Prescribing information and adverse event reporting information can be found on the back page.

Management and grading of EGFR inhibitor-associated cutaneous reactions

A summary for healthcare professionals of published guidance on

- Onset and time course of EGFRi-associated skin reactions[1-3]
- The importance of pre-emptive treatment[4]
- Guidance for the grading, prevention, and management of EGFRi-associated skin reactions[5,6]

AMGEN®

Vectibix® (panitumumab)

GBR-954-0923-80001. October 2023.

EGFRi-associated skin reactions

- EGFR inhibitors (EGFRis), such as Vectibix® (panitumumab), are a widely accepted anticancer treatment for *RAS* wild-type metastatic colorectal cancer[7]
- NICE recommends Vectibix® as an option for previously untreated *RAS* wild-type metastatic colorectal cancer in adults in combination with FOLFOX or FOLFIRI[8]

Skin reactions are the most commonly reported adverse events with EGFRis

- **Around 94% of patients treated with Vectibix® experience dermatologic-related reactions[7]**

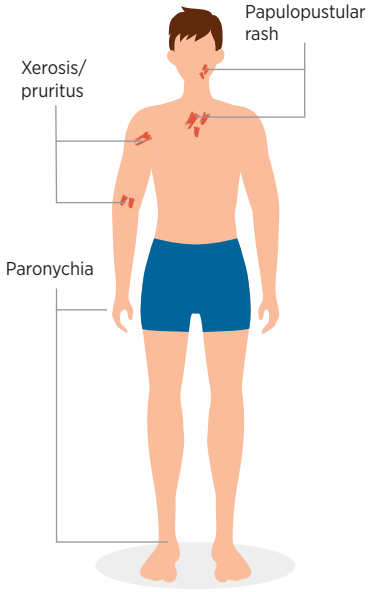


Image adapted from Lacouture (2006)[9]

Skin reactions may include:[5]

- Rash
- Eczema
- Pruritus (itchy skin)
- Xerosis (dry skin)
- Paronychia (skin infection or abscess around the nail)

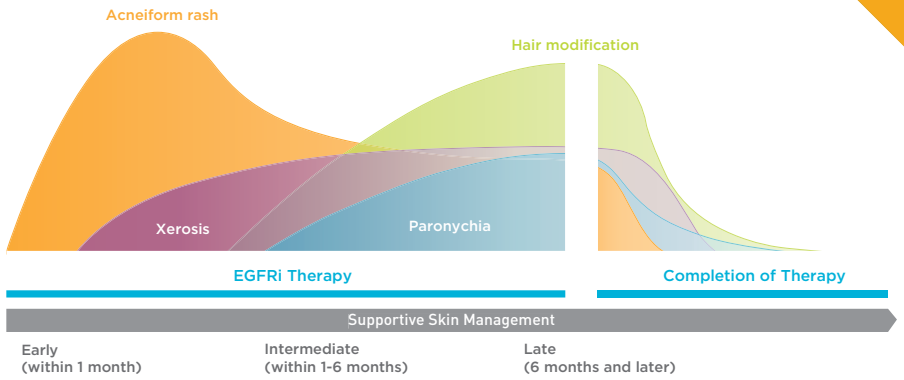
Skin reactions can lead to:[5]

- Decreased quality of life
- Treatment interruption
- Reduced EGFRi dose
- Increased use of healthcare resources

To maximise the potential treatment benefits of EGFRis in metastatic colorectal cancer, any associated skin toxicities require careful and optimal management.

EGFRi: Epidermal Growth Factor Receptor inhibitor.

Onset and time course of skin reactions during anti-EGFR treatment[1-3]



The graph gives a semi-quantitative and qualitative graphical impression of the proportion of patients who can be expected to experience anti-EGFR-associated skin reactions, the typical time courses of onset (i.e. Early, Intermediate, and Late), and resolution after completion of treatment.[1-3]

EGFRi: Epidermal Growth Factor Receptor inhibitor.

The benefits of prophylactic treatment were demonstrated in the open-label Phase II STEPP trial[4]

STEPP TRIAL DESIGN

Eligible patients

- Adult patients with metastatic adenocarcinoma of colon/rectum
- At least one (unresectable) lesion
- Disease progression or unacceptable toxicity with first-line treatment containing fluoropyrimidine and oxaliplatin-based chemotherapy with or without bevacizumab for metastatic colorectal cancer

Pre-emptive treatment n=48

Starting one day before administration of the first Vectibix® dose, **daily skin moisturiser, sunscreen, doxycycline, and topical steroid** from weeks 1 to 6

Reactive treatment n=47

Any treatments deemed necessary to manage emergent skin toxicity, administered at any time during weeks 1 to 6*

Endpoints

- ≥grade 2 skin toxicities during the 6-week period (primary endpoint)
- Patient-reported quality of life (measured using the Dermatology Life Quality Index)

*Patients randomly assigned to the reactive skin treatment arm were not prohibited from using skin moisturiser or sunscreen at any time during the study if they chose to do so.
STEPP: Skin toxicity evaluation protocol with panitumumab.

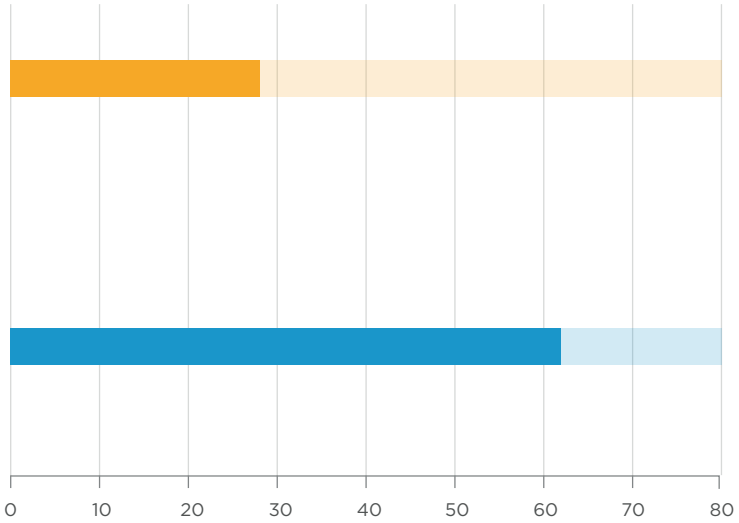
Prophylactic treatment management in the STEPP trial was based on four major alterations thought to occur in the skin of patients treated with EGFRis.[4]

Skin alteration	Pre-emptive treatment solution
Follicular and interfollicular inflammation	**Topical steroid** hydrocortisone 1% for cutaneous inflammation and pruritus
Bacterial superinfection	**Doxycycline** (an antibiotic with anti-inflammatory properties)
Dry skin	**Daily skin moisturiser** to restore the permeability barrier and to treat dry skin
Sensitivity to ultraviolet radiation	**Sunscreen** to prevent ultraviolet radiation-induced skin toxicity

EGFRi: Epidermal Growth Factor Receptor inhibitor; **STEPP**: Skin toxicity evaluation protocol with panitumumab.

STEPP trial: Lower incidence of ≥grade 2 skin toxicities with prophylactic treatment vs reactive treatment[4]

RESULTS FROM THE STEPP TRIAL[4]



OR=0.3; 95% CI: 0.1-0.6

29%

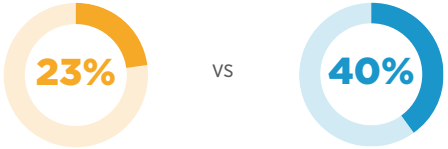
Pre-emptive treatment
n=49/95

62%

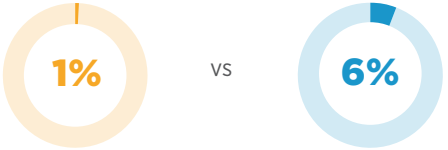
Reactive treatment
n=47/95

The pre-emptive treatment group vs reactive treatment group also had:

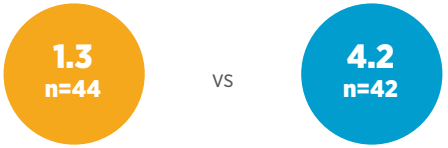
Lower incidence of grade 2 skin toxicities of interest



Fewer dose delays



Smaller decline in quality of life (DLQI score change from baseline at week 3)



CI: confidence interval; **OR**: odds ratio; **STEPP**: Skin toxicity evaluation protocol with panitumumab.

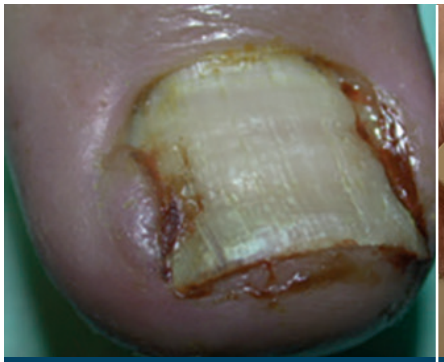
DLQI: Dermatology Life Quality Index.

Guidance on grading, preventing, and managing EGFRi-associated skin reactions

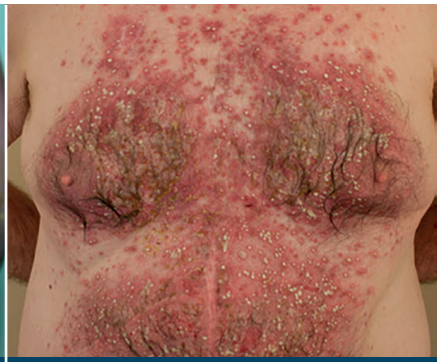
Guidance based on available evidence of EFGRI-associated reactions (focusing on rash, eczema, xerosis, and paronychia), clinical experience, and evidence of similar skin conditions not associated with EGFRi use was published in 2018[5]

GRADING

- Skin reactions must be assessed and their severity graded to guide appropriate treatment and EGFRi dose modifications[7]
- The National Cancer Institute Common Terminology Criteria for Adverse Events grading of skin reactions is predominantly based on the surface area affected rather than the location of the reaction and the subsequent impact on quality of life/ability to cope with EGFRi-based chemotherapy[5]
- The 2018 guidance provides a more clinically relevant grading system based on the **location, severity, and psychological impact** of skin reactions[5]



Example of moderate EGFRi-associated paronychia



Example of severe EGFRi-associated acneiform rash

EGFRi: Epidermal Growth Factor Receptor inhibitor.

Grading of skin reaction
(based on the location, severity, and psychological impact)[5]

Contributing factors	Grading		
	Mild	Moderate	Severe
Impact on patient's quality of life	Not limiting day-to-day life activities	Limiting certain daily activities	Intolerable to patient
Intervention needed	Can be self-managed by the patient	Requires several treatments to manage	Requires intensive local and possible systemic treatment to manage
Ability to continue EGFRi treatment	No dose modification required	No dose modification required	Treatment discontinuation until symptoms improve to mild, and possible dose reduction*
Skin appearance	Redness and flushing only, with or without itch	Papules, pustules, and irritation (acneiform)	Crusted, eroded pustular acneiform lesions
Nail appearance	Nail-fold oedema or erythema; disruption of the cuticle	Oedema or erythema with discharge or nail-plate separation resulting in discomfort	Oedema or erythema with discharge or nail-plate separation resulting in severe pain and reduced mobility

*Vectibix® Summary of Product Characteristics recommends withholding treatment for 1 or 2 doses. Once symptoms have improved (<grade 3 severity), continue infusion (please refer to the SmPC for further details).[7]
EGFRi: Epidermal Growth Factor Receptor inhibitor.

Guidance on grading, preventing, and managing EGFRi-associated skin reactions

PREVENTION

All patients should receive preventative advice and a preventative treatment pack according to their symptoms[5]

Preventative advice for patients[5,6]

DO

- Use sunblock (SPF 50) when outdoors
- Wear sun-protective clothes
- Apply light emollient (lotion) daily as required
- Use antiseptic-containing soap daily
- Apply petroleum jelly to periungual skin (skin around fingernails and toenails)
- **Patients with pre-existing eczema**: Intensify usual skin care routine
- **Patients with active rosacea, acne, or eczema**: Refer immediately to the dermatology department

AVOID

- Strong sun and weather extremes
- Hot baths, showers, and saunas
- Alcohol-based and fragranced skin-care products that may exacerbate dry skin
- Manicure/pedicures
- Tight-fitting shoes
- Blow-drying hair
- Shaving
- Synthetic clothes

Patients should contact the oncology team or pharmacy team at the onset of symptoms and for additional skin-care advice between clinic appointments

EGFRi: Epidermal Growth Factor Receptor inhibitor; **STEPP**: Skin toxicity evaluation protocol with panitumumab.

Beech *et al.* (2018) Guidelines[5]

Cycle 1
Offer preventative advice

No symptoms of skin toxicity

Provide patients with a prophylactic treatment pack:

- Light emollient (lotion) applied daily as required
- Antiseptic-containing soap substitute, used daily

Symptoms of skin toxicity (redness, dryness, and early acneiform spots including papules, pustules, and crusted sores)

Provide reactive prescription pack to prevent worsening:

- Mild topical steroid cream (e.g. 1% hydrocortisone), ± antifungal, 3 times daily for up to 14 days initially
- Oral tetracycline* (e.g. lymecycline or doxycycline at licensed dose) once daily for up to 14 days

*Or erythromycin/clarithromycin if tetracyclines are contraindicated

Cycle 2 onwards

No skin toxicity

1. Continue preventative treatment and advice as per Cycle 1
2. Record skin toxicity assessment in notes and continue to review at every treatment cycle

Skin toxicity evident (xerosis, eczema, acneiform rash, paronychia)

1. Continue prophylactic treatment
2. Treat aggressively according to severity and review at every treatment cycle (Management)

Guidance on grading, preventing, and managing EGFRi-associated skin reactions

MANAGEMENT

Cycle 2 onwards

If skin reaction is evident[5]

1. Continue to follow prophylactic advice
2. Grade severity
3. Treat/manage aggressively in accordance with severity
4. Review at every treatment cycle

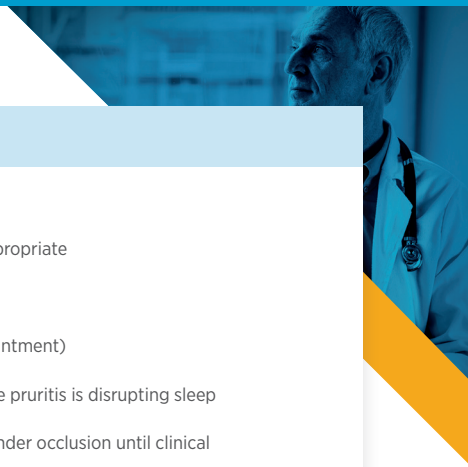
Management of skin reactions according to severity[5]

Mild

Continue EGFRi.
Assess adherence to current supportive treatment – if poor advise on correct use; if good intensify treatment as follows:

- **Acneiform rash**
  Mild topical steroid ± antifungal 3 times daily until clinical improvement or review; continue oral tetracycline once daily for ≥ 12 weeks
- **Scalp involvement**
  Betamethasone 0.1% scalp application daily until clinical improvement

EGFRi: Epidermal Growth Factor Receptor inhibitor.



Moderate

Treat as per mild and intensify treatment as follows:

- **Acneiform rash**
  Increase oral tetracycline to twice daily for 4 weeks where appropriate
- **Scalp involvement**
  Potent topical steroid lotion twice daily for 2 weeks
- **Xerosis or eczema**
  Consider switching emollient to a more greasy preparation (ointment)
- **Pruritus**
  Anti-histamine (e.g. hydroxyzine) once daily before bed where pruritis is disrupting sleep
- **Paronychia**
  Potent topical steroid cream (betamethasone 0.1%) applied under occlusion until clinical improvement.
  Culture and prescribe oral antibiotic based on sensitivity if purulent

Severe

Stop EGFRi until symptoms resolve to mild and consider dose reduction according to licence*.
Treat as per moderate and intensify treatment as follows:

- **Xerosis or eczema**
  1. Switch to a more potent topical steroid ± antifungal, use ointment preparation instead of cream;
  2. Advise more frequent application of emollient and switch to a more greasy preparation (if not already done);
  3. Prescribe oral steroid (e.g. prednisolone) ± gastroprotection; titrate down over 14 days and review (monitor blood sugars)
- **Acneiform rash**
  1. Switch to a lighter emollient;
  2. Switch to a moderate intensity topical steroid e.g. 0.025% betamethasone valerate;
  3. Prescribe oral steroid (as for severe xerosis/eczema)
- **All severe cutaneous reactions, including paronychia**
  Swab lesions for culture and susceptibility testing and prescribe antibiotic accordingly
  Seek advice from dermatology department

*Vectibix®: For severe (grade ≥3) skin reactions, withhold 1 or 2 doses. Continue treatment if symptoms improve (<grade 3). For initial occurrence continue at 100% of original dose; at 2nd occurrence continue at 80% of original dose; at 3rd occurrence continue at 60% of original dose. If symptoms do not improve after withholding 1 or 2 doses, or if its the 4th occurrence, discontinue treatment.[7]
EGFRi: Epidermal Growth Factor Receptor inhibitor.

Notes

References

1. Segaert S. Skin Toxicities of Targeted Therapies. Eur J Cancer. 2009;45(Suppl 1):295-308.

2. Osio A, *et al.* Cutaneous side effects in patients on long-term treatment with epidermal growth factor receptor inhibitor. Br J Dermatol. 2009;161:515-521.

3. Van Cutsem E, *et al.* Challenges in the Use of Epidermal Growth Factor Receptor Inhibitors in Colorectal Cancer. The Oncologist. 2006;11:1010-1017.

4. Lacouture ME, *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(8):1351-1357.

5. Beech J, *et al.* Management and grading of EGFR inhibitor-induced cutaneous toxicity. Future Oncol. 2018;14:2531-2541.

6. Hofheinz RD, *et al.* Recommendations for the prophylactic management of skin reactions induced by epidermal growth factor receptor inhibitors in patients with solid tumors. The Oncologist. 2016;21(12):1483-1491.

7. Vectibix® (panitumumab) Summary of Product Characteristics. Amgen Ltd. Available at: https://www.medicines.org.uk/emc/product/6178/smpc#about-medicine [updated June 2023]. Accessed September 2023.

8. National Institute for Health and Care Excellence (2017). Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (NICE guideline TA439). Available at: https://www.nice.org.uk/guidance/ta439. Accessed September 2023.

9. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006;6:803–812.

Vectibix® (panitumumab) Brief Prescribing Information

Please refer to the Summary of Product Characteristics before prescribing Vectibix. **Pharmaceutical Form:** Vectibix 20 mg/ml concentrate for solution for infusion. Each vial contains either 100 mg of panitumumab in 5 ml or 400 mg of panitumumab in 20 ml. Excipients: sodium chloride, sodium acetate trihydrate, acetic acid (glacial [for pH adjustment]), water for injection. **Indication:** Vectibix is indicated for the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer (mCRC): in first-line in combination with FOLFOX or FOLFIRI; in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine–based chemotherapy (excluding irinotecan); as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. **Dosage and Administration:** The recommended dose of Vectibix is 6 mg/kg of bodyweight given once every two weeks. The recommended infusion time is approximately 60 minutes. Doses higher than 1000 mg should be infused over approximately 90 minutes. Evidence of wild-type RAS (*KRAS* and *NRAS)* status is required before initiating treatment with Vectibix. Mutational status should be determined by an experienced laboratory using validated test methods for detection of KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4) mutations. If Vectibix is to be used in combination with FOLFOX or FOLFIRI then it is recommended that mutational status be determined by a laboratory that participates in a *RAS* European Quality Assurance programme or wild-type status be confirmed in a duplicate test. **Contraindications:** History of severe or life-threatening hypersensitivity to the active substance or to any of the excipients, interstitial pneumonitis or pulmonary fibrosis and combination of Vectibix with oxaliplatin-containing chemotherapy for patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown. **Special Warnings and Precautions:** ***Traceability*:** Clearly record name and batch number of administered product to improve traceability of biological products. ***Dermatologic reactions and soft tissue toxicity***: Dermatologic reactions are experienced with nearly all patients (approximately 94%) treated with Vectibix; with 23% severe (grade 3 NCI-CTC) and < 1% life threatening (grade 4 NCI-CTC). If a patient develops dermatologic reactions that are grade 3 (CTCAE v4.0) or higher or considered intolerable, dose modification, interruption, or discontinuation as per the Summary of Product Characteristics should be followed. Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients treated with Vectibix in the post-marketing setting. Proactive skin treatment may be useful in the management of dermatological reactions please refer to the Summary of Product Characteristics for more details. ***Pulmonary complications*:** If interstitial lung disease (ILD) is diagnosed, Vectibix should be permanently discontinued and the patient should be treated appropriately. In patients with a history of interstitial pneumonitis or pulmonary fibrosis, a risk benefit assessment should be conducted. ***Electrolyte disturbances*:** Patients should be periodically monitored for hypomagnesaemia and accompanying hypocalcaemia prior to initiating Vectibix treatment, and periodically for up to 8 weeks after the completion of treatment. Repletion of magnesium and other electrolytes is also recommended, as appropriate. ***Acute Renal Failure:*** Acute renal failure has been observed in patients who develop severe diarrhoea and dehydration. ***Infusion Related Reactions*:** Across monotherapy and combination mCRC clinical studies, infusion-related reactions (occurring within 24 hours of an infusion) were reported in Vectibix-treated patients, including severe infusion-related reactions (NCI-CTC grade 3 and 4). In the post-marketing setting, serious infusion-related reactions have been reported, including rare reports with a fatal outcome. If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion, Vectibix should be permanently discontinued. In patients experiencing a mild or moderate infusion-related reaction, the infusion rate should be reduced, then maintain this lower infusion rate in all subsequent infusions. Hypersensitivity reactions occurring more than 24 hours after infusion have been reported including a fatal case of angioedema. Patients should be informed of the possibility of a late onset reaction and instructed to contact their physician if symptoms of a hypersensitivity reaction occur. ***Ocular toxicities:*** Serious cases of keratitis and ulcerative keratitis, which may lead to corneal perforation, have been reported. Patients presenting with signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with Vectibix should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Vectibix should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. ***ECOG 2 performance status*:** For patients with ECOG 2 performance status, assessment of benefit-risk is recommended prior to initiation of Vectibix in combination with chemotherapy for treatment of mCRC. A positive benefit-risk balance has not been documented in patients with ECOG 2 performance status. ***Elderly patients:*** No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Vectibix monotherapy. However, an increased number of serious adverse events were reported in elderly patients treated with Vectibix in combination with FOLFIRI or FOLFOX chemotherapy compared to chemotherapy alone. The most increased serious adverse events were diarrhoea in patients treated with Vectibix in combination with either FOLFOX or FOLFIRI, and dehydration and pulmonary embolism when patients were treated with Vectibix in combination with FOLFIRI. ***Sodium content*:** Vectibix contains 3.45 mg sodium per ml, equivalent to 0.17% of the WHO recommended daily intake for an adult. **Interactions:** Vectibix should not be administered in combination with IFL chemotherapy or with bevacizumab-containing chemotherapy. A high incidence of severe diarrhoea was observed when Vectibix was administered in combination with IFL and increased toxicity and deaths were seen when Vectibix was combined with bevacizumab and chemotherapy. **Fertility, pregnancy and lactation:** There are no adequate data from the use of Vectibix in pregnant women. In women of childbearing potential, appropriate contraceptive measures must be used during treatment and for 2 months following the last dose. It is recommended that women do not breast-feed during treatment with Vectibix and for 2 months after the last dose. **Undesirable Effects:** Very common (≥ 1/10): Anaemia, conjunctivitis, paronychia, diarrhoea, nausea, vomiting, abdominal pain, stomatitis, constipation, fatigue, pyrexia, asthenia, mucosal inflammation, oedema peripheral, weight decreased, hypokalaemia, hypomagnesaemia, decreased appetite, back pain, insomnia, dyspnoea, cough, dermatitis acneiform, rash, erythema, pruritus, dry skin, skin fissures, acne and alopecia. Common (≥ 1/100 to < 1/10): Leucopenia, tachycardia, blepharitis, growth of eyelashes, lacrimation increased, ocular hyperaemia, dry eye, eye pruritus, eye irritation, rectal haemorrhage, dry mouth, dyspepsia, aphthous ulcer, cheilitis, gastrooesophageal reflux disease, chest pain, pain, chills, hypersensitivity, rash pustular, cellulitis, urinary tract infection, folliculitis, localised infection, decreased blood magnesium, hypocalcaemia, dehydration, hyperglycaemia, hypophosphataemia, pain in extremity, headache, dizziness, anxiety, pulmonary embolism, epistaxis, palmar-plantar erythrodysaesthesia syndrome, skin ulcer, skin exfoliation, exfoliative rash, dermatitis, rash papular, rash pruritic, rash erythematous, rash generalised, rash macular, rash maculo-papular, skin lesion, skin toxicity, scab, hypertrichosis, onychoclasis, nail disorder, hyperhidrosis, deep vein thrombosis, hypotension, hypertension and flushing. Uncommon (≥ 1/1000 to < 1/100): Anaphylactic reaction, cyanosis, ulcerative keratitis, keratitis, infusion-related reaction, interstitial lung disease, bronchospasm, toxic epidermal necrolysis, skin necrosis, Stevens-Johnson syndrome, and angioedema. 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. As with all therapeutic proteins, there is potential for immunogenicity. Please consult the Summary of Product Characteristics for a full list and more detailed description of side effects. **Overdose:** Doses up to 9 mg/kg have been tested in clinical trials. Overdose at doses up to approximately twice the recommended therapeutic dose have been reported. Adverse events observed included skin toxicity, diarrhoea, dehydration and fatigue. **Pharmaceutical Precautions:** Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original carton in order to protect from light. The product should be used immediately after dilution. Vectibix should be diluted in 0.9% sodium chloride injection using aseptic technique. Do not shake or vigorously agitate the vial. Do not administer Vectibix if discolouration is observed. **Legal Category:** POM. **Presentation, Basic NHS Costs and Marketing Authorisation Numbers Great Britain (GB):** Vectibix 100mg: Pack of 1: £379.29, 400mg: Pack of 1: £1517.16, PLGB 13832/0045. **Marketing Authorisation Holder GB:** Amgen Limited, 216 Cambridge Science Park, Milton Road, Cambridge, CB4 0WA, UK. **Presentation, Basic NHS Costs and Marketing Authorisation Numbers Northern Ireland (XI):** Vectibix 100mg: Pack of 1: £379.29, EU/1/07/423/001, 400mg: Pack of 1: £1517.16, EU/1/07/423/003. **Marketing Authorisation Holder XI:** Amgen Europe B.V., Minervum 7061, 4817 ZK Breda, The Netherlands. Further information is available from Amgen Limited, 216 Cambridge Science Park, Milton Road, Cambridge, CB4 0WA, UK. Vectibix is a registered trademark of Amgen Inc. **Date of PI preparation:** December 2021 (Ref: GB-VBX-1121-00001)

Adverse events should be reported. Reporting forms and information can be found at **https://yellowcard.mhra.gov.uk** or search for MHRA Yellow Card in the Google Play or Apple App store. Adverse events should also be reported to Amgen Limited on **+44 (0)1223 436441**

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