreasing serum magnesium levels leading to severe hypomagnesaemia have been observed in some patients. Patients should be monitored for hypomagnesaemia, and accompanying hypocalcaemia, prior to initiating panitumumab treatment, and periodically during and for up to 8 weeks after the completion of panitumumab treatment (see ADVERSE EFFECTS). Magnesium repletion is recommended, as appropriate.

Other electrolyte disturbances, including hypokalaemia, have also been observed. Repletion of these electrolytes is also recommended, as appropriate.

KRAS Testing

KRAS mutational status should be determined by an experienced laboratory using the TheraScreen®: *K-RAS* Mutation Kit or by using test methodologies with high concordance with the TheraScreen kit.*

Effects on Fertility

Panitumumab may impair fertility in women of childbearing potential. Prolonged menstrual cycles and/or amenorrhoea, accompanied by changes in the cycling of progesterone and 17 β -oestradiol levels, were observed in female cynomolgus monkeys following weekly doses of panitumumab resulting in exposure similar to that at the maximum recommended human doses (based on AUC). These effects in monkeys were likely to be due to the reduced food consumption and body weight loss observed in the treated animals. Normal menstrual cycling resumed in most animals after discontinuation of panitumumab treatment.

Formal fertility studies have not been conducted; however, no effects of panitumumab treatment on the male reproductive organs were observed in cynomolgus monkeys given panitumumab for up to 26 weeks at exposures (based on AUC) about 5-fold that at the maximum recommended human dose.

Use in Pregnancy

Pregnancy Category: C

There are no studies of panitumumab in pregnant women. However, EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis. Therefore, panitumumab has the potential to cause foetal harm when administered to pregnant women and has shown to be embryolethal and abortifacient in cynomolgus monkeys when administered during the period of organogenesis (gestation day 20 to 50) at doses achieving an exposure (on an AUC basis) similar to that at the recommended human dose.

Human IgG is known to cross the placental barrier, therefore panitumumab may be transmitted from the mother to the developing foetus. In women of childbearing potential, appropriate contraceptive measures must be used during treatment with panitumumab, and for 6 months following the last dose of panitumumab. If panitumumab is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be aware of the potential risk for loss of the pregnancy or potential hazard to the foetus. These patients are encouraged to enrol in Amgen's Pregnancy Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Use in Lactation

Studies have not been conducted to assess the excretion of panitumumab in human milk. Because human IgG is excreted into human milk, and because of the potential for adverse reactions in infants, women must be advised to discontinue breast-feeding during treatment with panitumumab and for 8 weeks after the last dose of panitumumab.

Paediatric Use

The safety and effectiveness of panitumumab in paediatric patients have not been established.

Use in the Elderly

No overall differences in efficacy or safety were observed in elderly patients (aged ³ 65 years) and younger patients treated with Vectibix monotherapy. However, an increased number of serious adverse events were reported in elderly patients treated with Vectibix in combination with FOLFOX or FOLFIRI chemotherapy compared to chemotherapy alone.*

Carcinogenicity

The carcinogenic potential of panitumumab has not been evaluated.

Genotoxicity

The genotoxic potential of panitumumab has not been evaluated in vitro or in vivo.

Interactions with Other Medicines

Data from a drug-drug interaction study involving panitumumab and irinotecan in patients with mCRC indicated that the pharmacokinetics of irinotecan and its active metabolite, SN-38, are not altered when the drugs are co-administered.

Results from a cross-study comparison indicated that irinotecan-containing regimens (IFL or FOLFIRI) have no effect on the pharmacokinetics of panitumumab.

Effects on Ability to Drive and Use Machines

None known.

ADVERSE EFFECTS

Based on an analysis of all mCRC clinical trial patients receiving Vectibix monotherapy and in combination with chemotherapy (N = 2588), the most commonly reported adverse reactions are skin reactions occurring in 93% of patients. These reactions are related to the pharmacologic effects of panitumumab, and the majority are mild to moderate in nature with 25% severe (grade 3 NCI-CTC) and < 1% life threatening (grade 4 NCI-CTC).

Commonly reported adverse reactions occurring in $\geq 20\%$ of patients were gastrointestinal disorders [diarrhoea (50%), nausea (41%), vomiting (27%), constipation (23%) and abdominal pain (23%)]; general disorders [fatigue (37%), pyrexia (20%)]; metabolism and nutrition disorders [anorexia (27%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (45%), dermatitis acneiform (39%), pruritus (35%), erythema (30%) and dry skin (22%)].*

The data in table 2 describe adverse reactions reported from clinical studies in patients with mCRC who received Vectibix as a single agent or in combination with chemotherapy (N = 2588). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3. Incidence of Adverse Reactions in Patients with Metastatic Colorectal Cancer (Vectibix Monotherapy or Vectibix in Combination with Chemotherapy)*

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1000)
Blood and lymphatic system disorders	Anaemia	Leukopenia		
Cardiac disorders		Tachycardia	Cyanosis	
Eye disorders	Conjunctivitis	Blepharitis Dry eye Eye irritation Eye pruritus Growth of eyelashes Lacrimation increase Ocular hyperaemia	Eyelid irritation	
Gastrointestinal disorders	Diarrhoea Vomiting Abdominal pain Nausea Constipation Stomatitis	Rectal haemorrhage Dry mouth Dyspepsia Aphthous stomatitis Cheilitis Gastroesophageal reflux disease	Chapped lips	
General disorders and administration site conditions	Pyrexia Asthenia Fatigue Mucosal inflammation Oedema peripheral	Chest pain Pain Chills	Infusion related reaction	
Immune system disorders		Hypersensitivity		Anaphylactic reaction
Infections and infestations	Paronychia	Cellulitis Folliculitis Localised infection Rash pustular	Eye infection Eyelid infection	
Investigations	Weight decrease	Blood magnesium decrease		
Metabolism and nutrition disorders	Hypokalaemia Anorexia Hypomagnesaemia	Dehydration Hypocalcaemia Hyperglycaemia Hypophosphataemia		
Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity		
Nervous system disorders		Dizziness Headache		
Psychiatric disorders	Insomnia	Anxiety		
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Epistaxis	Bronchospasm Nasal dryness	

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1000)
Skin and subcutaneous tissue disorders	Rash Dermatitis acneiform Acne Erythema Skin fissures Pruritus Alopecia Dry skin	Skin toxicity Skin exfoliation Rash pruritic Exfoliative rash Hypertrichosis Nail disorder Onychoclasia Palmar-plantar erythrodysesthesia syndrome Rash erythematous Rash generalised Rash macular Rash maculo-papular Rash papular Scab Skin lesion Skin ulcer	Angioedema Hirsutism Ingrowing nail Onycholysis	
Vascular disorders		Deep vein thrombosis Hypotension Hypertension Flushing		

The safety profile of Vectibix in combination with chemotherapy consisted of the reported adverse reactions of Vectibix (as a monotherapy) and the toxicities of the background chemotherapy regimen. No new toxicities or worsening of previously recognised toxicities beyond the expected additive effects were observed. Skin reactions were the most frequently occurring adverse reactions in patients receiving Vectibix in combination with chemotherapy. Other toxicities that were observed with a greater frequency relative to monotherapy included hypomagnesaemia, diarrhoea, and stomatitis. These toxicities infrequently led to discontinuation of panitumumab or of chemotherapy.*

Gastrointestinal Disorders*

Diarrhoea when reported was mainly mild or moderate in severity. Severe diarrhoea (NCI-CTC grade 3 and 4) was reported in 2% of patients treated with Vectibix as a monotherapy and in 17% of patients treated with Vectibix in combination with chemotherapy.

There have been reports of acute renal failure in patients who develop diarrhoea and dehydration.

Dermatologic Toxicity and Related Disorders

As expected from EGFR inhibitors, dermatologic toxicity and related disorders were observed in 93% patients receiving Vectibix as monotherapy or in combination with chemotherapy. These events consisted predominantly of rash and dermatitis acneiform

and were mostly mild to moderate in severity. Severe (NCI-CTC grade 3) skin reactions were reported in 34% and life-threatening (NCI-CTC grade 4) skin reactions in 1% of patients who received Vectibix in combination with chemotherapy.*

Skin rash most commonly occurred on the face and trunk, but could extend to the extremities and was characterised by multiple pustular-, macular-, or papular-appearing lesions. Palmar-plantar erythrodysesthesia (PPE) syndrome was commonly reported in the setting of panitumumab in combination with chemotherapy. Skin drying and fissures were common and in some cases were associated with inflammatory and infectious sequelae, including sepsis, in rare cases leading to death, and local abscesses requiring incisions and drainage (see PRECAUTIONS: Dermatologic Toxicity and Related Disorders). The median time to first symptom of dermatologic toxicity was 10 days, and the median time to resolution after the last dose of panitumumab was 28 days. Overall, while the incidence and duration of dermatologic and related disorders were correlated with panitumumab exposure, the duration of severe dermatologic and related disorders was not.

Infusion Reactions

Across all clinical studies, potential infusion reactions (defined as any identified allergic reaction, anaphylactoid reaction, chills, fever, or dyspnoea, occurring within 24 hours of any dose that were not otherwise designated as either anaphylactoid or allergic reaction) were identified in 3% of patients treated with panitumumab, of which 0.5% were severe (NCI-CTC grade 3 and 4). Most of the symptoms of potential infusion reactions were mild in intensity, resolved without treatment, were isolated occurrences and did not require alteration or interruption of panitumumab administration.

In clinical studies with irinotecan-based chemotherapy, severe infusion reactions (NCI-CTC grade 3 and 4) occurred in 0.1% of patients administered Vectibix in combination with irinotecan-based chemotherapy (n = 951) and in 0.2% of patients administered only irinotecan-based chemotherapy (n = 594). In clinical studies with oxaliplatin-based chemotherapy, severe infusion reactions (NCI-CTC grade 3 and 4) occurred in 2.4% of patients administered Vectibix in combination with oxaliplatin-based chemotherapy (n = 585) and 2.4% of patients administered only oxaliplatin-based chemotherapy (n = 584).*

Other Hypersensitivity Reactions

A case of fatal angioedema occurred in a patient with recurrent and metastatic squamous cell carcinoma of the head and neck treated with panitumumab in a clinical trial. The fatal event occurred after re-exposure following a prior episode of angioedema; both episodes occurred more than 24 hours after administration.

Electrolyte Depletion

In clinical studies in which magnesium levels were collected at specified time intervals during treatment with panitumumab, hypomagnesaemia (any grade) was observed in 250/649 (39%) of patients assessed and occurred at various time points during treatment. Grade 3 or higher hypomagnesaemia was reported in 32/649 (5%) of patients, most of

whom received IV electrolyte repletion. Serious cases of hypomagnesaemia occurred 6 weeks or longer after the initiation of panitumumab. In 5/649 (< 1%) of patients, adverse reactions of hypomagnesaemia were associated with adverse reactions of hypocalcaemia. Patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of panitumumab therapy (see PRECAUTIONS).

Postmarketing Experience

Infusion Reactions

Serious infusion reactions have been reported in < 1% of patients, very rarely with a fatal outcome (< 0.01%). Adverse events associated with serious infusion reactions have included cardiorespiratory arrest, anaphylaxis, and increased blood pressure.*

Dermatologic Toxicity and Related Disorders

Cases of skin necrosis have been reported.*

Ocular Toxicities

Serious cases of keratitis and/or ulcerative keratitis have been reported very rarely.*

DOSAGE AND ADMINISTRATION

The recommended dose of Vectibix is 6 mg/kg given once every 2 weeks. It is recommended that Vectibix treatment be continued until progression of the underlying disease.

Dose Modifications

Infusion Reactions

The infusion rate should be reduced by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.

The infusion should be stopped if a severe or life-threatening infusion reaction occurs. Depending on the severity and/or persistence of the reaction, permanent discontinuation of Vectibix should be considered.*

Dermatological Reactions

If a patient develops dermatologic reactions that are \geq grade 3 (NCI-CTC/CTCAE), or considered intolerable, the following dose modifications are recommended:*

Occurrence of skin symptom(s): \geq grade 3[†]	Administration of Vectibix	Outcome	Dose regulation
Initial occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 100% of original dose
		Not recovered	Discontinue
At the second occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 80% of original dose
		Not recovered	Discontinue
At the third occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 60% of original dose

		Not recovered	Discontinue
At the fourth occurrence	Discontinue	-	-

† Greater than or equal to Grade 3 is defined as severe or life-threatening

Preparation and Administration

DO NOT ADMINISTER Vectibix AS AN IV PUSH OR BOLUS.

Vectibix must be administered using a low protein binding 0.2 µm or 0.22 µm in-line filter.

Vectibix is supplied as a sterile, colourless, preservative-free solution containing 20 mg/mL panitumumab in a single-use vial. The solution may contain a small amount of visible translucent to white, amorphous, proteinaceous panitumumab particulates.

DO NOT SHAKE.

Prepare infusion using an appropriate aseptic technique.

Vectibix MUST BE ADMINISTERED BY IV INFUSION PUMP:

- Withdraw the necessary amount of Vectibix for a dose of 6 mg/kg.
- Dilute in a volume of 100 mL in 0.9% sodium chloride injection. Final concentration should not exceed 10 mg/mL.
- Diluted solution should be mixed by gentle inversion. **DO NOT SHAKE.**
- Infuse over approximately 60 minutes through a peripheral line or indwelling catheter.† If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes.
- Flush line before and after Vectibix administration with 0.9% sodium chloride injection to avoid mixing with other drug products or IV solutions.

† Doses higher than 1000 mg should be diluted in 150 mL 0.9% sodium chloride injection and should be infused over approximately 90 minutes via infusion pump.

The solution may contain a small amount of visible amorphous panitumumab particulates that will be removed during infusion by a low protein binding 0.2 µm or 0.22 µm in-line filter; the filtration does not impact the quality of the administered product. Vectibix should not be administered if discoloration is observed.

In the absence of compatibility studies, Vectibix must not be mixed with other medicinal products.

No incompatibilities have been observed between Vectibix and 0.9% sodium chloride injection in polyvinyl chloride bags or polyolefin bags.

Use in one patient on one occasion only.

Do not use beyond the expiration date.

OVERDOSAGE

Doses of Vectibix higher than 9 mg/kg have not been tested in clinical studies. There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose (12 mg/kg). Adverse events observed included skin toxicity, diarrhoea, dehydration and fatigue and were consistent with the safety profile at the recommended dose. In the event of overdosage, the patient should be observed and appropriate supportive treatment given.

PRESENTATION AND STORAGE CONDITIONS

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

Vectibix is provided as one vial per carton.

Presentation Available in Australia:

Each 5 mL single-use vial contains 100 mg of panitumumab in 5 mL.

Presentations Not Available in Australia:

Each 10 mL single-use vial contains 200 mg of panitumumab in 10 mL.

Each 20 mL single-use vial contains 400 mg of panitumumab in 20 mL.

Store vials in the original carton under refrigeration at 2°C to 8°C until time of use.

Protect from direct sunlight. **DO NOT FREEZE. DO NOT SHAKE.**

Vectibix does not contain any antimicrobial preservative or bacteriostatic agent. To reduce microbiological hazard, the product should be used immediately after dilution. If storage is necessary, the diluted infusion of Vectibix should be stored at 2°C to 8°C, and used within 24 hours of dilution. The diluted infusion should be mixed by gentle inversion. **DO NOT SHAKE. DO NOT FREEZE.**

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

20 March 2012

* Please note changes in Product Information