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YOUR HEALTH AT HEART

4th Nov 2013

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 Medicines Authority.

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).

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 via the national Adverse Drug Reactions(ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Reports can also be made to Amgen Europe B.V. by contacting

RP Cherubino LTD

DELF Building

Sliema Road

Gzira

▼ This medicinal product is subject to additional monitoring because it has a conditional authorisation.

Company contact point

Should you have any questions or require additional information regarding the use of Vectibix, please contact medical information on luisa@cherubino.com.mt

Yours sincerely,

Luisa de Piro O'Connell

RP Cherubino LTD

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