# Announcement regarding harshment (safety information) in the Physician Leaflet

# הודעה על החמרה ( מידע בטיחות) בעלון לרופא

**תאריך: 07.07.2014**

**Name of the product:**

**שם תכשיר באנגלית: Vectibix 20mg/ml**

**Registration No's:**

**מספר רישום: 142923295100**

**Name of the registration owner:**

**שם בעל הרישום Amgen Europe B.V.**

| Current | Proposed |
|---|---|
| **4.4 Special warnings and precautions for use**<br><br>Dermatologic reactions and soft tissue toxicity<br><br>In clinical studies, subsequent to the development of severe dermatologic reactions (including stomatitis), infectious complications including sepsis, in rare cases leading to death, and local abscesses requiring incisions and drainage were reported. Patients who have severe dermatologic reactions or soft tissue toxicity or who develop worsening reactions whilst receiving Vectibix should be monitored for the development of inflammatory or infectious sequelae (including cellulitis), and appropriate treatment promptly initiated. Life threatening and fatal infectious complications including events of necrotizing fasciitis and/or sepsis have been observed in patients treated with Vectibix. Withhold or discontinue Vectibix for dermatologic or soft tissue toxicity associated with severe or life threatening inflammatory or infectious complications.<br><br>……..<br><br>*RAS* mutational status should be determined using a validated test method by an experienced laboratory (see section 4.2). 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* External Quality Assurance program or wild-type status be confirmed in a duplicate test. | **4.4 Special warnings and precautions for use**<br><br>Dermatologic reactions and soft tissue toxicity<br><br>In clinical studies, subsequent to the development of severe dermatologic reactions (including stomatitis), infectious complications including sepsis, in rare cases leading to death, and local abscesses requiring incisions and drainage were reported. Patients who have severe dermatologic reactions or soft tissue toxicity or who develop worsening reactions whilst receiving Vectibix should be monitored for the development of inflammatory or infectious sequelae (including cellulitis), and appropriate treatment promptly initiated. Life threatening and fatal infectious complications including events of necrotizing fasciitis and/or sepsis have been observed in patients treated with Vectibix. Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients treated with Vectibix in the post-marketing setting. Withhold or discontinue Vectibix for dermatologic or soft tissue toxicity associated with severe or life threatening inflammatory or infectious complications.<br><br>……..<br><br>*RAS* mutational status should be determined using a validated test method by an experienced laboratory (see section 4.2). 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 ~~*K*~~*RAS* External Quality Assurance program or wild-type status be confirmed in a duplicate test. |

## 4.8 Undesirable effects

| | Adverse reactions | | | | |
|---|---|---|---|---|---|
| **MedDRA system organ class** | **Very common (≥ 1/10)** | **Common (≥ 1/100 to < 1/10)** | **Uncommon (≥ 1/1000 to < 1/100)** | **Rare (≥ 1/10,000 to < 1/1000** | **Frequency not known*** |
| Infections and infestations | Paronychia[1] | Rash pustular<br>Cellulitis[1]<br>Folliculitis<br>Localised infection | Eye infection<br>Eyelid infection | | |
| Blood and lymphatic system disorders | Anaemia | Leukopenia | | | |
| Immune system disorders | | Hypersensitivity[1] | | Anaphylactic reaction[1] | |
| Metabolism and nutrition disorders | Hypokalaemia<br>Anorexia<br>Hypomagnesaemia | Hypocalcaemia<br>Dehydration<br>Hyperglycaemia<br>Hypophosphataemia | | | |
| Psychiatric disorders | Insomnia | Anxiety | | | |
| Nervous system disorders | | Headache<br>Dizziness | | | |
| Eye disorders | Conjunctivitis | Blepharitis<br>Growth of eyelashes<br>Lacrimation increased<br>Ocular hyperaemia<br>Dry eye<br>Eye pruritus<br>Eye irritation | Eyelid irritation<br>Keratitis[1] | Ulcerative Keratitis[1] | |
| Cardiac disorders | | Tachycardia | Cyanosis | | |
| Vascular disorders | | Deep vein thrombosis<br>Hypotension<br>Hypertension<br>Flushing | | | |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea<br>Cough | Pulmonary embolism<br>Epistaxis | Bronchospasm<br>Nasal dryness | | Interstitial lung disease |
| Gastrointestinal disorders | Diarrhoea[1]<br>Nausea<br>Vomiting<br>Abdominal pain<br>Stomatitis<br>Constipation | Rectal haemorrhage<br>Dry mouth<br>Dyspepsia<br>Aphthous stomatitis<br>Cheilitis<br>Gastrooesophageal reflux disease | Chapped lips | | |
| Skin and subcutaneous tissue disorders | Dermatitis acneiform<br>Rash[1,2]<br>Erythema<br>Pruritus<br>Dry skin<br>Skin fissures<br>Acne<br>Alopecia | Palmar-plantar erythrodysaesthesia syndrome<br>Skin ulcer<br>Scab<br>Hypertrichosis<br>Onychoclasis<br>Nail disorder | Angioedema[1]<br>Hirsutism<br>Ingrowing nail<br>Onycholysis | Skin Necrosis[1] | |

## 4.9 Undesirable effects

| | Adverse reactions | | | | |
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| Immune system disorders | | Hypersensitivity[1] | | Anaphylactic reaction[1] | |
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| Nervous system disorders | | Headache<br>Dizziness | | | |
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| Cardiac disorders | | Tachycardia | Cyanosis | | |
| Vascular disorders | | Deep vein thrombosis<br>Hypotension<br>Hypertension<br>Flushing | | | |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea<br>Cough | Pulmonary embolism<br>Epistaxis | Bronchospasm<br>Nasal dryness | | Interstitial lung disease[2] |
| Gastrointestinal disorders | Diarrhoea[1]<br>Nausea<br>Vomiting<br>Abdominal pain<br>Stomatitis<br>Constipation | Rectal haemorrhage<br>Dry mouth<br>Dyspepsia<br>Aphthous stomatitis<br>Cheilitis<br>Gastrooesophageal reflux disease | Chapped lips | | |
| Skin and subcutaneous tissue disorders | Dermatitis acneiform<br>Rash[1,2]<br>Erythema<br>Pruritus<br>Dry skin<br>Skin fissures<br>Acne<br>Alopecia | Palmar-plantar erythrodysaesthesia syndrome<br>Skin ulcer<br>Scab<br>Hypertrichosis<br>Onychoclasis<br>Nail disorder | Angioedema[1]<br>Hirsutism<br>Ingrowing nail<br>Onycholysis | Skin Necrosis[1]<br>Stevens-Johnson syndrome[1]<br>Toxic epidermal necrolysis[1] | |

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|---|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | Back pain | Pain in extremity | | | |
| General disorders and administration site conditions | Fatigue<br>Pyrexia<br>Asthenia<br>Mucosal inflammation<br>Oedema peripheral | Chest pain<br>Pain<br>Chills | Infusion-related reaction[1] | | |
| Investigations | Weight decreased | Blood magnesium decreased | | | |

[1] See section "Description of selected adverse reactions" below
[2] 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
* Frequency cannot be estimated from the available data

……..

*Skin and subcutaneous tissue disorders*

Skin rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities. Subsequent to the development of severe skin and subcutaneous reactions, infectious complications including sepsis, in rare cases leading to death, cellulitis and local abscesses requiring incisions and drainage were reported. The median time to first symptom of dermatologic reaction was 10 days, and the median time to resolution after the last dose of Vectibix was 28 days.

Paronychial inflammation was associated with swelling of the lateral nail folds of the toes and fingers.

Dermatological reactions (including nail effects), observed in patients treated with Vectibix or other EGFR inhibitors, are known to be associated with the pharmacologic effects of therapy.

Across all clinical trials, skin reactions occurred in 93% of patients receiving Vectibix as monotherapy or in combination with chemotherapy (n = 2588). These events consisted predominantly of rash and dermatitis acneiform and were mostly mild to moderate in severity. Severe (NCI-CTC grade 3) skin reactions were reported in 34% and life-threatening (NCI-CTC grade 4) skin reactions in < 1% of patients who received Vectibix in combination with chemotherapy (n = 1536).

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| Musculoskeletal and connective tissue disorders | Back pain | Pain in extremity | | | |
| General disorders and administration site conditions | Fatigue<br>Pyrexia<br>Asthenia<br>Mucosal inflammation<br>Oedema peripheral | Chest pain<br>Pain<br>Chills | Infusion-related reaction[1] | | |
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[1] See section "Description of selected adverse reactions" below
[2] 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
[3] See Section 4.4 Pulmonary complications
* Frequency cannot be estimated from the available data

……..

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Skin rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities. Subsequent to the development of severe skin and subcutaneous reactions, infectious complications including sepsis, in rare cases leading to death, cellulitis and local abscesses requiring incisions and drainage were reported. The median time to first symptom of dermatologic reaction was 10 days, and the median time to resolution after the last dose of Vectibix was 28 days.

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| | |
|---|---|
| For clinical management of dermatological reactions, including dose modification recommendations, see section 4.4.<br><br>In the post-marketing setting, cases of skin necrosis have been reported. | chemotherapy (n = 1536).<br><br>For clinical management of dermatological reactions, including dose modification recommendations, see section 4.4.<br><br>In the post-marketing setting, rare cases of skin necrosis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4) have been reported. |

| | |
|---|---|
| **5. PHARMACOLOGICAL PROPERTIES**<br><br>**5.1 Pharmacodynamic properties**<br><br>Clinical efficacy as monotherapy<br><br>The efficacy of Vectibix as monotherapy in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in a randomised controlled trial (463 patients) and open-label, single-arm trials (384 patients).<br><br>A multinational, randomised, controlled trial was conducted in 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum after confirmed failure of oxaliplatin and irinotecan-containing regimens. Patients were randomised 1:1 to receive Vectibix at a dose of 6 mg/kg given once every two weeks plus best supportive care (not including chemotherapy) (BSC) or BSC alone. Patients were treated until disease progression or unacceptable toxicity occurred. Upon disease progression BSC alone patients were eligible to crossover to a companion study and receive Vectibix at a dose of 6 mg/kg given once every two weeks.<br><br>Of 463 patients, 63% were male. The median age was 62 years (range 27 to 83), and 99% were Caucasian. Three hundred and ninety-six (86%) patients had a baseline ECOG Performance Status of 0 or 1. Sixty-seven percent of patients had colon cancer and 33% had rectal cancer.<br><br>The primary endpoint was progression-free survival (PFS). In an analysis adjusting for potential bias from unscheduled assessments, the rate of disease progression or death in patients who received Vectibix was reduced by 40% relative to patients that received BSC [Hazard Ratio = 0.60, (95% CI: 0.49, 0.74), stratified log-rank p < 0.0001]. There was no difference seen in median PFS times as more than 50% of patients progressed in both treatment groups before the first scheduled visit.<br><br>The study was retrospectively analysed by wild-type *KRAS* status versus | **5. PHARMACOLOGICAL PROPERTIES**<br><br>**5.1 Pharmacodynamic properties**<br><br>Clinical efficacy as monotherapy<br><br>The efficacy of Vectibix as monotherapy in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in ~~a randomised controlled trial (463 patients) and~~ open-label, single-arm trials (384 patients) and in two randomised controlled trials versus best supportive care (463 patients) and versus cetuximab (1010 patients).~~.~~<br><br>A multinational, randomised, controlled trial was conducted in 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum after confirmed failure of oxaliplatin and irinotecan-containing regimens. Patients were randomised 1:1 to receive Vectibix at a dose of 6 mg/kg given once every two weeks plus best supportive care (not including chemotherapy) (BSC) or BSC alone. Patients were treated until disease progression or unacceptable toxicity occurred. Upon disease progression BSC alone patients were eligible to crossover to a companion study and receive Vectibix at a dose of 6 mg/kg given once every two weeks.<br><br>~~Of 463 patients, 63% were male. The median age was 62 years (range 27 to 83), and 99% were Caucasian. Three hundred and ninety-six (86%) patients had a baseline ECOG Performance Status of 0 or 1. Sixty-seven percent of patients had colon cancer and 33% had rectal cancer.~~<br><br>The primary endpoint was progression-free survival (PFS). In an analysis adjusting for potential bias from unscheduled assessments, the rate of disease progression or death in patients who received Vectibix was reduced by 40% relative to patients that received BSC [Hazard Ratio = 0.60, (95% CI: 0.49, 0.74), stratified log-rank p < 0.0001]. There was no difference seen in median PFS times as more than 50% of patients progressed in both treatment groups before the first scheduled visit. |

mutant *KRAS* status. *KRAS* mutation status was determined by analysis of archived paraffin embedded tumour tissue.

Tumour samples obtained from the primary resection of colorectal cancer were analysed for the presence of the seven most common activating mutations in the codon 12 and 13 (Gly12Asp, Gly12Ala, Gly12Val, Gly12Ser, Gly12Arg, Gly12Cys, and Gly13Asp) of the *KRAS* gene by using an allele-specific polymerase chain reaction. 427 (92%) patients were evaluable for *KRAS* status of which 184 had mutations. The efficacy results from an analysis adjusting for potential bias from unscheduled assessments are shown in the table below. There was no difference in overall survival (OS) seen in either group.

| | **Wild-type *KRAS* (exon 2) population** | | **Mutant *KRAS* (exon 2) population** | |
|---|---|---|---|---|
| | **Vectibix plus BSC (n = 124)** | **BSC (n = 119)** | **Vectibix plus BSC (n = 84)** | **BSC (n = 100)** |
| **ORR n (%)** | 17% | 0% | 0% | 0% |
| Response rate (investigator assessed)[a] (95% CI) | 22% (14, 32) | | 0% (0, 4) | |
| **Stable Disease** | 34% | 12% | 12% | 8% |
| **PFS** | | | | |
| Hazard ratio (95% CI) | 0.49 (0.37,0.65), p<0.0001 | | 1.07 (0.77,1.48), p = 0.6880 | |
| Median (weeks) | 16.0 | 8.0 | 8.0 | 8.0 |
| Difference in median (weeks) | 8.0 | | 0.0 | |
| Rate at week 8 | 60% | 21% | 21% | 28% |

CI = confidence interval

[a] In patients that crossed over to panitumumab after progression on BSC alone (95% CI)

The study was retrospectively analysed by wild-type *KRAS* (exon 2) status versus mutant *KRAS* (exon 2) status. *KRAS* mutation status was determined by analysis of archived paraffin embedded tumour tissue.

Tumour samples obtained from the primary resection of colorectal cancer were analysed for the presence of the seven most common activating mutations in the codon 12 and 13 ~~(Gly12Asp, Gly12Ala, Gly12Val, Gly12Ser, Gly12Arg, Gly12Cys, and Gly13Asp)~~ of the *KRAS* gene by using an allele-specific polymerase chain reaction. 427 (92%) patients were evaluable for *KRAS* status of which 184 had mutations. The efficacy results from an analysis adjusting for potential bias from unscheduled assessments are shown in the table below. There was no difference in overall survival (OS) seen in either group.

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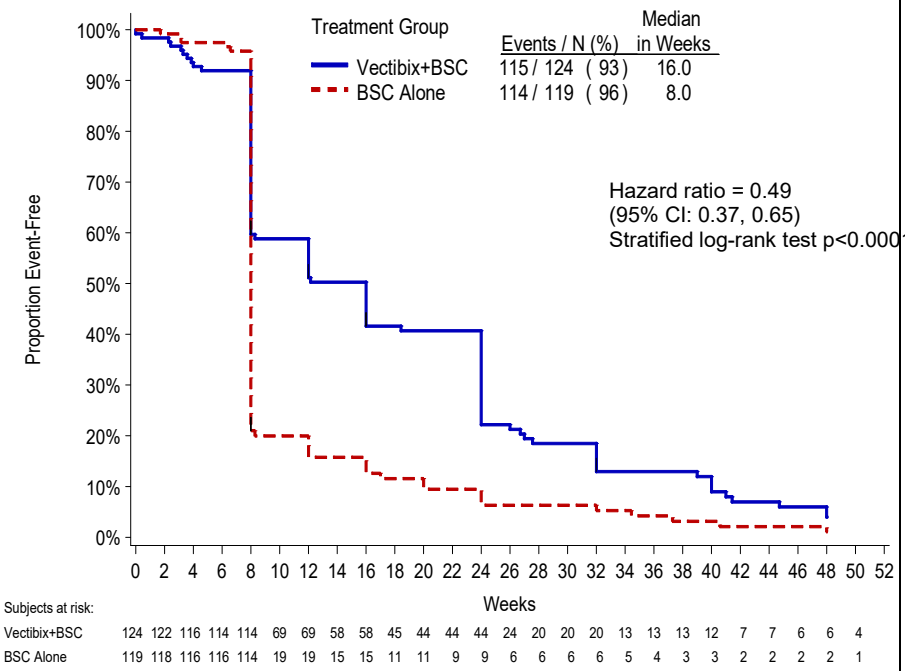
~~***PFS – Patients with mutant and wild-type KRAS (exon 2)***~~

***PFS – Patients with mutant and wild-type KRAS (exon 2)***

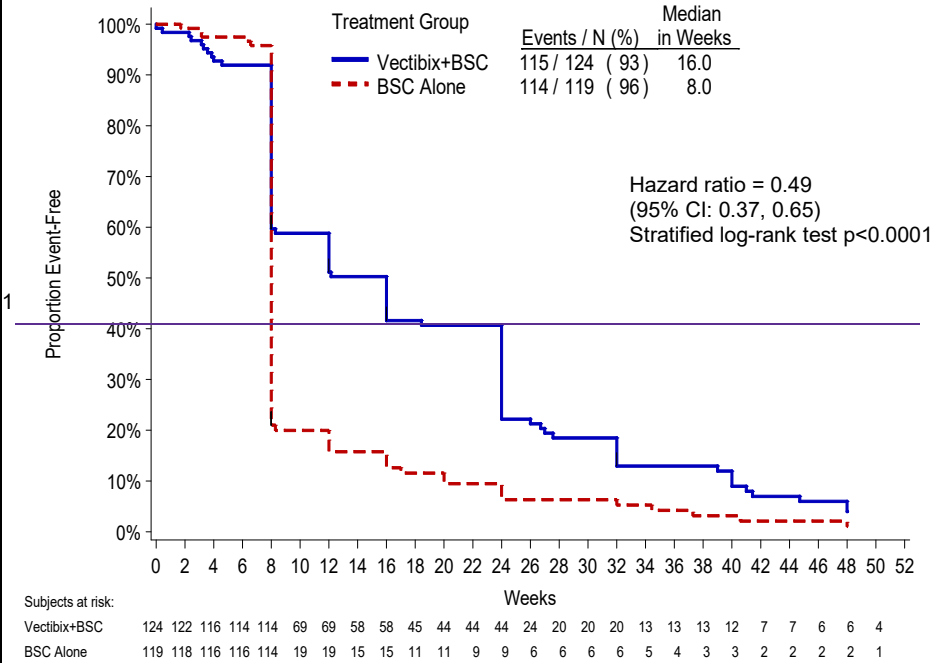
PFS – Patients with wild-type *KRAS*




*Unscheduled tumour assessments were moved to the nearest scheduled timepoint*

PFS – Patients with mutant *KRAS*

~~PFS – Patients with wild-type *KRAS*~~

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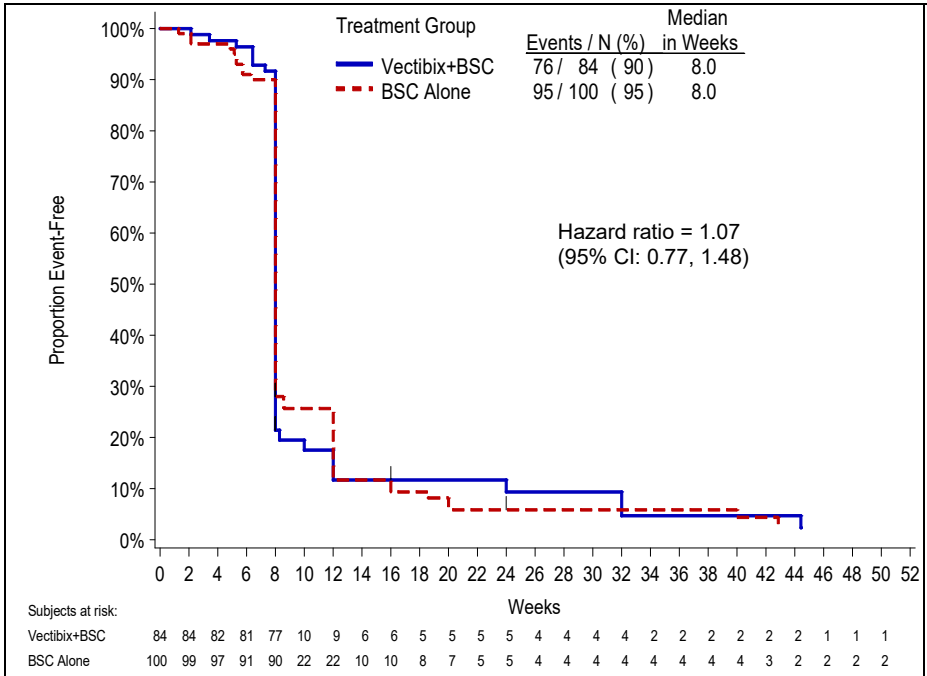
~~PFS – Patients with mutant *KRAS*~~




*Unscheduled tumour assessments were moved to the nearest scheduled timepoint*

In an exploratory analysis of banked tumour specimens from this study, 11 of 72 patients (15%) with wild-type *RAS* tumours receiving panitumumab had an objective response compared to only 1 of 95 patients (1%) with mutant *RAS* tumour status. Moreover, panitumumab treatment was associated with improved PFS compared to BSC in patients with wild-type *RAS* tumours (HR = 0.38 [95% CI: 0.27, 0.56]), but not in patients with tumours harbouring a *RAS* mutation (HR = 0.98 [95% CI: 0.73, 1.31]).

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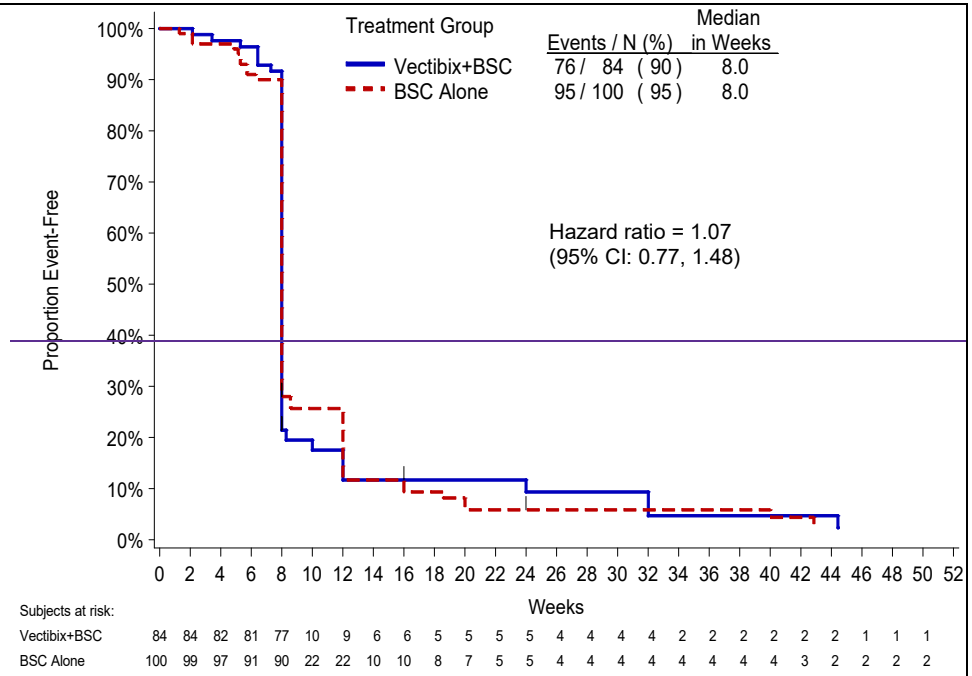
*First-line combination with bevacizumab and oxaliplatin or irinotecan-based chemotherapy*

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The efficacy of Vectibix was also evaluated in an open-label trial in patients with wild-type *KRAS* (exon 2) mCRC. A total of 1010 patients refractory to chemotherapy were randomised 1:1 to receive Vectibix or cetuximab to test whether Vectibix is non-inferior to cetuximab. The primary endpoint was overall survival (OS). Secondary endpoints included progression free

In a randomised, open label, controlled clinical trial, chemotherapy (oxaliplatin or irinotecan) and bevacizumab were given with and without panitumumab in the first line treatment of patients with metastatic colorectal cancer (n = 1053 [n = 823 oxaliplatin cohort, n = 230 irinotecan cohort]). Panitumumab treatment was discontinued due to a statistically significant reduction in PFS in patients receiving panitumumab observed in an interim analysis.

The major study objective was comparison of PFS in the oxaliplatin cohort. In the final analysis, the hazard ratio for PFS was 1.27 (95% CI: 1.06, 1.52). Median PFS was 10.0 (95% CI: 8.9, 11.0) and 11.4 (95% CI: 10.5, 11.9) months in the panitumumab and the non-panitumumab arm, respectively. There was an increase in mortality in the panitumumab arm. The hazard ratio for overall survival was 1.43 (95% CI: 1.11, 1.83). Median overall survival was 19.4 (95% CI: 18.4, 20.8) and 24.5 (95% CI: 20.4, 24.5) in the panitumumab arm and the non-panitumumab arm.

An additional analysis of efficacy data by *KRAS* (exon 2) status did not identify a subset of patients who benefited from panitumumab in combination with oxaliplatin- or irinotecan based chemotherapy and bevacizumab. For the wild-type *KRAS* subset of the oxaliplatin cohort, the hazard ratio for PFS was 1.36 with 95% CI: 1.04-1.77. For the mutant *KRAS* subset, the hazard ratio for PFS was 1.25 with 95% CI: 0.91-1.71. A trend for OS favouring the control arm was observed in the wild-type *KRAS* subset of the oxaliplatin cohort (hazard ratio = 1.89; 95% CI: 1.30, 2.75). A trend towards worse survival was also observed with panitumumab in the irinotecan cohort regardless of *KRAS* mutational status. Overall, panitumumab treatment combined with chemotherapy and bevacizumab is associated with an unfavourable benefit-to-risk profile irrespective of tumour *KRAS* mutational status.

This medicinal product has been authorised under a "conditional approval" scheme. This means that further evidence on this medicinal product is awaited, in particular data are required to confirm the effect in patients with

survival (PFS) and objective response rate (ORR).

The efficacy results for the study are presented in the table below.

| **Wild-type *KRAS* (exon 2) population** | **Vectibix** (n = 499) | **Cetuximab** (n = 500) |
|---|---|---|
| **OS** | | |
| Median (months) (95% CI) | 10.4 (9.4, 11.6) | 10.0 (9.3, 11.0) |
| Hazard ratio (95% CI) | 0.97 (0.84, 1.11) | |
| **PFS** | | |
| Median (months) (95% CI) | 4.1 (3.2, 4.8) | 4.4 (3.2, 4.8) |
| Hazard ratio (95% CI) | 1.00 (0.88, 1.14) | |
| **ORR** | | |
| n (%) (95% CI) | 22% (18%, 26%) | 20% (16%, 24%) |
| Odds ratio (95% CI) | 1.15 (0.83, 1.58) | |

Overall, the safety profile of panitumumab was similar to that of cetuximab, in particular regarding skin toxicity. However, infusion reactions were more frequent with cetuximab (13% vs. 3%) but electrolyte disturbances were more frequent with panitumumab, especially hypomagnesaemia (29% vs. 19%).

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*First-line combination with bevacizumab and oxaliplatin or irinotecan-based chemotherapy*

In a randomised, open label, controlled clinical trial, chemotherapy (oxaliplatin or irinotecan) and bevacizumab were given with and without panitumumab in the first line treatment of patients with metastatic colorectal cancer (n = 1053 [n = 823 oxaliplatin cohort, n = 230 irinotecan cohort]). Panitumumab treatment was discontinued due to a statistically significant reduction in PFS in patients receiving panitumumab observed in an interim analysis.

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|---|---|
| wild-type *KRAS* tumours which is currently supported by a retrospective analysis. Further evidence is also awaited regarding the effect of panitumumab in combination with chemotherapy on PFS in patients with wild-type *KRAS* tumours. Studies investigating this effect are currently ongoing. The European Medicines Agency (EMA) will review new information on this medicinal product at least every year and this SPC will be updated as necessary | The major study objective was comparison of PFS in the oxaliplatin cohort. In the final analysis, the hazard ratio for PFS was 1.27 (95% CI: 1.06, 1.52). Median PFS was 10.0 (95% CI: 8.9, 11.0) and 11.4 (95% CI: 10.5, 11.9) months in the panitumumab and the non-panitumumab arm, respectively. There was an increase in mortality in the panitumumab arm. The hazard ratio for overall survival was 1.43 (95% CI: 1.11, 1.83). Median overall survival was 19.4 (95% CI: 18.4, 20.8) and 24.5 (95% CI: 20.4, 24.5) in the panitumumab arm and the non-panitumumab arm.<br><br>An additional analysis of efficacy data by *KRAS* (exon 2) status did not identify a subset of patients who benefited from panitumumab in combination with oxaliplatin- or irinotecan based chemotherapy and bevacizumab. For the wild-type *KRAS* subset of the oxaliplatin cohort, the hazard ratio for PFS was 1.36 with 95% CI: 1.04-1.77. For the mutant *KRAS* subset, the hazard ratio for PFS was 1.25 with 95% CI: 0.91-1.71. A trend for OS favouring the control arm was observed in the wild-type *KRAS* subset of the oxaliplatin cohort (hazard ratio = 1.89; 95% CI: 1.30, 2.75). A trend towards worse survival was also observed with panitumumab in the irinotecan cohort regardless of *KRAS* mutational status. Overall, panitumumab treatment combined with chemotherapy and bevacizumab is associated with an unfavourable benefit-to-risk profile irrespective of tumour *KRAS* mutational status.<br><br>This medicinal product has been authorised under a “conditional approval” scheme. This means that further evidence on this medicinal product is awaited~~, in particular data are required to confirm the effect in patients with wild-type *KRAS* tumours which is currently supported by a retrospective analysis. Further evidence is also awaited regarding the effect of panitumumab in combination with chemotherapy on PFS in patients with wild-type *KRAS* tumours. Studies investigating this effect are currently ongoing~~. The European Medicines Agency (EMA) will review new information on this medicinal product at least every year and this SPC will be updated as necessary. |

**מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.**

The leaflet, in which the changes requested are yellow highlighted, was sent by e-mail on……..

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.