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Vectibix® (panitumumab): DHPC EU

Direct Healthcare Professional Communication on the changes to the* Vectibix® SmPC including safety information on the *importance of establishing KRAS status prior to treatment with Vectibix®.

Dear Healthcare Professional

Summary

- **The European Commission has recently approved a change to the Vectibix® product information to include treatment of mCRC with Vectibix® in combination with FOLFOX and FOLFIRI for patients whose tumours are wild-type KRAS (see details below and Annex).**
- **The combination of Vectibix® with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *KRAS* mCRC or for whom *KRAS* mCRC status is unknown**
- **Vectibix® should not be used as monotherapy in patients whose tumours are mutant KRAS or patients whose tumours have not been tested for KRAS status**
- **Vectibix® has shown no benefit in patients whose tumours carry mutated *KRAS*.**
- **A detrimental effect on progression free survival and overall survival has been demonstrated in patients with mutant *KRAS* status receiving Vectibix® with FOLFOX chemotherapy.**
- **Evidence of wild-type *KRAS* status is required prior to initiating treatment with Vectibix®.**

The information in this communication has been agreed with the European Medicines Agency and the Irish Medicines Board.

Further Information on the changes to the SmPC and Safety information s

The European Commission has recently approved a change to the Vectibix® product information to include treatment of mCRC with Vectibix® in combination with FOLFOX and FOLFIRI (see Annex). The approved indication is:

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

- in first-line in combination with FOLFOX
- 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.

In addition the following contraindication has been included:

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

Vectibix® has shown no benefit in patients whose tumours carry mutated *KRAS*. In addition, phase III clinical data have demonstrated a detrimental effect on progression free survival and overall survival in patients with mutant *KRAS* status receiving Vectibix® with FOLFOX chemotherapy.

Therefore evidence of wild-type *KRAS* status is required prior to initiating treatment with Vectibix®. *KRAS* mutational status should be determined using a validated test method by an experienced laboratory.

If Vectibix® is to be used in combination with FOLFOX then it is recommended that mutational status be determined by a laboratory that participates in a *KRAS* European Quality Assurance program or wild-type status be confirmed in a duplicate test.

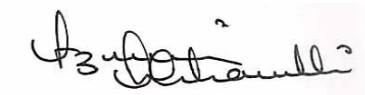
Reporting of suspected adverse reactions with the use of Vectibix®

Any suspected adverse reactions should be reported to the Pharmacovigilance section of the Irish Medicines Board (via post or using the on-line form available at www.imb.ie) or alternatively to Amgen Europe B.V. by contacting Amgen UK/Ireland Drug Safety Department directly on 00 44 1223 436712.

Communication Information

Should you have any questions or require additional information regarding the use of Vectibix®, please contact Amgen UK/Ireland Medical Information on 00 44 1223 436441 or by email to gbinfoline@amgen.com.

Yours sincerely,



Dr Azmina Khanbhai MBChB, MRCP, MBA
Acting Medical Director, UK & Ireland

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 patients with wild-type *KRAS* metastatic colorectal cancer (mCRC): in first-line in combination with FOLFOX; 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 *KRAS* status is required before initiating treatment with Vectibix®. *KRAS* mutational status should be determined using a validated test method by an experienced laboratory. If Vectibix® is to be used in combination with FOLFOX then it is recommended that mutational status be determined by a laboratory that participates in a *KRAS* European Quality Assurance programme or wild-type status be confirmed in a duplicate test. **Contra-indications:** 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 *KRAS* mCRC or for whom *KRAS* mCRC status is unknown. **Special Warnings and Precautions:** *Dermatologic reactions*: Dermatologic reactions are experienced with nearly all patients (approximately 90%) treated with Vectibix®; the majority are mild to moderate in nature with 25% 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 modifications as per the Summary of Product Characteristics should be followed. 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 pneumonitis or lung infiltrates are diagnosed, Vectibix® should be discontinued and the patient should be treated appropriately. *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 3% of Vectibix®-treated patients, of which < 1% were severe (CTCAE v4.0 grade 3 and grade 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 have been rarely (<1/1000) reported in the post-marketing setting. Non-serious cases of keratitis have been observed in 0.2 to 0.7% of clinical trial patients. 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. **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. **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 6 months following the last dose. It is recommended that women do not breast-feed during treatment with Vectibix® and for 3 months after the last dose. **Undesirable Effects:** Very common (≥ 1/10): Anaemia, conjunctivitis, diarrhoea, nausea, vomiting, abdominal pain, stomatitis, constipation, fatigue, pyrexia, asthenia, mucosal inflammation, oedema peripheral, paronychia, weight decreased, hypokalaemia, anorexia, hypomagnesaemia, back pain, insomnia, dyspnoea, cough, dermatitis acneiform, rash (includes common terms of skin toxicity, skin exfoliation, exfoliative rash, rash papular, rash pruritic, rash erythematous, rash generalised, rash macular, rash maculo-papular, skin lesion), erythema, pruritus, dry skin, skin fissures, acne and alopecia. Common (≥ 1/100 to < 1/10): Leukopenia, tachycardia, blepharitis, growth of eyelashes, lacrimation increased, ocular hyperaemia, dry eye, eye pruritus, eye irritation, rectal haemorrhage, dry mouth, dyspepsia, aphthous stomatitis, cheilitis, gastrooesophageal reflux disease, chest pain, pain, chills, hypersensitivity, rash pustular, cellulitis, folliculitis, localised infection, blood magnesium decreased, hypocalcaemia, dehydration, hyperglycaemia, hypophosphataemia, pain in

extremity, headache, dizziness, anxiety, pulmonary embolism, epistaxis, palmar-plantar erythrodysaesthesia syndrome, skin ulcer, scab, hypertrichosis, onychoclasis, nail disorder, deep vein thrombosis, hypotension, hypertension and flushing. Uncommon (≥ 1/1000 to < 1/100): Cyanosis, keratitis, infusion-related reaction, bronchospasm and angioedema. Rare (≥ 1/10000 to < 1/1000): Anaphylactic reaction and ulcerative keratitis. 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 Vectibix® or of chemotherapy. 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 Costs and Marketing Authorisation Numbers:** Vectibix® 100mg: Pack of 1, EU/1/07/423/001, 400mg: Pack of 1, EU/1/07/423/003. Price in Republic of Ireland is available on request. **Marketing Authorisation Holder:** Amgen Europe B.V., Minervum 7061, 4817 ZK Breda, The Netherlands. Further information is available from Amgen Limited, 240 Cambridge Science Park, Milton Road, Cambridge, CB4 0WD. Vectibix® is a registered trademark of Amgen Inc. **Date of PI preparation:** November 2011 (Ref. PMO-IRL-AMG-158-2011)

Adverse events should be reported to Amgen Limited on +44 (0)1223 436712