Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

PANitumumab

COMMON TRADE NAME(S): Vectibix®

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B - Mechanism of Action and Pharmacokinetics

Panitumumab is a recombinant, fully humanized IgG2 monoclonal antibody. It binds competitively to the extracellular domain of epidermal growth factor receptor (EGFR) on normal or tumour cells, and thus inhibits ligand-induced receptor autophosphorylation and pathway activation. The KRAS gene encodes a protein involved in signal transduction. Patients with mutated KRAS colorectal tumours do not appear to benefit from EGFR monoclonal antibody inhibitor therapy.

Distribution	After IV administration, panitumumab demonstrates two-compartmental pharmacokinetics. Pharmacokinetics are non-linear at lower doses until receptor saturation occurs, but is dose-proportional at doses > 2mg/kg. Steady state reached after 3 doses q2w. Age, gender, tumour type, race, hepatic function, renal function, EGFR membrane expression do not appear to affect panitumumab pharmacokinetics.	
	Cross blood brain barrier?	low levels
	PPB	No information found
Metabolism	Active metabolites	none
	Inactive metabolites	none
Elimination	Eliminated via the reticuloendothelial system, or bound to EGFR (saturable pathway) to be internalized and degraded.	

Half-life	7.5 days

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C - Indications and Status

Health Canada Approvals:

- Colorectal cancer

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following side effects were mainly observed in the pivotal colorectal trial in RAS wild type patients where the incidence was >1% higher than the control arm.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (5%)	E
	Venous thromboembolism (<1%)	E
Dermatological	Abnormal eyelash growth (<10%)	D
	Hand-foot syndrome (3%)	E
	Other (24%) (skin fissures)	E
	Paronychia (33%)	E
	Rash, pruritus (70%) (including acneiform rash, 8% severe)	E
	Skin necrosis / soft tissue necrosis (rare)	E
	Stevens-Johnson syndrome (rare)	E

	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Abdominal pain (27%)	E
	Anorexia, weight loss (30%)	E
	Constipation (24%)	E
	Diarrhea (24%) (may be severe)	E
	Gastritis (3%)	E
	GI obstruction (7%)	E
	Mucositis (7%)	E
	Nausea, vomiting (18%)	I
General	Edema (11%)	E
	Fatigue (33%)	E
Hematological	Anemia (7%)	E
	Hemorrhage (5%) (including hemoptysis, epistaxis)	E
Hepatobiliary	↑ LFTs (7%)	E
Hypersensitivity	Hypersensitivity (3%) (<1% severe)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (4%) (↓Mg, Ca, K; may be severe)	E D
Musculoskeletal	Musculoskeletal pain (13%)	E
Nervous System	Depression (5%)	E
	Insomnia (5%)	E
	Paresthesia (3%)	E
Ophthalmic	Conjunctivitis (3%)	E
	Keratitis (may be ulcerative - rare)	E
Renal	Renal failure (2%)	E
Respiratory	Cough, dyspnea (20%)	E
	Pneumonitis (rare)	D
Urinary	Urinary symptoms (4%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for panitumumab include rash, pruritus, fatigue, paronychia, anorexia, weight loss, abdominal pain, constipation, diarrhea, skin fissures, cough, dyspnea, nausea and vomiting.

Increased toxicity and decreased overall survival has been reported in combination with bevacizumab and chemotherapy.

Dermatological toxicities are seen in most patients, most notably a typical **acneiform rash**. Paronychia and skin fissures are also seen. Complications such as infection, necrotizing fasciitis, sepsis (death in rare cases), and local abscesses requiring drainage have been reported. Most commonly affected sites included the face, upper back and chest, and sometimes in the extremities. The median time of developing dermatologic toxicity was 10 days, and the median time to resolution after discontinuing panitumumab was 37 days. As sun exposure may exacerbate skin reactions, patients should be advised to use sunscreen, wear a hat and limit sun exposure. Refer to the Canadian recommendations for the management of skin rash during EGFR-targeted monoclonal antibody treatment for GI malignancies (Melosky 2009).

Rare cases of severe rash including **Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)** have been reported, presenting within 7-14 days of starting treatment. Panitumumab should be discontinued.

Interstitial Lung Disease (ILD) is a rare but possibly fatal adverse event with EGFR inhibitors. Patients with acute or worsening respiratory symptoms should have panitumumab held pending diagnosis. If ILD, lung infiltrates, or pneumonitis is confirmed, panitumumab should be discontinued. Patients with history of pulmonary fibrosis or interstitial pneumonitis may have increased risks of developing ILD.

Less than 1% of patients experienced severe (grade 3 to 4) **infusion reactions**, characterized by anaphylaxis, angioedema, bronchospasm, fever, chills, and hypotension. Fatal or late reactions (>24 h after infusion) have been reported.

Hypomagnesemia of any grade occurred at various time points during treatment and may be progressive and associated with hypocalcemia and/or hypokalemia. Serious cases occurred 6 weeks or longer after start of panitumumab. Most grade 3 or higher hypomagnesemic patients received IV electrolyte supplementation. Hypocalcemia was also observed in less than 1% of patients with hypomagnesemia. Electrolytes should be monitored periodically during and for 8 weeks after the end of panitumumab treatment.

Ocular toxicities have been reported, including severe cases of keratitis and ulcerative keratitis.

Neutralizing antibodies develop in <1% of patients (excluding pre-dose and transient positive patients) and do not appear to be clinically relevant.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

RAS wild type status should be confirmed by validated test prior to starting treatment.

Other Supportive Care:

- As sun exposure may exacerbate skin reactions, patients should be advised to use sunscreen, wear a hat and limit sun exposure.
- The following has been shown to be of benefit when used from the day before treatment to week 6: (Lacouture et al, 2010)
  - Skin moisturizer applied to the face, hands, feet, neck, back and chest in the morning
  - Sunscreen to exposed areas (SPF ≥ 15, UVA and UVB) before going outdoors
  - Hydrocortisone 1% cream to the face, hands, feet, neck, back and chest at bedtime
  - Doxycycline (or minocycline) PO
- Refer to the product monograph and Canadian recommendations for the management of skin rash during EGFR-targeted monoclonal antibody treatment for GI malignancies. (Melosky 2009)

Adults:

No loading dose or premedications are required.

Intravenous: 6 mg/kg every 14 days

Dosage with Toxicity:

Toxicity	Action^	Dose Modification (% previous dose)
≥ grade 3 skin (1st occurrence)	Hold until ≤ grade 2*	Restart at 100%
≥ grade 3 skin (2nd occurrence)	Hold until ≤ grade 2*	Restart at 80%
≥ grade 3 skin (3rd occurrence)	Hold until ≤ grade 2*	Restart at 60%
≥ grade 3 skin (4th occurrence)	Discontinue	n/a
Skin or soft tissue with severe or life-threatening inflammatory or infectious complications	Hold or discontinue, depending on severity	n/a
SJS/TEN	Discontinue	n/a
≥ grade 3 diarrhea or dehydration	Hold until ≤ grade 2	Consider dose reduction, if appropriate
ILD/pneumonitis	Hold and investigate	If confirmed, discontinue.
Keratitis or ulcerative keratitis	Hold or discontinue, depending on severity or persistence	n/a
*Hold for 1 to 2 doses until recovery. Discontinue if no recovery within 4 weeks. ^For treatment of skin reactions, may refer to the Canadian recommendations for the management of skin rash during EGFR-targeted monoclonal antibody treatment for GI malignancies (Melosky 2009).		

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • Restart the infusion at 50% of the rate at which the IR occurred.	• Re-challenge the infusion at 50% of the rate at which the IR occurred.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with Hepatic Impairment:

The safety and efficacy of panitumumab have not been studied in hepatic impairment.

Dosage with Renal Impairment:

The safety and efficacy of panitumumab have not been studied in renal impairment. Acute renal failure has been observed in patients experiencing severe diarrhea and dehydration (see dosage with toxicity table for management).

Dosage in the elderly:

No dose modifications are required. No overall differences in safety or efficacy were observed for monotherapy in patients aged 65 and older compared to younger patients. An increased number of severe adverse effects were reported in elderly patients treated with panitumumab in combination with irinotecan or oxaliplatin-based chemotherapy compared to chemotherapy alone.

Children:

The safety and efficacy of panitumumab in pediatric patients have not been established.

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F - Administration Guidelines

- DO NOT administer as an IV push or bolus; MUST be administered using an IV infusion pump.
- Diluted with 0.9% sodium chloride only. Do not mix with other drugs or IV solutions.
- Dilute in a total volume of 100mL in sodium chloride 0.9% (Final concentration must be ≤ 10mg/mL). Infuse IV over 60 minutes. May give via peripheral line or in-dwelling catheter. If the first infusion is tolerated, subsequent infusions may be given over 30 to 60 minutes.
- Doses higher than 1000mg should be diluted in 150mL 0.9% sodium chloride injection, and infused IV over 90 minutes.
- Compatible with 0.9% sodium chloride in PVC bags or polyolefin bags
- Administer using a low-protein binding 0.2 micron or 0.22 micron in-line filter.
- Solution may contain a small amount of visible, amorphous, panitumumab particulates that will be removed by the low protein binding in-line filter during infusion.
- Do not shake. Mix diluted solution by gentle inversion.
- Flush line before and after administration with 0.9% sodium chloride.
- Missed Dose: Panitumumab should be given within 3 days of scheduled dose. If a dose is missed, it should be administered as soon as possible and the next dose should be given on a new schedule relative to last administered dose.
- Keep unopened vials refrigerated (2 to 8°C) in the original carton. Protect from direct sunlight and do not freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Panitumumab is NOT indicated for patients with RAS mutant mCRC or for whom RAS mutation status is unknown.

Other Warnings/Precautions:

- Consider risks and benefits before starting treatment in patients with a history of pulmonary fibrosis or ILD. These patients were excluded from clinical trials.
- It should not be used in combination with bevacizumab and chemotherapy due to unacceptable toxicity, including deaths and shorter survival.
- In a phase III panitumumab trial, patients with ECOG 2 had increased toxicity and shortened survival compared to those with ECOG 0-1. Assess risk vs. benefit prior to treatment in patients with ECOG 2.
- Use with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.
- If patients experience treatment-related effects on vision and/or ability to concentrate and react, they should not drive or operate machinery until the effect subsides.
- The panitumumab formulation contains 0.15 mmol sodium (= 3.45 mg sodium) per mL of concentrate. This sodium content should be taken into consideration in patients on sodium restriction.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Fetotoxicity: Yes
- Crosses placental barrier: Yes
  Panitumumab is not recommended for use in pregnancy as it may cause fetal harm. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose.
- Breastfeeding: Not recommended
  As human IgG is excreted in milk, discontinue breastfeeding during panitumumab therapy and for **2 months** following the last dose.
- Fertility effects: Probable

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H - Interactions

Interactions with other drugs, food, herbal products, and laboratory tests have not been established.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Electrolytes (including calcium, magnesium and potassium)	Baseline, before each dose, and monthly for 8 weeks after completion of therapy
CBC	Baseline and as clinically indicated
Liver function tests	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Clinical pulmonary exam	Baseline and as clinically indicated
Clinical toxicity assessment (including infusion reactions, dermatological, gastrointestinal, dehydration, pulmonary, ophthalmic).	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Panitumumab - Metastatic Colorectal Small Bowel or Appendiceal Cancer
- Panitumumab - In Combination with Chemotherapy for Metastatic Colorectal, Small Bowel, or Appendiceal Cancer
- Panitumumab - In Combination with Encorafenib for Previously Treated Metastatic Colorectal Cancer
- Panitumumab - First-Line Treatment for Left-Sided Metastatic Colorectal Cancer

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K - References

Product Monograph: Vectibix® (Panitumumab). Amgen Canada, March 2017.

Product Monograph: Vectibix® (Panitumumab). Amgen Canada, October 25, 2021.

Vectibix® (Panitumumab) Prescribing Information. Amgen USA, August 2012.

Kang P et al. Infusion-Related and Hypersensitivity Reactions of Monoclonal Antibodies Used to Treat Colorectal Cancer—Identification, Prevention, and Management. Journal of Supportive Oncology 2007; 5(9): 451-7.

Lacouture, ME, Mitchell EP, Piperdi B et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 2010; 28: 1351-7.

Melosky B, Burkes R, Rayson D, et al. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Current Oncology 2009; 16(10): 14-24.

Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014;32(21):2240-7.

Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007; 25: 1658-64.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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