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8th August 2013

Vectibix: DHPC EU

Direct Healthcare Professional Communication on the importance of establishing wild-type *RAS* (exons 2, 3 and 4 of *KRAS* and *NRAS*) status before treatment with Vectibix® (panitumumab)

Dear Healthcare Professional,

Amgen Europe B.V. would like to inform you of the following:

Summary

- **Evidence of wild-type *RAS* (exons 2, 3 and 4 of *KRAS* and *NRAS*) status is required before initiating treatment with Vectibix**
- ***RAS* mutational status should be determined by an experienced laboratory using a validated test method**
- **The contraindication for Vectibix in combination with oxaliplatin-containing chemotherapy (eg FOLFOX) now includes all patients with mutant *RAS* or unknown *RAS* status.**
- **Inferior progression-free survival (PFS) and overall survival (OS) have been shown in patients with *RAS* mutations beyond *KRAS* exon 2 who received Vectibix in combination with FOLFOX chemotherapy versus FOLFOX alone.**

This new guidance supersedes a previous communication sent to you in November 2011 relating to *KRAS* status.

This information has been agreed with the European Medicines Agency and the Irish Medicines Board.

Further information on the safety concern

This new safety information is based on a predefined retrospective subset analysis of data from a randomised, multicentre phase 3 study (PRIME study 20050203) of Vectibix plus FOLFOX versus FOLFOX alone in patients with previously untreated wild-type *KRAS* metastatic colorectal cancer (mCRC).

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Place of Registration: Ireland
Company Registration Number: 379345
Directors: Michael Byrne, Thomas Dittrich (German), Rolf Hoffman (German), John Kearney (British)

Patient tumour samples with wild-type *KRAS* exon 2 (codons 12/13) status were assessed using Sanger bidirectional sequencing and Surveyor®/WAVE® analysis in parallel for additional *RAS* mutations in:

- *KRAS* exon 3 (codons 59/61)
- *KRAS* exon 4 (codons 117/146)
- *NRAS* exon 2 (codons 12/13)
- *NRAS* exon 3 (codons 59/61)
- *NRAS* exon 4 (codons 117/146)

The incidence of these additional *RAS* mutations in the wild-type *KRAS* exon 2 population was approximately 16%.

The outcomes of this retrospective analysis indicate inferior PFS and OS in patients with *RAS* mutations beyond *KRAS* exon 2 who received Vectibix in combination with FOLFOX chemotherapy versus FOLFOX alone. No new toxicities were identified. These results are similar to those observed for mutations in *KRAS* exon 2.

	Vectibix plus FOLFOX (months) (95% CI)	**FOLFOX (months) (95% CI)**	**Difference (months)**	**Hazard ratio (95% CI)**
Wild-type *RAS* population				
PFS	10.1 (9.3, 12.0)	7.9 (7.2, 9.3)	2.2	0.72 (0.58, 0.90)
OS	26.0 (21.7, 30.4)	20.2 (17.7, 23.1)	5.8	0.78 (0.62, 0.99)
Mutant *RAS* population				
PFS	7.3 (6.3, 7.9)	8.7 (7.6, 9.4)	-1.4	1.31 (1.07, 1.60)
OS	15.6 (13.4, 17.9)	19.2 (16.7, 21.8)	-3.6	1.25 (1.02, 1.55)

CI = confidence interval

The data above do not include codon 59. Additional mutations in *KRAS* and *NRAS* at exon 3 (codon 59) were subsequently identified (n = 7). An exploratory analysis showed similar results to those in the table above.

These findings emphasize the importance of not using Vectibix in combination with oxaliplatin-based chemotherapy in patients with mutant *RAS* (exons 2, 3, 4 of *KRAS* and *NRAS*) mCRC or for whom *RAS* status is unknown. *RAS* mutational status should be determined by an experienced laboratory using a validated test method.

The product information for Vectibix has been updated to communicate this important information (see Annex).

Call for reporting

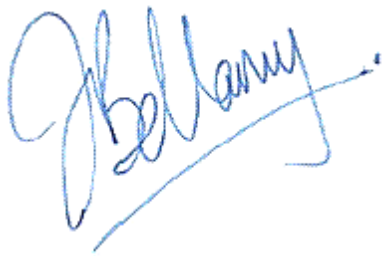
Any suspected adverse reactions should be reported to the Irish Medicines Board using a Yellow Card obtained from the Irish Medicines Board or electronically via the online reporting system at *www.imb.ie*. Adverse reactions can also be reported to the Irish Medicines Board by calling on (01) 676 4971.

Reports can also be made to Amgen Europe B.V. by contacting Amgen UK/Ireland Drug Safety Department directly on 0044 1223 436712.

Company contact point

Should you have any questions or require additional information regarding the use of Vectibix, please contact Amgen UK/Ireland Medical Information on 0044 1223 436441 or by email to gbinfoline@amgen.com.

Yours sincerely,



Dr Steven Bellamy MBChB
Medical Director, UK & Ireland

Annex: Revised wording for Vectibix Summary of Product Characteristics (SmPC) and Package Leaflet (PL)

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; 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®. *M*utational 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 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 *RAS* mCRC or for whom *RAS* mCRC status is unknown. **Special Warnings and Precautions:** ***Dermatologic reactions and soft tissue toxicity***: Dermatologic reactions are experienced with nearly all patients (approximately 90%) treated with Vectibix®; with 34% 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. 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 approximately 4% of Vectibix®-treated patients, of which < 1% were severe (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 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. **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, 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, ulcerative keratitis, skin necrosis and life threatening and fatal infectious complications including necrotising fasciitis and sepsis. 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 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:** July 2013 (Ref: PMO-IRL-AMG-199-2013-P)

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