MANAGING TREATMENT WITH VECTIBIX® (PANITUMUMAB FOR INJECTION)

A Guide for Healthcare Professionals

VICTORY® Program
Patient Assistance Program
by AMGEN Entrust®

Vectibix®
panitumumab for injection

This summary has been prepared to provide information about dosing and the management of selected toxicities during Vectibix treatment. Any treatment decisions are the sole responsibility of the healthcare professional.

A Guide for Healthcare Professionals

Vectibix (panitumumab for injection) is indicated for the treatment of previously untreated patients with non-mutated (wild-type) *RAS* metastatic colorectal carcinoma (mCRC) in combination with FOLFOX (infusional 5-fluorouracil, leucovorin, and oxaliplatin).

Vectibix is indicated as monotherapy for the treatment of patients with non-mutated (wild-type) *RAS* mCRC after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

The safety and effectiveness of Vectibix have not been established in pediatric patients (<18 years old).

No overall differences in safety or efficacy were observed in elderly patients (≥65 years of age) compared to patients <65 years of age treated with Vectibix monotherapy.

An increased number of serious adverse events were reported in elderly patients (≥65 years old) with wild-type *RAS* mCRC treated with Vectibix + FOLFOX (57%) vs. FOLFOX alone (38%).

RAS TESTING

Evidence of wild-type *RAS* (*KRAS* and *NRAS*) status is required before initiating treatment with Vectibix (panitumumab for injection)[1]

- *KRAS* and *NRAS* mutations (collectively referred to as *RAS* mutations) are found in patients with metastatic colorectal cancer.[2]*
- Mutations may occur at codons 12 and 13 (exon 2), codons 59 and 61 (exon 3), and codons 117 and 146 (exon 4) of both *KRAS* and *NRAS*.[2]
- In patients being considered for Vectibix therapy, tumour genetic marker testing should include detection of *KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4) mutations.[1]

The National Comprehensive Cancer Network® (NCCN) recommends *RAS* analysis (*KRAS/NRAS*) of tumour tissue in all patients with metastatic colorectal cancer.[3†]

The NCCN Colon/Rectal Cancer Panel believes that *RAS* mutation status should be determined at diagnosis of stage IV mCRC.[3†]

* Clinical significance has not been established. Vectibix is not indicated for patients with mutant *RAS* (*KRAS/NRAS*) mCRC or for whom *RAS* status is unknown.

† Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V4. 2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed October 7, 2025. To view the most recent and complete version of the guideline, visit NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

National Comprehensive Cancer Network® (NCCN®)

STORAGE[1]

Vials

- Vectibix (panitumumab for injection) is supplied as a sterile, colourless, and preservative-free solution (20 mg/mL) containing 100 or 400 mg of panitumumab in 5 and 20 mL single-use vials, respectively.
- Store vials in the original carton under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) until time of use.
- Protect from direct sunlight.
- **Do not freeze.**
- **Do not shake.**
- Discard any unused portion remaining in the vial after the single use.

Diluted infusion solutions

- Use immediately after dilution.
- If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should be no longer than 24 hours at 2 °C to 8 °C (36 °F to 46 °F).
- Do not freeze or shake diluted infusion solution.

PREPARATION[1]

Recommended dose: 6 mg/kg

- Prepare using appropriate aseptic technique.
- Withdraw the necessary amount of Vectibix (panitumumab for injection) for a dose of 6 mg/kg of body weight.
  - Do not use a hypodermic needle with a gauge less than 21-gauge to withdraw
  - Do not use needle-free devices (e.g., vial adapters) to withdraw vial contents
- Dilute in 0.9% sodium chloride injection USP:
  - Dilute to a maximum concentration of ≤10 mg/mL
  - Dilute to a total volume of 100 mL
- **Do not shake;** mix diluted solution by gentle inversion.

ADMINISTRATION[1]

Dosing frequency: every 2 weeks (Q2W)

The ONLY FULLY HUMAN IgG2
anti-EGFR monoclonal antibody for mCRC*

First infusion time: 60 minutes at doses ≤1000 mg†

Subsequent infusion times, if the first infusion is tolerated: 30–60 minutes at doses ≤1000 mg†

† The infusion time for doses >1000 mg is approximately 90 minutes.

* Comparative clinical significance unknown.

ADMINISTRATION[1]

- Vectibix (panitumumab for injection) should be inspected visually prior to administration.
- The solution may contain a small amount of visible, translucent-to-white amorphous, proteinaceous panitumumab particulates (which will be removed by in-line filtration).
- Do not administer Vectibix if its appearance is not as described above.
- Do not mix or administer Vectibix infusion with other medicinal products.
- Do not add other medications to solutions containing Vectibix.
- Flush line before and after Vectibix administration with 0.9% sodium chloride injection USP to avoid mixing with other drug products or IV solutions.
- Do not administer Vectibix as an IV push or bolus.
- Vectibix must be administered using an IV infusion pump.
- Administer using a low protein binding 0.2 µm or 0.22 µm in-line filter.

DOSE MODIFICATIONS

Infusion reactions:

- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.
- Stop infusion if a severe or life-threatening infusion reaction occurs. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix.

Severe infusion reactions reported in clinical trials:

- In patients enrolled in monotherapy trials (N=842), NCI-CTC grade 3 and 4 reactions occurred in 0.6% of patients administered Vectibix.
- In patients with *RAS*‡ wild-type mCRC enrolled in the PRIME study:
  - NCI-CTC grade ≥3 reactions occurred in 2.7% of patients administered Vectibix + FOLFOX (n=256) and in 2.0% of patients administered FOLFOX alone (n=250).

See page 18 for dose modifications for dermatologic reactions.

‡ *KRAS* (exons 2, 3, 4) and *NRAS* (exons 2, 3, 4)

PRIME STUDY TOXICITIES[1]

Most Frequent (≥25%*) Adverse Reactions in Patients With Wild-Type *RAS* mCRC†

		Vectibix (panitumumab for injection) + FOLFOX (n=256)		FOLFOX alone (n=250)	
System Organ Class	Preferred Term	Any Grade n (%)	Grade 3–4 n (%)	Any Grade n (%)	Grade 3–4 n (%)
Gastrointestinal disorders	Diarrhea	167 (65)	48 (19)	129 (52)	22 (9)
	Stomatitis	77 (30)	14 (5)	36 (14)	1 (<1)
	Abdominal pain	71 (28)	12 (5)	62 (25)	13 (5)
General disorders and administration site conditions	Fatigue	100 (39)	26 (10)	90 (36)	7 (3)
	Pyrexia	81 (32)	2 (<1)	71 (28)	7 (3)
	Mucosal inflammation	64 (25)	13 (5)	40 (16)	1 (<1)
Metabolism and nutrition disorders	Anorexia	93 (36)	11 (4)	66 (26)	5 (2)
	Hypomagnesemia	77 (30)	19 (7)	17 (7)	NR
Nervous system disorders	Paraesthesia	83 (32)	23 (9)	75 (30)	15 (6)
Skin and subcutaneous tissue disorders	Rash	142 (55)	44 (17)	20 (8)	1 (<1)
	Dermatitis acneiform	86 (34)	26 (10)	NR	NR
	Pruritus	66 (26)	3 (1)	11 (4)	NR

NR=not reported in the Vectibix Product Monograph.

* ≥25% and a ≥2% difference between treatment arms.

† Patients with wild-type *KRAS* (exons 2, 3, 4) and *NRAS* (exons 2, 3, 4) mCRC enrolled in Study 20050203 (PRIME=The **P**anitumumab **R**andomized Trial **I**n Combination With Chemotherapy for **M**etastatic Colorectal Cancer to Determine **E**fficacy).

ASPECCT STUDY TOXICITIES[1]

Most Frequent (≥20%*) Adverse Reactions in Patients With Wild-Type *KRAS* (exon 2) mCRC†

		Vectibix (panitumumab for injection) (n=496)		Cetuximab (n=503)	
System Organ Class	Preferred Term	Any Grade n (%)	Grade 3–4 n (%)	Any Grade n (%)	Grade 3–4 n (%)
Metabolism and nutrition disorders	Hypomagnesemia	136 (27)	35 (7)	89 (18)	13 (3)
Skin and subcutaneous tissue disorders	Rash	249 (50)	24 (5)	257 (51)	18 (4)
	Dermatitis acneiform	138 (28)	17 (3)	136 (27)	14 (3)

Infusion reactions were reported in 3% of patients receiving Vectibix and 13% of patients receiving cetuximab.

*In the Vectibix arm.

† Patients with wild-type *KRAS* (exon 2) mCRC enrolled in Study 20080763.

(ASPECCT=**A** **S**tudy of **P**anitumumab **E**fficacy and Safety **C**ompared to **C**e**T**uximab).

STUDY 007 TOXICITIES[1]

Most Frequent (≥20%*) Adverse Reactions in Patients With Wild-Type *RAS* mCRC

		Vectibix (panitumumab for injection) + BSC (n=142)		BSC alone (n=128)	
System Organ Class	Preferred Term	Any Grade n (%)	Grade 3–4 n (%)	Any Grade n (%)	Grade 3–4 n (%)
Metabolism and nutrition disorders	Hypomagnesemia	44 (31)	10 (7)	1 (<1)	NR
Skin and subcutaneous tissue disorders	Rash	56 (39)	11 (8)	1 (<1)	NR
	Dermatitis acneiform	40 (28)	9 (6)	NR	NR
	Pruritus	35 (25)	3 (2)	NR	NR

*In the Vectibix arm.

BSC = best supportive care; NR = not reported in the Vectibix Product Monograph.

STUDY 408 TOXICITIES[1]

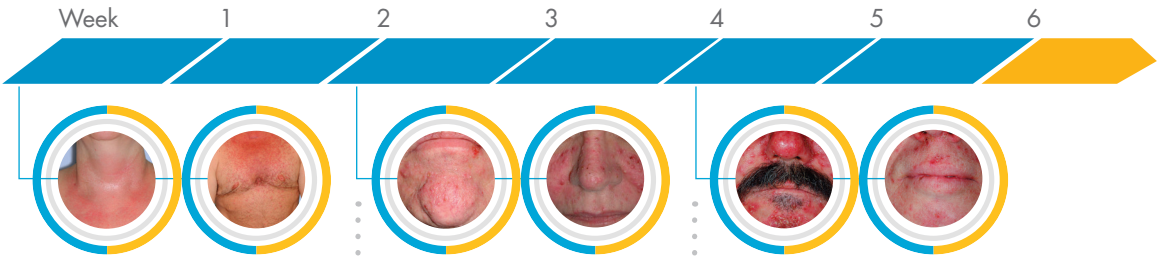
Most Frequent (≥20%*) Adverse Reactions in Patients With Wild-Type *RAS* mCRC

		Vectibix (panitumumab for injection) + BSC (n=72)		BSC alone (n=64)	
System Organ Class	Preferred Term	Any Grade n (%)	Grade 3–4 n (%)	Any Grade n (%)	Grade 3–4 n (%)
Gastrointestinal disorders	Diarrhea	16 (22)	NR	5 (8)	NR
General disorders and administration site conditions	Fatigue	28 (39)	2 (3)	9 (14)	1 (2)
Infections and infestations	Paronychia	30 (42)	4 (6)	NR	NR
Respiratory, thoracic, and mediastinal disorders	Cough	15 (21)	NR	5 (8)	NR
Skin and subcutaneous tissue disorders	Pruritus	51 (71)	4 (6)	2 (3)	NR
	Erythema	49 (68)	4 (6)	1 (2)	NR
	Dermatitis acneiform	45 (63)	5 (7)	NR	NR
	Skin fissures	22 (31)	1 (1)	NR	NR
	Exfoliative rash	21 (29)	2 (3)	NR	NR

*In the Vectibix arm.

BSC = best supportive care; NR = not reported in the Vectibix Product Monograph.

SKIN RASH TIMELINES



Initially, patients may experience sensory disturbance with erythema and edema.[4,5]

From weeks 1 to 3, the papulopustular eruption manifests, followed by crusting.[4,5]

- Interfollicular and follicular-based erythematous papules and pustules, primarily limited to the face, neck, and upper trunk.

Despite appropriate management, erythema and dry skin may persist in the areas previously affected by the skin rash through weeks 4 to 6.[4,5]

- Yellowish/brown crust overlying inflammatory eruptions with oozing of fluid from lesions, which may indicate a bacterial secondary infection.

Patient images may not be representative of the general population.
Images: Data on file, Amgen.

GENERAL MANAGEMENT GUIDELINES

A proactive skin regimen should be discussed before Vectibix (panitumumab for injection) treatment begins.

- Management of dermatologic toxicities requires a multidisciplinary approach, including consultation with nurses, physicians, pharmacists, and other allied healthcare professionals.[4,5]
- When prescribed by a physician, the following skin treatments* may be useful in the management of skin toxicities:[1]
  - Moisturizers
  - Sunscreens (SPF >15 UVA and UVB)
  - Topical steroid creams (not stronger than 1% hydrocortisone)
  - Oral antibiotics (e.g., doxycycline)

Dermatologic and soft tissue toxicity: Clinical manifestations included, but were not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. Patients should be monitored for development of inflammatory or infectious sequelae. Life-threatening and fatal complications including necrotizing fasciitis, abscesses, and/or sepsis have been observed. Reported in post-marketing setting: life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, including rare cases of Stevens-Johnson syndrome (SJS), skin necrosis, and toxic epidermal necrolysis (TEN). Discontinue treatment in cases of SJS and TEN. Stop or discontinue treatment for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications.

* Any treatment decisions are the sole responsibility of the healthcare professional. Please consult the Product Monograph of any treatment option before use.

PROACTIVE SKIN CARE FOR PATIENTS ON VECTIBIX (PANITUMUMAB FOR INJECTION) THERAPY

Avoid harmful products and/or activities[4,5]

Patients should be counselled to avoid activities and skin care products that dry the skin:

- Long, hot showers; saunas.
- Alcohol-based or perfumed products.
- Over-the-counter acne medications.
- Greasy ointments.

Sun protection[1,4,5]

- Sun exposure can exacerbate rash severity on unprotected areas of the body.
- Patients may be advised to apply sunscreen (SPF >15 UVA and UVB) to their face, hands, feet, neck, back, and chest every morning during treatment.

Protect high-risk areas of the body[1,4,5,6]

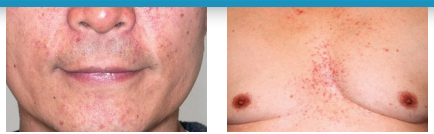
- Patients may be advised to moisturize frequently with alcohol-free emollient creams. Applications to the face, hands, feet, neck, back, and chest every morning during treatment is recommended.
- Creams are more effective than lotions, and when kept cool (e.g., refrigerated), they can provide symptomatic benefit.
- Keep nails short and wear protective clothing (e.g., socks and loose-fitting shoes, gloves for housework).
- Liquid bandages may be helpful for sealing fissures or in places where traditional bandages may be awkward (e.g., at the fingertips).
- Consider regular eyelash trimming for patients with elongation or curling of the eyelashes.

Proactive monitoring is key[4,5]

- Encouraging patients and helping them manage their side effects is an important part of therapy.
- Teaching patients how to recognize and manage side effects, along with early intervention by healthcare professionals, is necessary.
- Patients should be told to contact their healthcare provider immediately if their side effects worsen.

VECTIBIX (PANITUMUMAB FOR INJECTION)-RELATED RASH: GRADING AND MANAGEMENT RECOMMENDATIONS[1,4-7]

MILD / GRADE 1

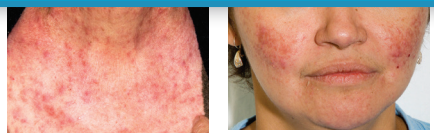


Mild pustular or papular eruption with few or no symptoms.

TREATMENT

TOPICAL:
Clindamycin 2% + HC 1% in lotion base
Apply BID to affected area until resolution of rash.

MODERATE / GRADE 2



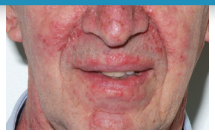
Moderate pustular or papular eruption or erythema; moderately symptomatic; may or may not interfere with daily life.

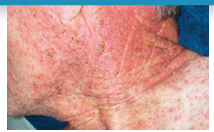
TREATMENT

TOPICAL:
Clindamycin 2% + HC 1% in lotion base
Apply BID to affected area until improvement of rash by 1 grade.
AND
ORAL:
Minocycline 100 mg PO BID OR Doxycycline 100 mg PO OD to BID
Take for a minimum of 4 weeks and continue for the duration of treatment as long as rash is symptomatic.
TOPICAL – Scalp lesions:
Clindamycin 2% + triamcinolone acetonide 0.1% in equal parts of propylene glycol and water
Apply lotion until resolution.

BID=twice daily; HC=hydrocortisone; OD=once daily; PO=*per os*.
Patient images may not be representative of the general population.
Images used with permission from B. Melosky.

SEVERE / GRADE 3





Severe, extensive, painful, intolerable rash; interferes with daily life.

Stop 1 or 2 doses of Vectibix.

TREATMENT

TOPICAL:
Clindamycin 2% + HC 1% in lotion base
Apply BID to affected area until improvement of rash to grade 1 or 2.

AND

ORAL:
Minocycline 100 mg PO BID OR
Doxycycline 100 mg PO OD to BID
Take for a minimum of 4 weeks and continue for the duration of treatment as long as rash is symptomatic.
Corticosteroid (e.g., prednisone 0.5–1 mg/kg for 7 days) (taper over 4–6 weeks)

TOPICAL – Scalp lesions:
Clindamycin powder 2% in amcinonide lotion
Apply BID.

Improvement (<Grade 3)

Resume Vectibix treatment according to Product Monograph.*

No Improvement

Discontinue Vectibix treatment permanently.

* Please refer to the Vectibix Product Monograph or to page 18 of this guide for dose modifications related to severe dermatologic toxicities.

Patient images may not be representative of the general population.

Images a–b used with permission of B. Melosky.

Image c used with permission of Geisler et al.[8]

Adapted from the Vectibix Product Monograph,[1] Melosky et al.,[4] and Lacouture et al.[5,7]

ADDITIONAL DERMATOLOGIC TOXICITIES: DESCRIPTIONS AND MANAGEMENT GUIDELINES[1,5-7]

PRURITUS

- Itching sensation.[5]
- Can occur in relation to rash or as a consequence of dry skin.[5]

PROACTIVE OPTIONS

- Gentle skin care.[5]

REACTIVE OPTIONS

- Treatment of underlying rash.[5]
- Topical menthol 0.5%; topical pramoxine 1%.[5]
- Topical steroid creams[1,4,5,7] OR systemic antihistamines[5,7] OR
- GABA agonists.[7]

DRY SKIN

- Also referred to as xerosis or cutaneous dryness.[5]
- Scaly areas.[5]
- In some cases, associated with inflammatory and infectious sequelae.[1]

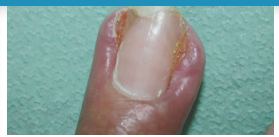
PROACTIVE OPTIONS

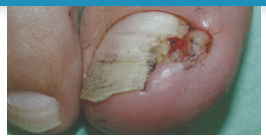
- Avoid extreme temperatures and direct sunlight.[5]
- Bathe in tepid water with bath oils or mild cleansers.[5]
- Moisturizing creams.[5]

REACTIVE OPTIONS

- Petroleum-based creams; emollients containing urea, colloidal oatmeal.[5]
- Topical zinc oxide (13–40%); urea creams (10–40%).[5]
- Topical steroid creams (not stronger than 1% HC).[1]

PARONYCHIA*





- Inflammation of the nail folds of the toes and fingers.[5,7]
- Bleeding.[5–7]
- Significant pain, functional limitation, impairment of activities.[5,7]
- May develop into onycholysis or onychodystrophy.[5,7]

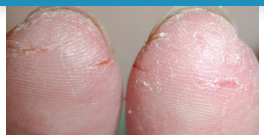
PROACTIVE OPTIONS

- Antimicrobial soaks[5,7] (e.g., diluted bleach soak[5†]).
- Avoid irritants.[5]
- Topical emollients.[7]
- Biotin.[7]

REACTIVE OPTIONS

- Topical povidone iodine 2%[7]
- Topical antibiotics[7]
- Topical steroids[1,7]
- Topical beta-blocking agents[7]
- Oral antibiotics[5,7] (e.g., tetracycline)

FISSURES*



- Cracked skin.[5]
- Can be very painful.[5]
- Can result from significant xerosis.[5]
- In some cases, associated with inflammatory and infectious sequelae.[1]

PROACTIVE OPTIONS

- Protective footwear and gloves.[5]
- Avoid friction with fingertips, toes, heels.[5]

REACTIVE OPTIONS

- Thick moisturizers; zinc oxide (13–40%) creams.[5]
- Wound sealing: Cyanoacrylate preparations.[5]
- Hydrocolloid dressings; topical antibiotics.[5]
- Bleach soaks to prevent infection.[5‡]

HC = hydrocortisone.

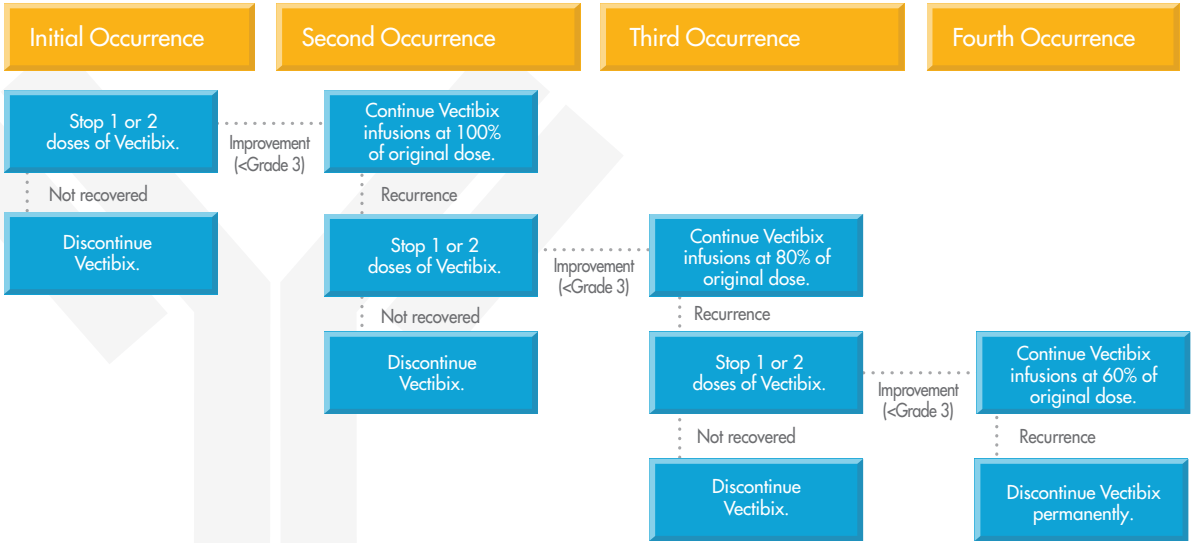
* Patient images may not be representative of the general population. Images: Data on file, Amgen (Europe) GmbH.

† Recommended final concentration of approximately 0.005%, 30–59 mL (⅛–¼ cup) of 6% bleach to 11–19 L (3–5 gal) of water.

‡ 59 mL (¼ cup) of bleach to 11 L (3 gal) of water.

VECTIBIX (PANITUMUMAB) DOSE MODIFICATIONS FOR DERMATOLOGIC REACTIONS[1]

- For severe (grade 3 or higher) or intolerable dermatologic toxicities, the following actions are recommended:



HYPOMAGNESEMIA

Monitoring[1]

Monitor patients for hypomagnesemia and accompanying hypocalcemia or hypokalemia:

- Prior to initiating Vectibix (panitumumab for injection) treatment
- Periodically during treatment
- For up to 8 weeks after completion of Vectibix treatment

Grading[6]

Grade 1	Grade 2	Grade 3	Grade 4
<LLN–1.2 mg/dL	<1.2–0.9 mg/dL	<0.9–0.7 mg/dL	<0.7 mg/dL
<LLN–0.5 mmol/L	<0.5–0.4 mmol/L	<0.4–0.3 mmol/L	<0.3 mmol/L

Management[1]

- Institute appropriate treatment (e.g., oral or intravenous electrolyte repletion) as needed.

Institutional or provincial recommendations for the management of hypomagnesemia associated with Vectibix treatment may also be available.

Consult the Product Monograph at www.amgen.ca/Vectibix_PM.pdf for important information about:

- Contraindication in patients with *RAS* (*KRAS/NRAS*) status that is either mutant or unknown;
- Most serious warnings and precautions regarding dermatologic and soft tissue toxicity and infusion reactions;
- Other relevant warnings and precautions such as required evidence of wild-type *RAS* (*KRAS* exons 2, 3, 4; *NRAS* exons 2, 3, 4) before treatment with Vectibix (panitumumab), hypersensitivity reactions, combination with IFL regimen or bevacizumab (with or without chemotherapy), interstitial lung disease, ocular toxicity, risk-benefit assessment for patients with ECOG 2 performance status prior to initiating Vectibix in combination with chemotherapy, controlled sodium diets, potential effects on driving and machinery use, electrolyte disturbances and monitoring, acute renal failure in patients with severe diarrhea and dehydration, use during pregnancy, nursing, and in women of childbearing potential (may impair fertility; appropriate contraceptive measures required);
- Conditions of clinical use, adverse reactions, drug interactions, and dosing information.

For the Product Monograph and questions about Vectibix, contact Amgen Canada Medical Information at 1-866-502-6436 or visit www.amgenmedinfo.ca.

Pr Vectibix®
panitumumab for injection

VICTORY® PROGRAM BY AMGEN ENTRUST® PATIENT SUPPORT SERVICES

The following services from the VICTORY Program (by Amgen Entrust Patient Support Services*) have been developed to provide helpful support services and reimbursement navigation to patients who have been prescribed Vectibix.

The VICTORY Program offers skin care support for patients taking Vectibix.

SKIN CARE KITS ARE AVAILABLE IN ADDITION TO REIMBURSEMENT SERVICES

A skin care sample kit that includes various products is available to help patients manage some of the skin reactions they may experience while on Vectibix. The products include*:

- Soap for sensitive skin
- Sunscreen
- Moisturizing body lotion and hand cream
- Gentle cleanser and moisturizer
- Lip balm

PATIENTS CAN ENROL BY:

Calling the VICTORY Program Care Coordinator at 1-888-706-4717, ext. 32

ENROLLED PATIENTS CAN BE REIMBURSED FOR OUT-OF-POCKET EXPENSES FOR SKIN CARE PRODUCTS†

- Both over-the-counter and prescription skin care products may be reimbursed (up to a maximum of $150 per month) if the product is not covered by provincial plans.
- Dispensing and pharmacy compounding fees not covered by provincial plans may be covered (up to a maximum of $50 total per prescription renewal).

HERE'S HOW IT WORKS:

1. Patient enrols by calling the VICTORY Program Care Coordinator at 1-888-706-4717, ext. 32.
2. Patient submits a receipt of their purchased product to the VICTORY Program by email, fax, or mail-in.
   - victory@adjuvantz.com
   - 1-833-884-5608
   - McKesson Canada, VICTORY Program
     70 Wynford Drive
     PO Box 383
     North York, ON M3C 2S7
3. VICTORY Program verifies that the product is not provincially covered.
4. Patient receives a reimbursement cheque for the eligible amount within 1 to 2 weeks.

* Exact items may vary.
† Amgen maintains a list of approved products; only products on this list are eligible for reimbursement.

REFERENCES:

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