AUSTRALIAN PRODUCT INFORMATION –VECTIBIX® (PANITUMUMAB) CONCENTRATED INJECTION VIAL

1. NAME OF THE MEDICINE

Panitumumab.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 20 mg panitumumab. Each vial contains either 100 mg of panitumumab in 5 mL, or 400 mg of panitumumab in 20 mL. The concentrated solution pH is between 5.6 to 6.0.

When prepared, according to the instructions in section 4.2 Dose and method of administration, the final panitumumab concentration should not exceed 10 mg/mL.

Excipient with known effects

Contains sodium. For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

VECTIBIX is a sterile colourless concentrated solution for intravenous (IV) infusion. The concentrated solution may contain visible translucent to white, amorphous, proteinaceous panitumumab particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VECTIBIX monotherapy is indicated for the treatment of patients with wild-type *RAS* metastatic colorectal cancer (mCRC) after the failure of standard chemotherapy.

VECTIBIX in combination with FOLFOX is indicated as first-line therapy for the treatment of patients with wild-type *RAS* metastatic colorectal cancer (mCRC).

VECTIBIX in combination with FOLFIRI is indicated as second-line therapy for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Efficacy may be influenced by patient performance status (see section 5.1 Pharmacodynamic properties, Clinical trials and section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

VECTIBIX treatment should be supervised by a physician experienced in the use of anti-cancer therapy.

Evidence of wild-type RAS (*KRAS* and *NRAS*) status is required before initiating treatment with VECTIBIX (see section 4.4 Tumour genetic marker testing).

Dosage (adult dose and interval)

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 or unacceptable toxicity.

Dose modifications

The management of VECTIBIX adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 1).

Infusion Reactions

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

The VECTIBIX 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.

Dermatologic reactions

If a patient develops dermatologic reactions that are ≥ Grade 3 (NCI-CTC/CTCAE), or considered intolerable, refer to the recommended dose modifications in Table 1.

Table 1. Recommended VECTIBIX dose modifications in the event of severe or life-threatening dermatologic reactions during treatment

Occurrence of skin symptom(s): ≥ Grade 3†	Administration of VECTIBIX	Outcome	Dose modification
Initial occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 100% of original dose
		Not recovered	Discontinue VECTIBIX
At the second occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 80% of original dose
		Not recovered	Discontinue VECTIBIX
At the third occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 60% of original dose
		Not recovered	Discontinue VECTIBIX
At the fourth occurrence	Discontinue	-	-

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

Special populations

Hepatic impairment

The safety and efficacy of VECTIBIX have not been studied in patients with hepatic impairment.

Renal impairment

The safety and efficacy of VECTIBIX have not been studied in patients with renal impairment.

Use in the elderly

There is no clinical data to support dose adjustments in the elderly.

Paediatric use

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

Method of administration

VECTIBIX MUST BE ADMINISTERED BY IV INFUSION PUMP.

DO NOT ADMINISTER VECTIBIX CONCENTRATED INJECTION 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.

- **Do not shake.**

Prepare infusion using an appropriate aseptic technique.

- Withdraw the necessary amount of VECTIBIX for a dose of 6 mg/kg. Do not use a hypodermic needle with a gauge less than a 21-gauge or needle-free devices (e.g. vial adapters) to withdraw contents.
- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection. The 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.

VECTIBIX should be inspected visually prior to administration. The solution should be colourless and may contain a small amount of visible translucent to white, amorphous, proteinaceous 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 its appearance is not as described above.

Use in one patient on one occasion only. Discard the vial and any liquid remaining in the vial after the single-use.

Do not use VECTIBIX beyond the expiration date.

4.3 Contraindications

VECTIBIX is contraindicated in patients with a history of life-threatening hypersensitivity reactions to panitumumab, or any product excipients (see section 6.1 List of excipients).

VECTIBIX in combination with oxaliplatin-based chemotherapy is contraindicated in patients with mutant *RAS* mCRC or for whom *RAS* status is unknown (see section 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

Tumour genetic marker testing

Wild type *RAS* (*KRAS* and *NRAS*) mutational status should be determined by an experienced laboratory using a validated test method for detection of *KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4) mutations. *KRAS* mutational status should be determined using the TheraScreen®: *K-RAS* Mutation Kit or by using test methodologies with high concordance with the TheraScreen kit.

Combination with oxaliplatin-based chemotherapy in patients with mutant *RAS* mCRC or for whom *RAS* tumour status is unknown

Panitumumab should not be administered in combination with oxaliplatin-containing chemotherapy to patients with mutant *RAS* mCRC or for whom *RAS* status is unknown (see section 4.3 Contraindications).

In the primary analysis of a phase 3 study (N = 1183; with wild-type (n = 656) and mutant (n = 440) *KRAS* (exon 2) mCRC) evaluating panitumumab in combination with infusional FOLFOX compared to FOLFOX alone as first-line therapy for mCRC, a significant shortening of Progression-free survival (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 Overall survival (OS) time was also observed in the mutant *KRAS* mCRC population.

A predefined retrospective subset analysis of 641 patients of the 656 patients with wild-type *KRAS* (exon 2) mCRC from the phase 3 study identified additional *RAS* (*KRAS* [exons 3 and 4] or *NRAS* [exons 2, 3, 4]) mutations in 16% (n = 108) of patients. A shortening of PFS and OS was observed in patients with mutant *RAS* mCRC who received panitumumab and FOLFOX (n = 51) versus FOLFOX alone (n = 57).

Patients with ECOG 2 performance status treated with VECTIBIX in combination with chemotherapy

In a phase 3 study (N = 1183; 656 patients with wild-type *KRAS* and 440 patients with mutant *KRAS* mCRC) evaluating panitumumab in combination with infusional FOLFOX compared to FOLFOX alone as first-line therapy, wild-type *KRAS* mCRC patients with ECOG 2 performance status (n = 37; n = 19 (panitumumab + FOLFOX), n = 18 (FOLFOX alone)) were observed to have increased toxicity and significant shortening of PFS relative to ECOG 0 or 1 performance status (n = 611). In patients with wild-type *KRAS* mCRC, adverse events with > 20% difference between treatment arms within either ECOG group, and a > 5% difference between ECOG groups of the panitumumab plus FOLFOX arm were hypomagnesaemia, hypokalaemia, anaemia, and weight decreased. Similar safety findings were observed in patients with wild-type *RAS* mCRC. 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 related reactions, soft tissue toxicity and related disorders

Dermatologic related reactions, a pharmacological effect observed with EGFR inhibitors, were reported in approximately 93% of patients with mCRC receiving panitumumab monotherapy in clinical trials (N = 1052). 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.

Patients developing dermatologic or soft tissue 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. Rare cases of Stevens-Johnson syndrome and

toxic epidermal necrolysis have been reported in patients treated with panitumumab in the post marketing setting.

In cases of severe dermatologic toxicities, dose modifications of panitumumab should be instituted (see section 4.2 Dose and method of administration). In cases of dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications, panitumumab should be withheld or discontinued.

Management of Skin Toxicities

Proactive skin treatment including skin moisturiser, sunscreen (SPF > 15 UVA and UVB), topical steroid cream (≤ 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.

Infusion Reactions

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

Across the monotherapy mCRC clinical studies (n = 1052), panitumumab administration resulted in severe infusion reactions (NCI-CTC Grade 3 and 4) 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 post marketing setting, serious infusion reactions have also been reported, very rarely with a fatal outcome. If a severe or life-threatening infusion reaction occurs (e.g. presence of bronchospasm, angioedema, hypotension, need for parenteral treatment, or anaphylaxis), the infusion should be stopped. 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 sections 4.3 Contraindications and 4.8 Adverse effects (Undesirable 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 monotherapy trial, panitumumab treatment was associated with an increased risk of venous thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism). Venous thromboembolic 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 IFL experienced a high incidence of severe diarrhoea (58%). As 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 mCRC

A randomised, open-label, multicentre study of 1053 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% of patients 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. The overall frequency of serious infections was higher with panitumumab versus control (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 mCRC 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, and corneal perforation have been reported in the post marketing setting. Patients developing ocular toxicities while receiving panitumumab should be monitored for evidence of keratitis, ulcerative keratitis, or corneal perforation.

Information for patients

Patients must be informed of the possible adverse effects (AEs) of panitumumab, including dermatologic reactions, and instructed to report these, or any other adverse effects, to the prescribing physician (see section 4.8 Adverse effects (Undesirable effects)).

Special Populations

Use in the elderly

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

Paediatric use

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

Effects on 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 eight weeks after the completion of panitumumab treatment (see section 4.8 Adverse effects (Undesirable 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.

4.5 Interaction with other medicines and other forms of interaction

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 (PK) of panitumumab.

4.6 Fertility, pregnancy and lactation

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 17β-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 of 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 embryo lethal 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.

Women of reproductive potential should be advised to avoid becoming pregnant. In women of childbearing potential, appropriate effective 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.

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 breastfeeding during treatment with panitumumab and for 8 weeks after the last dose of panitumumab.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (Undesirable effects)

Summary of safety profile

Clinical trials - monotherapy and combination therapy

Based on an analysis of mCRC clinical trial patients receiving VECTIBIX monotherapy and in combination with chemotherapy (N = 2224), the most commonly reported adverse reactions are skin reactions occurring in 94% of patients. These reactions are related to the pharmacologic effects of panitumumab, and the majority are mild to moderate in

nature with 23% severe (Grade 3 NCI-CTC) and < 1% life threatening (Grade 4 NCI-CTC). (NCI-CTC is the US National Cancer Institute Common Toxicity Criteria).

Very commonly reported adverse reactions occurring in ≥ 20% of patients were gastrointestinal disorders [diarrhoea (46%), nausea (39%), vomiting (26%), constipation (23%) and abdominal pain (23%)]; general disorders [fatigue (35%), pyrexia (21%)]; metabolism and nutrition disorders [decreased appetite (30%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (47%), dermatitis acneiform (39%), pruritus (36%), erythema (33%) and dry skin (21%)].

Tabulated list of adverse events

The data in Table 2 describe adverse reactions reported from clinical studies in patients with mCRC who received VECTIBIX monotherapy or in combination with chemotherapy (N = 2224). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following convention (CIOMS III) has been utilised for the classification of frequency:

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000

Table 2. Incidence of adverse reactions in patients with metastatic colorectal cancer (VECTIBIX monotherapy or VECTIBIX in combination with chemotherapy)

Adverse reactions				
MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**
Blood and lymphatic system disorders	Anaemia	Leukopenia	Not applicable	Not applicable
Eye disorders	Not applicable	Lacrimation increased Dry eye Growth of eyelashes Blepharitis Eye irritation Eye pruritus Ocular hyperaemia	Eyelid irritation Keratitis	Not applicable
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	Dyspepsia Dry mouth Rectal haemorrhage	Chapped lips Lip dry	Not applicable

Adverse reactions				
MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**
	Constipation Stomatitis	Gastroesophageal reflux disease Abdominal pain lower Oral pain Cheilitis Aphthous ulcer		
General disorders and administration site conditions	Fatigue Pyrexia Asthenia Mucosal inflammation Oedema peripheral	Chest pain Pain Chills	Not applicable	Not applicable
Immune system disorders	Not applicable	Hypersensitivity	Anaphylactic reaction	Not applicable
Infections and infestations	Paronychia Conjunctivitis	Urinary tract infection Rash pustular Folliculitis Cellulitis Localised infection	Eye infection Nail infection Eyelid infection	Not applicable
Injury, poisoning and procedural complications	Not applicable	Not applicable	Infusion-related reaction	Not applicable
Investigations	Weight decreased	Blood magnesium decreased	Not applicable	Not applicable
Metabolism and nutrition disorders	Decreased appetite Hypomagnesaemia Hypokalaemia	Dehydration Hypocalcaemia Hyperglycaemia Hypophosphataemia	Not applicable	Not applicable
Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity	Not applicable	Not applicable
Nervous system disorders	Paraesthesia	Headache Dizziness	Cholinergic syndrome	Not applicable

Adverse reactions				
MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**
Psychiatric disorders	Insomnia	Anxiety	Not applicable	Not applicable
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	Epistaxis Pulmonary embolism	Nasal dryness Bronchospasm	Not applicable
Skin and subcutaneous tissue disorders	Rash Dermatitis acneiform Pruritus Erythema Dry skin Skin fissures Acne Alopecia	Exfoliative rash Nail disorder Skin exfoliation Palmar-plantar erythrodysaesthesia syndrome Skin ulcer Rash papular Scab Rash erythematous Hyperhidrosis Rash macular Hypertrichosis Rash maculo-papular Skin toxicity Onychoclasis Rash pruritic Hair growth abnormal Pain of skin Skin lesion Dermatitis Rash generalised	Ingrowing nail Onycholysis Hirsutism Angioedema	Not applicable
Vascular disorders	Not applicable	Deep vein thrombosis Flushing Hypotension Hypertension	Not applicable	Not applicable
Cardiac disorders	Not applicable	Tachycardia	Cyanosis	Not applicable

The worst grade event was included in the summary

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.

Description of selected adverse reactions

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 16% 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 94% of 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) and life-threatening (NCI-CTC Grade 4) skin reactions were reported in 32% and < 1%, respectively, 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 erythrodysaesthesia (PPE) syndrome was commonly reported in the setting of panitumumab in combination with chemotherapy. Skin drying and fissures were very 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 section 4.4 Special warnings and precautions for use, Dermatologic and soft tissue 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 31 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 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 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).

For clinical management of infusion-related reactions, see section 4.4 Special warnings and precautions for use, infusion reactions.

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

section 4.4 Special warnings and precautions for use).

Post marketing experience

Table 3 lists serious post marketing adverse reactions with VECTIBIX.

Table 3. VECTIBIX Post marketing adverse reactions in mCRC patients

Adverse reaction	Frequency
Toxic epidermal necrolysis	Uncommon
Keratitis	Rare
Ulcerative keratitis	Rare
Corneal perforation (including keratorhexis)	Unknown
Infusion reactions[#] (very rarely with a fatal outcome)	Unknown
Skin necrosis	Unknown
Stevens-Johnson syndrome	Unknown

[#]AEs associated with serious infusion reactions have included cardiorespiratory arrest, anaphylaxis, and increased blood pressure.

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

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 12 mg/kg (twice the recommended therapeutic dose of VECTIBIX).

Symptoms and Signs

Adverse events observed included skin toxicity, diarrhoea, dehydration and fatigue and are consistent with the safety profile at the recommended dose.

Treatment

In the event of overdosage, the patient should be observed and appropriate supportive treatment given.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulatory agents; monoclonal antibodies.

ATC code: L01XC08

Mechanism of action

Panitumumab is a fully human IgG2 monoclonal antibody that binds with high affinity and specifically to the human epidermal growth factor receptor (EGFR). Panitumumab binds 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.

Pharmacodynamic effects

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.

KRAS (Kirsten rat sarcoma 2 viral oncogene homologue) and *NRAS* (Neuroblastoma *RAS* viral oncogene homologue) are highly related members of the *RAS* oncogene family. *KRAS* and *NRAS* genes encode small, GTP-binding proteins involved in signal transduction. A variety of stimuli, including those from the EGFR, activate *KRAS* and *NRAS* which in turn stimulate other intracellular proteins to promote cell proliferation, cell survival and angiogenesis.

Activation of mutations in the *RAS* genes occurs frequently in a variety of human tumours and have been implicated in both oncogenesis and tumour progression.

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 pre-dose 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 pre-dose and transient positive patients) was < 1%;
- Compared with patients who did not develop antibodies, no relationship between the presence of anti-panitumumab antibodies and PK, efficacy and safety has been observed.

In combination with irinotecan- or oxaliplatin-based chemotherapy

- The incidence of binding antibodies (excluding pre-dose 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 pre-dose 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 section 5.1 Pharmacodynamic properties, 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 were 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 out of 463 patients (67%) 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 PFS and secondary endpoints including response rate and 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], $p < 0.001$).

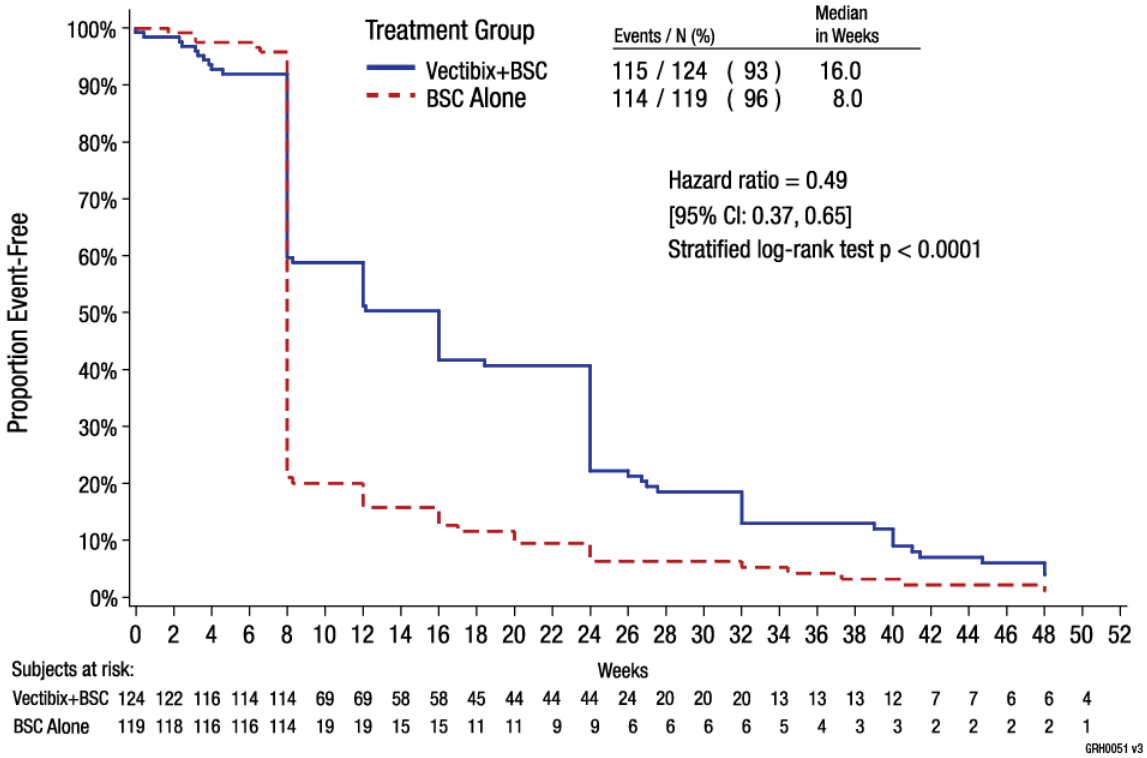
The relationship between clinical efficacy and *KRAS* mutational status was evaluated in tumour tissue in a prospectively defined analysis of the randomised controlled trial described above.

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.

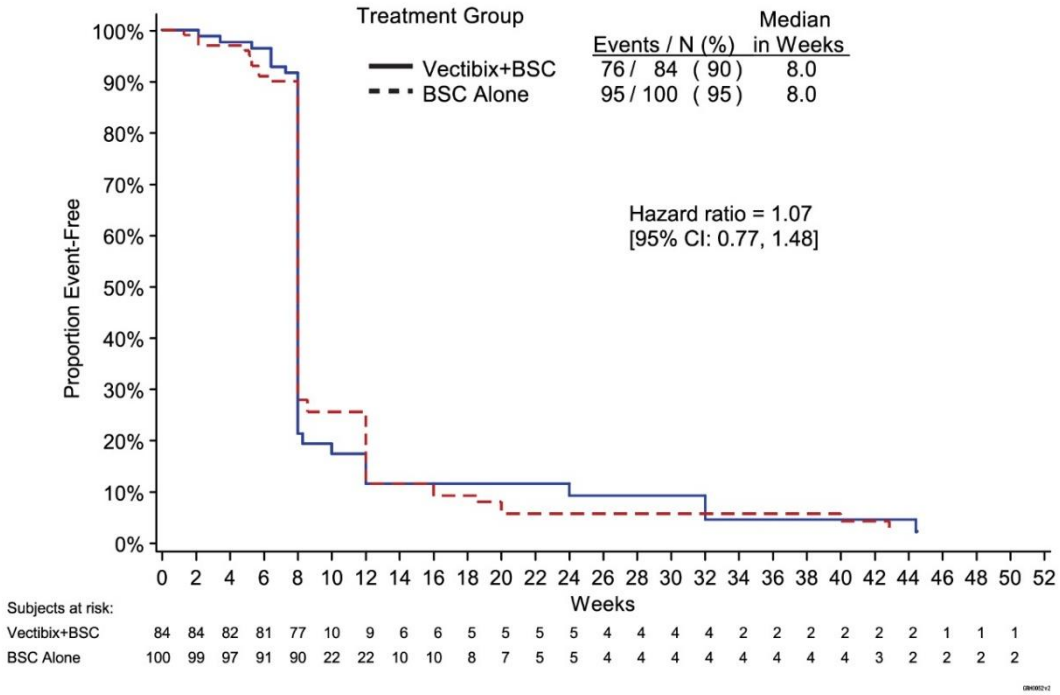
The HR for PFS was 0.45 [95% CI: 0.34-0.59] in patients with wild-type *KRAS* mCRC and 0.99 [95% CI: 0.73-1.36] in patients with mutant *KRAS* mCRC. In an analysis adjusting for potential bias from unscheduled assessments, the hazard ratio for PFS was 0.49 [95% CI: 0.37-0.65] in favour of panitumumab 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
(i) Wild-type *KRAS*



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

(ii) Mutant KRAS



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

In an exploratory analysis of banked tumour specimens from this study, 11 of 72 patients (15%) with wild-type *RAS* tumours receiving panitumumab had an objective response compared to only 1 of 95 patients (1%) with mutant *RAS* tumour status. Moreover, panitumumab treatment was associated with improved PFS compared to BSC in patients with wild-type *RAS* tumours (HR = 0.38 [95% CI: 0.27, 0.56]), but not in patients with tumours harbouring a *RAS* mutation (HR = 0.98 [95% CI: 0.73, 1.31]).

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.

Primary analysis

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 (HR = 0.80 [95% CI: 0.66, 0.97]; p-value = 0.02). PFS was significantly improved in the panitumumab plus FOLFOX arm compared to 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 (HR = 0.83 [95% CI: 0.67, 1.02]; p-value = 0.072). The difference did not achieve statistical significance.

Predefined retrospective subset analysis of efficacy and safety by RAS (i.e., KRAS and NRAS) and RAS/BRAF biomarker status

A predefined retrospective subset analysis of 641 patients of the 656 patients with wild-type *KRAS* (exon 2) mCRC was performed. The primary objective of this analysis was to examine the treatment effect of panitumumab plus FOLFOX compared with FOLFOX alone in patients who were wild-type for *RAS* (*KRAS* and *NRAS* exons 2, 3, and 4) or wild-type for *RAS* and *BRAF* (*KRAS* and *NRAS* exons 2, 3, and 4 and *BRAF* exon 15). In this analysis, patient tumour samples with wild-type *KRAS* exon 2 (codons 12/13) status were tested using Sanger bidirectional sequencing and Surveyor®/WAVE® analysis in parallel for additional *RAS* mutations in:

- *KRAS* exon 3 (codon 61) and exon 4 (codons 117/146), and
- *NRAS* exon 2 (codons 12/13), exon 3 (codon 61), and exon 4 (codons 117/146).

In the analysis, the incidence of these additional RAS mutations in the wild-type KRAS (exon 2) population was approximately 16%.

In this analysis, *BRAF* mutation was found to be prognostic of worse outcome but not predictive of negative outcome for panitumumab treatment.

In patients with wild-type *RAS* mCRC (n = 512) the estimated median PFS was 10.1 months (95% CI: 9.3, 12.0) in the panitumumab plus FOLFOX arm and 7.9 months (95% CI: 7.2, 9.3) in the FOLFOX alone arm, an absolute difference of 2.2 months. The estimated hazard ratio was 0.72 (95% CI: 0.58, 0.90) favouring the panitumumab plus FOLFOX arm.

The estimated median OS was 26.0 months (95% CI: 21.7, 30.4) in the panitumumab plus FOLFOX arm and 20.2 months (95% CI: 17.7, 23.1) in the FOLFOX alone arm, an absolute difference of 5.8 months. The estimated hazard ratio was 0.78 (95% CI: 0.62, 0.99), favouring the panitumumab plus FOLFOX arm.

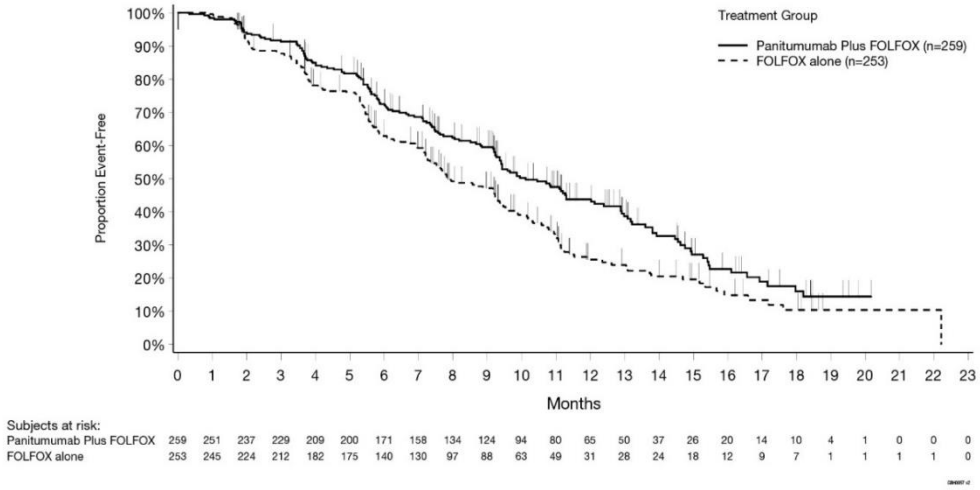
In patients with mutant *RAS* mCRC (n = 548), the PFS was inferior in patients receiving panitumumab in combination with FOLFOX (7.3 months; [95% CI: 6.3, 7.9]) than in those patients receiving FOLFOX alone (8.7 months; [95% CI: 7.6, 9.4]). The estimated median OS was shorter in patients receiving panitumumab in combination with FOLFOX (15.6 months; [95% CI: 13.4, 17.9]) compared with those receiving FOLFOX alone (19.2 months; [95% CI: 16.7, 21.8]) (see section 4.3 Contraindications).

In patients with wild-type *KRAS* (exon 2) mutant *RAS* mCRC (n = 108) (patients with wild-type *KRAS* exon 2 mCRC in the original primary analysis who had additional newly identified *KRAS* or *NRAS* mutations in the predefined retrospective subset analysis), the PFS was inferior in patients receiving panitumumab in combination with FOLFOX (7.3 months; [95% CI: 5.3, 9.2]) than those patients receiving FOLFOX alone (8.0 months; [95% CI: 6.4, 11.3]). The estimated median OS was shorter in patients receiving panitumumab in combination with FOLFOX (17.1 months; [95% CI: 10.8, 19.4]) compared with those receiving FOLFOX alone (18.3 months; [95% CI: 13.0, 23.2]) (see section 4.3 Contraindications).

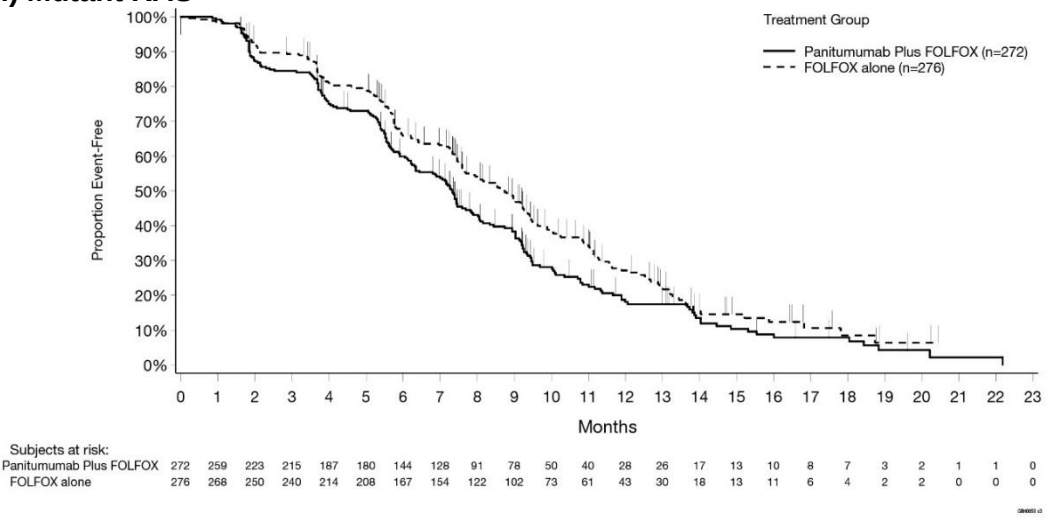
Results in patients with wild-type *RAS* mCRC, mutant *RAS* mCRC and wild-type *KRAS* (exon 2) mutant *RAS* mCRC from the primary analysis are presented in Figure 2 and Figure 3.

Figure 2. PFS (Primary analysis) – Patients with wild-type *RAS* mCRC, mutant *RAS* mCRC and wild-type *KRAS* (exon 2) mutant *RAS* mCRC

(i) Wild-type RAS



(ii) Mutant RAS



(iii) Wild-type *KRAS* Exon 2 Mutant *RAS*

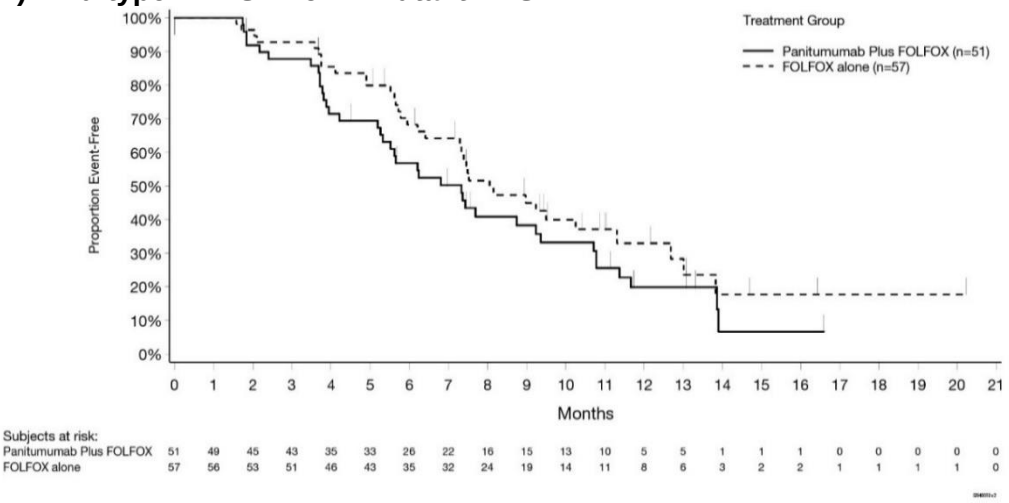
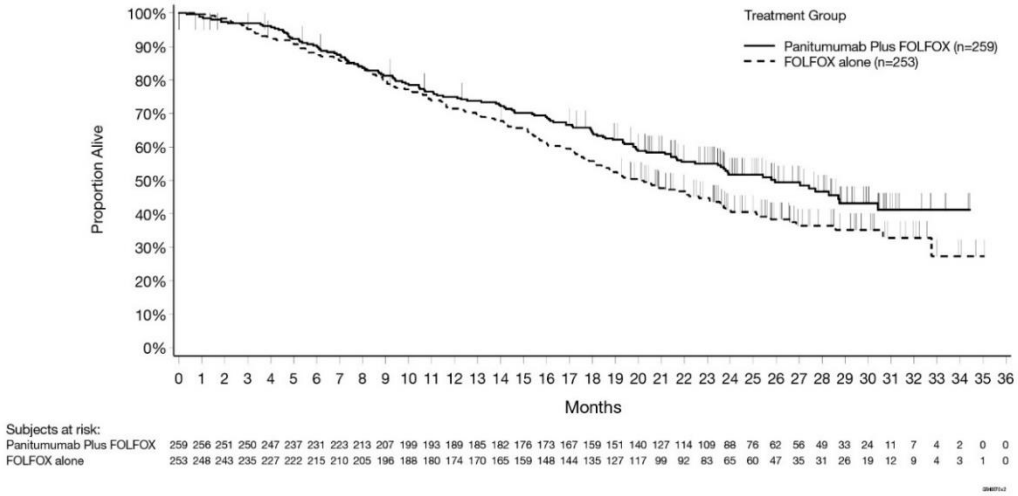
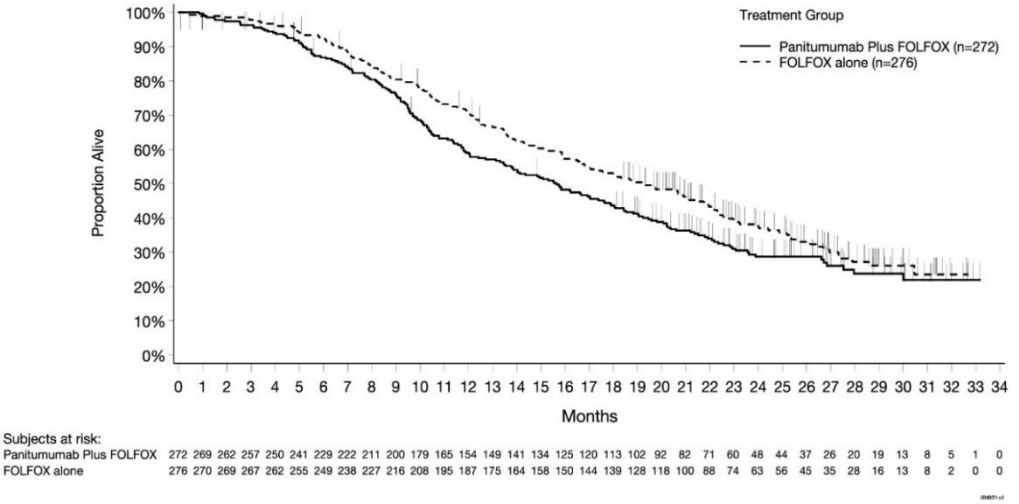


Figure 3. OS (Primary analysis) – Patients with wild-type *RAS* mCRC, mutant *RAS* mCRC and wild-type *KRAS* (exon 2) mutant *RAS* mCRC

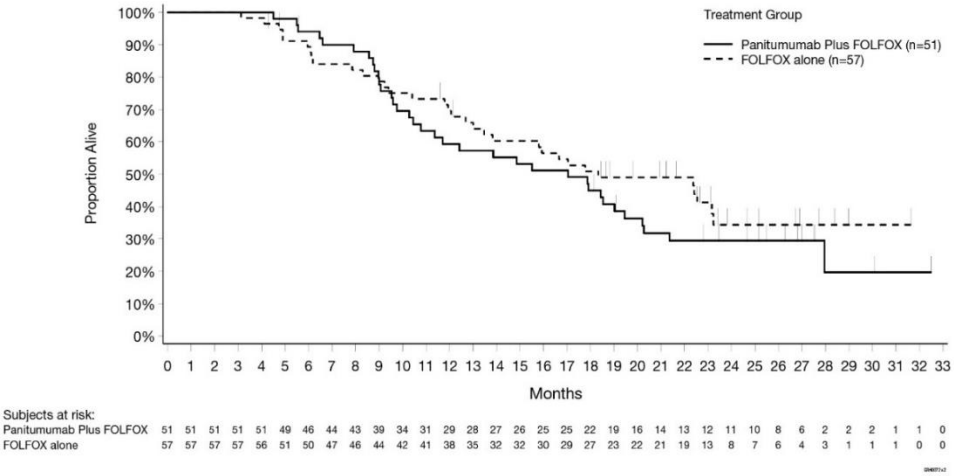
(i) Wild-type RAS



(ii) Mutant RAS



(iii) Wild-type KRAS Exon 2 Mutant RAS



In an exploratory covariate analysis of patients with wild-type *RAS* mCRC and an ECOG 2 performance status (n = 33), 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): 1.66 (0.73, 3.78)]. In patients with an ECOG performance status of 0 or 1 (n = 479), the median OS was 27.4 months in the panitumumab plus FOLFOX arm and 20.7 months in the FOLFOX alone arm [HR (95% CI): 0.73 (0.57, 0.94)] (Table 4).

Table 4. Study 20050203 - efficacy results by baseline ECOG performance status in patients with wild-type *RAS* mCRC

	ECOG 0/1 Status		ECOG 2 Status	
	Panitumumab + FOLFOX n = 243	**FOLFOX Alone n = 236**	**Panitumumab + FOLFOX n = 16**	**FOLFOX Alone n = 17**
PFS Hazard Ratio (95% CI)	0.68 (0.54, 0.85)		2.03 (0.85, 4.82)	
Median PFS (months)	10.8	7.9	4.8	8.9
OS Hazard Ratio (95% CI)	0.73 (0.57, 0.94)		1.66 (0.73, 3.78)	
Median OS (months)	27.4	20.7	7.0	11.7
Objective Response Rate[a]	61%	47%	25%	35%

[a] of patients with measurable disease

Subsequent to the predefined analysis, additional mutations in *KRAS* and *NRAS* at exon 3 (codon 59) were identified (n = 7). In an exploratory analysis, adding codon 59 also appeared to be predictive of negative outcomes for panitumumab treatment.

Second-line combination with FOLFIRI

The efficacy of VECTIBIX in combination with irinotecan, 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.

Primary analysis

In patients with wild-type *KRAS* mCRC (n = 597) a statistically significant difference in PFS in favour of panitumumab was demonstrated. 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 (HR = 0.73 [95% CI: 0.59, 0.90]; p-value = 0.004). 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 (HR= 0.85 [95% CI: 0.70, 1.04]; p-value = 0.12). The OS difference did not achieve statistical significance.

Although in an exploratory covariate analysis of patients with wild-type KRAS mCRC, 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 5).

Table 5. Study 20050181 - efficacy results by baseline ECOG performance status in patients with wild-type *KRAS* mCRC

	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

Given the limited patient numbers in the ECOG 2 subgroup, no conclusion should be made regarding this population (Table 6).

Table 6. Study 20050181 - efficacy results by baseline ECOG performance status in patients with wild-type *RAS* mCRC

	ECOG 0/1 Status		ECOG 2 Status	
	Panitumumab + FOLFOX	**FOLFOX Alone**	**Panitumumab + FOLFOX**	**FOLFOX Alone**
	n = 394		**n = 27**	
PFS Hazard Ratio (95% CI)	0.76 (0.58, 0.98)		0.71 (0.30, 1.66)	
OS Hazard Ratio (95% CI)	0.83 (0.65, 1.07)		1.05 (0.48, 2.29)	

Predefined retrospective subset analysis of efficacy and safety by RAS (i.e., KRAS and NRAS) and RAS/BRAF biomarker status

A predefined retrospective subset analysis of 586 patients of the 597 patients with wild-type *KRAS* (exon 2) mCRC was performed. Additional *RAS* mutations beyond *KRAS*

exon 2 (i.e, *KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4) and mutations in *BRAF* exon 15 were examined to assess the effect of panitumumab when added to the FOLFIRI chemotherapy backbone in the second-line mCRC treatment setting. In this analysis, patient tumour samples with wild-type *KRAS* exon 2 status were tested using Sanger bidirectional sequencing for additional *RAS* mutations in:

- *KRAS* exon 3 (codons 59 and 61) and exon 4 (codons 117 and 146),
- *NRAS* exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146), and
- *BRAF* exon 15 (codon 600).

The *RAS* and *RAS*/*BRAF* ascertainment rates were both 85% overall (1014 of 1186 randomised patients). In this analysis, the incidence of these additional *RAS* mutations (*KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4) in the wild-type *KRAS* (exon 2) population was approximately 19%. The incidence of *BRAF* exon 15 mutation in the wild-type *KRAS* (exon 2) population was approximately 8%.

Among patients with wild-type *RAS* mCRC, panitumumab plus FOLFIRI conferred a modest gain in PFS (absolute difference of 1.8 months), with non-significant benefit in OS, and improvement in ORR, compared with those receiving FOLFIRI alone. Patients with additional *RAS* mutations beyond *KRAS* exon 2 were unlikely to benefit from the addition of panitumumab to FOLFIRI (Table 7).

Table 7. Study 20050181 - efficacy results by *RAS* status

	Wild-type *RAS*		**Mutant *RAS***		**Wild-type *KRAS* (exon 2) Mutant *RAS***	
	Panitumumab + FOLFIRI n = 208	**FOLFIRI Alone n = 213**	**Panitumumab + FOLFIRI n = 299**	**FOLFIRI Alone n = 294**	**Panitumumab + FOLFIRI n = 61**	**FOLFIRI Alone n = 46**
PFS						
Hazard Ratio (95% CI)	0.70 (0.54, 0.91)		0.86 (0.71, 1.05)		0.89 (0.56, 1.42)	
p-value	0.007		0.144		0.627	
Median PFS (months)	6.4 (5.5, 7.4)	4.6 (3.7, 5.6)	4.8 (3.7, 5.5)	4.0 (3.6, 5.5)	3.7 (2.3, 5.8)	3.7 (2.8, 5.1)
OS						
Hazard Ratio (95% CI)	0.81 (0.63, 1.03)		0.91 (0.76, 1.10)		0.83 (0.53, 1.29)	
p-value	0.080		0.345		0.402	
Median OS (months)	16.2 (14.5, 19.7)	13.9 (11.9, 16.0)	11.8 (10.4, 13.1)	11.1 (10.2, 12.4)	11.3 (8.3, 13.1)	9.2 (7.0, 12.9)

In this analysis, *BRAF* mutation appears to be a negative prognostic factor associated with reduced PFS and OS among patients with wild-type *KRAS* exon 2 mCRC,

regardless of treatment arm. The data, from a small number of patients, also suggest that *BRAF* mutation did not have additional predictive value for the effect of panitumumab therapy; although in this study, for patients with BRAF mutant tumours the OS was shorter in the combination arm.

5.2 Pharmacokinetic properties

Panitumumab administered as a single agent or in combination with chemotherapy exhibits nonlinear pharmacokinetic properties (PK).

Distribution

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.

Excretion

The concentration-time profile is best described by a 2-compartment (central and peripheral) PK 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).

Special populations

A population PK analysis was performed to explore the potential effects of selected covariates on panitumumab PK. 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 PK of panitumumab.

Use in hepatic impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK panitumumab.

Use in renal impairment

No clinical studies have been conducted to evaluate the effect of renal impairment on the PK of panitumumab.

Use in the elderly

No age-related differences in the PK of panitumumab were observed in clinical studies in patients 26 to 85 years of age (see section 4.4 Special warnings and precautions for use, Use in the elderly).

5.3 Preclinical safety data

Genotoxicity

The genotoxic potential of panitumumab has not been evaluated.

Carcinogenicity

The carcinogenic potential of panitumumab has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

VECTIBIX contains the following inactive ingredients: sodium acetate, sodium chloride, and water for injections. Each mL of concentrate contains 3.45 mg sodium.

6.2 Incompatibilities

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.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

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 FREEZE. **DO NOT SHAKE**.

6.5 Nature and contents of container

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.

Presentations available in Australia:

- 5 mL single-use vial containing 100 mg of panitumumab
- 20 mL single-use vial containing 400 mg of panitumumab

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.

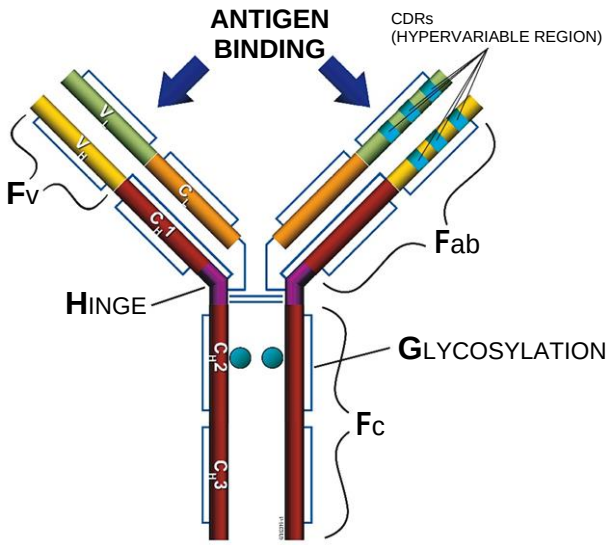
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Panitumumab is produced using recombinant DNA technology in Chinese hamster ovary (CHO) and/or genetically engineered mammalian cell line. It consists of two gamma heavy chains and two kappa light chains. The molecular weight (MW) of panitumumab is approximately 147 kilodaltons (kDa).



CAS number

339177-26-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (S4) - Prescription Only Medicine

8. SPONSOR

Amgen Australia Pty Ltd

Level 11, 10 Carrington St

Sydney NSW 2000

Ph: 1800 803 638

www.amgenmedinfo.com.au

Email: medinfo.JAPAC@amgen.com

9. DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: 14 May 2008

10. DATE OF REVISION

1 September 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Update sponsor address