ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Erbitux 5 mg/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for infusion contains 5 mg cetuximab.

Each vial of 20 mL contains 100 mg cetuximab.
Each vial of 100 mL contains 500 mg cetuximab.

Cetuximab is a chimeric monoclonal IgG_1 antibody produced in a mammalian cell line (Sp2/0) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer

- in combination with irinotecan-based chemotherapy,
- in first-line in combination with FOLFOX,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

For details, see section 5.1.

Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck

- in combination with radiation therapy for locally advanced disease,
- in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

4.2 Posology and method of administration

Erbitux must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.

<u>Posology</u>

Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions.

In all indications, Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m^2 body surface area. All subsequent weekly doses are 250 mg cetuximab per m^2 each.

Colorectal cancer

In patients with metastatic colorectal cancer, cetuximab is used in combination with chemotherapy or as a single agent (see section 5.1). Evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with Erbitux. Mutational status should be determined by an experienced laboratory using validated test methods for detection of KRAS and NRAS (exons 2, 3, and 4) mutations (see section 4.4 and 5.1).

For the dosage or recommended dose modifications of concomitantly used chemotherapeutic agents, refer to the product information for these medicinal products. They must not be administered earlier than 1 hour after the end of the cetuximab infusion.

It is recommended that cetuximab treatment be continued until progression of the underlying disease.

Squamous cell cancer of the head and neck

In patients with locally advanced squamous cell cancer of the head and neck, cetuximab is used concomitantly with radiation therapy. It is recommended to start cetuximab therapy one week before radiation therapy and to continue cetuximab therapy until the end of the radiation therapy period.

In patients with recurrent and/or metastatic squamous cell cancer of the head and neck, cetuximab is used in combination with platinum-based chemotherapy followed by cetuximab as maintenance therapy until disease progression (see section 5.1). Chemotherapy must not be administered earlier than 1 hour after the end of the cetuximab infusion.

Special populations

Only patients with adequate renal and hepatic function have been investigated to date (see section 4.4).

Cetuximab has not been studied in patients with pre-existing haematological disorders (see section 4.4).

No dose adjustment is required in older people, but the experience is limited in patients 75 years of age and above.

Paediatric population

There is no relevant use of cetuximab in the paediatric population in the granted indications.

Method of administration

Erbitux 5 mg/mL is administered intravenously with an infusion pump, gravity drip or a syringe pump (for handling instructions, see section 6.6).

The initial dose should be given slowly and speed of infusion must not exceed 5 mg/min (see section 4.4). The recommended infusion period is 120 minutes. For the subsequent weekly doses, the recommended infusion period is 60 minutes. The infusion rate must not exceed 10 mg/min.

4.3 Contraindications

Erbitux is contraindicated in patients with known severe (grade 3 or 4) hypersensitivity reactions to cetuximab.

The combination of Erbitux with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant RAS metastatic colorectal cancer (mCRC) or for whom RAS mCRC status is unknown (see also section 4.4).

Before initiation of combination treatment, contraindications for concomitantly used chemotherapeutic agents or radiation therapy must be considered.

4.4 Special warnings and precautions for use

Infusion-related, including anaphylactic, reactions

Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a cytokine release syndrome (CRS). Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. It is recommended to warn patients of the possibility of such a late onset and instruct them to contact their physician if symptoms or signs of an infusion-related reaction occur. Symptoms may include bronchospasm, urticaria, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.

Anaphylactic reactions may occur as early as within a few minutes of the first infusion e.g. due to preformed IgE antibodies cross-reacting with cetuximab. These reactions are commonly associated with bronchospasm and urticaria. They can occur despite the use of premedication.
The risk for anaphylactic reactions is much increased in patients with a history of allergy to red meat or tick bites or positive results of tests for IgE antibodies against cetuximab (α-1-3-galactose). In these patients cetuximab should be administered only after a careful assessment of benefit/risk, including alternative treatments, and only under close supervision of well trained personnel with resuscitation equipment ready.

The first dose should be administered slowly and the speed must not exceed 5 mg/min whilst all vital signs are closely monitored for at least two hours. If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have preformed IgE antibodies before a subsequent infusion is given.

If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity:

a) Grade 1: continue slow infusion under close supervision

b) Grade 2: continue slow infusion and immediately administer treatment for symptoms

c) Grade 3 and 4: stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab

A cytokine release syndrome (CRS) typically occurs within one hour after infusion and is less commonly associated with bronchospasm and urticaria. CRS is normally most severe in relation to the first infusion.

Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first cetuximab infusion. If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions.

A close monitoring of patients, particularly during the first administration, is required. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.

Respiratory disorders

Cases of interstitial lung disease have been reported, with the majority of patients from the Japanese population. If interstitial lung disease is diagnosed, cetuximab must be discontinued and the patient be treated appropriately.

Skin reactions

Main adverse reactions of cetuximab are skin reactions which may become severe, especially in combination with chemotherapy. The risk for secondary infections (mainly bacterial) is increased and cases of staphylococcal scalded skin syndrome, necrotising fasciitis and sepsis, in some cases with fatal outcome, have been reported (see section 4.8).

Skin reactions are very common and treatment interruption or discontinuation may be required. According to clinical practice guidelines prophylactic use of oral tetracyclines (6 - 8 weeks) and topical application of 1% hydrocortisone cream with moisturiser should be considered. Medium to high-potency topical corticosteroids or oral tetracyclines have been used for the treatment of skin reactions.

If a patient experiences an intolerable or severe skin reaction (≥ grade 3; Common Terminology Criteria for Adverse Events, CTCAE), cetuximab therapy must be interrupted. Treatment may only be resumed if the reaction has resolved to grade 2.

If the severe skin reaction occurred for the first time, treatment may be resumed without any change in dose level.

With the second and third occurrences of severe skin reactions, cetuximab therapy must again be interrupted. Treatment may only be resumed at a lower dose level (200 mg/m² after the second occurrence and 150 mg/m² after the third occurrence), if the reaction has resolved to grade 2.

If severe skin reactions occur a fourth time or do not resolve to grade 2 during interruption of treatment, permanent discontinuation of cetuximab treatment is required.

Electrolyte disturbances

Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Hypomagnesaemia is reversible following discontinuation of cetuximab. In addition, hypokalaemia may develop as a consequence of diarrhoea. Hypocalcaemia may also occur; in particular in combination with platinum-based chemotherapy the frequency of severe hypocalcaemia may be increased.

Determination of serum electrolyte levels is recommended prior to and periodically during cetuximab treatment. Electrolyte repletion is recommended, as appropriate.

Neutropenia and related infectious complications

Patients who receive cetuximab in combination with platinum-based chemotherapy are at an increased risk for the occurrence of severe neutropenia, which may lead to subsequent infectious complications such as febrile neutropenia, pneumonia or sepsis. Careful monitoring is recommended in such patients, in particular in those who experience skin lesions, mucositis or diarrhoea that may facilitate the occurrence of infections (see section 4.8).

Cardiovascular disorders

An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed in the treatment of non-small cell lung cancer, squamous cell carcinoma of the head and neck and colorectal carcinoma. In some studies association with age ≥ 65 years or

performance status has been observed. When prescribing cetuximab, the cardiovascular and performance status of the patients and concomitant administration of cardiotoxic compounds such as fluoropyrimidines should be taken into account.

Eye disorders

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Cetuximab should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Colorectal cancer patients with RAS mutated tumours

Cetuximab should not be used in the treatment of colorectal cancer patients whose tumours have RAS mutations or for whom RAS tumour status is unknown. Results from clinical studies show a negative benefit-risk balance in tumours with RAS mutations. In particular, in these patients negative effects on progression-free survival (PFS) and overall survival (OS) were seen as add-on to FOLFOX4 (see section 5.1).

Similar findings were also reported when cetuximab was given as add-on to XELOX in combination with bevacizumab (CAIRO2). However, in this study no positive effects on PFS or OS were demonstrated in patients with KRAS wild-type tumours, either.

Special populations

Only patients with adequate renal and hepatic function have been investigated to date (serum creatinine ≤ 1.5fold, transaminases ≤ 5fold and bilirubin ≤ 1.5fold the upper limit of normal).

Cetuximab has not been studied in patients presenting with one or more of the following laboratory parameters:

- haemoglobin < 9 g/dL
- leukocyte count < 3000/mm³
- absolute neutrophil count < 1500/mm³
- platelet count < 100000/mm³

There is limited experience in the use of cetuximab in combination with radiation therapy in colorectal cancer.

Paediatric population

The efficacy of cetuximab in paediatric patients below the age of 18 years has not been established. No new safety signals were identified in paediatric patients as reported from a phase-I study.

4.5 Interaction with other medicinal products and other forms of interaction

In combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis compared to platinum-based chemotherapy alone (see section 4.4).

In combination with fluoropyrimidines, the frequency of cardiac ischaemia including myocardial

infarction and congestive heart failure as well as the frequency of hand-foot syndrome (palmar-plantar erythrodysaesthesia) were increased compared to that with fluoropyrimidines.

In combination with capecitabine and oxaliplatin (XELOX) the frequency of severe diarrhoea may be increased.

A formal interaction study showed that the pharmacokinetic characteristics of cetuximab remain unaltered after co-administration of a single dose of irinotecan (350 mg/m^2 body surface area). Similarly, the pharmacokinetics of irinotecan were unchanged when cetuximab was co-administered.

No other formal interaction studies with cetuximab have been performed in humans.

4.6 Fertility, pregnancy and lactation

Pregnancy

EGFR is involved in foetal development. Limited observations in animals are indicative of a placental transfer of cetuximab, and other IgG_1 antibodies have been found to cross the placental barrier. Animal data revealed no evidence of teratogenicity. However, dependent on the dose, an increased incidence of abortion was observed (see section 5.3). Sufficient data from pregnant or lactating women are not available.

It is strongly recommended that Erbitux be given during pregnancy or to any woman not employing adequate contraception only if the potential benefit for the mother justifies a potential risk to the foetus.

Breast-feeding

It is recommended that women do not breast-feed during treatment with Erbitux and for 2 months after the last dose, because it is not known whether cetuximab is excreted in breast milk.

Fertility

There are no data on the effect of cetuximab on human fertility. Effects on male and female fertility have not been evaluated within formal animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

The main undesirable effects of cetuximab are skin reactions, which occur in more than 80% of patients, hypomagnesaemia which occurs in more than 10% of patients and infusion-related reactions, which occur with mild to moderate symptoms in more than 10% of patients and with severe symptoms in more than 1% of patients.

The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Frequency not known (cannot be estimated from the available data)

An asterisk (*) indicates that additional information on the respective undesirable effect is provided below the table.

Metabolism and nutrition disorders

Very common: Hypomagnesaemia (see section 4.4).
Common: Dehydration, in particular secondary to diarrhoea or mucositis; hypocalcaemia (see section 4.4); anorexia which may lead to weight decrease.

Nervous system disorders

Common: Headache.
Frequency not known: Aseptic meningitis.

Eye disorders

Common: Conjunctivitis.
Uncommon: Blepharitis, keratitis.

Vascular disorders

Uncommon: Deep vein thrombosis.

Respiratory, thoracic and mediastinal disorders

Uncommon: Pulmonary embolism, interstitial lung disease.

Gastrointestinal disorders

Common: Diarrhoea, nausea, vomiting.

Hepatobiliary disorders

Very common: Increase in liver enzyme levels (ASAT, ALAT, AP).

Skin and subcutaneous tissue disorders

Very common: Skin reactions*.
Very rare: Stevens-Johnson syndrome/toxic epidermal necrolysis.
Frequency not known: Superinfection of skin lesions*.

General disorders and administration site conditions

Very common: Mild or moderate infusion-related reactions (see section 4.4); mucositis, in some cases severe. Mucositis may lead to epistaxis.
Common: Severe infusion-related reactions, in some cases with fatal outcome (see section 4.4); fatigue.

Additional information

Overall, no clinically relevant difference between genders was observed.

Skin reactions

Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g. paronychia).

Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. The majority of skin reactions develop within the first three weeks of therapy. They generally resolve, without sequelae, over time following cessation of treatment if the recommended adjustments in dose regimen are followed (see section 4.4).
Skin lesions induced by cetuximab may predispose patients to superinfections (e.g. with *S. aureus*), which may lead to subsequent complications, e.g. cellulitis, erysipelas, or, potentially with fatal outcome, staphylococcal scalded skin syndrome, necrotising fasciitis or sepsis.

Combination treatment

When cetuximab is used in combination with chemotherapeutic agents, also refer to their respective product information.

In combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis compared to platinum-based chemotherapy alone (see section 4.4).

In combination with fluoropyrimidines, the frequency of cardiac ischaemia including myocardial infarction and congestive heart failure as well as the frequency of hand-foot syndrome (palmar-plantar erythrodysaesthesia) were increased compared to that with fluoropyrimidines.

In combination with local radiation therapy of the head and neck area, additional undesirable effects were those typical of radiation therapy (such as mucositis, radiation dermatitis, dysphagia or leukopenia, mainly presenting as lymphocytopenia). In a randomised controlled clinical study with 424 patients, reporting rates of severe acute radiation dermatitis and mucositis as well as of late radiation-therapy-related events were slightly higher in patients receiving radiation therapy in combination with cetuximab than in those receiving radiation therapy alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited experience with single doses higher than 400 mg/m^2 body surface area to date or weekly administrations of doses higher than 250 mg/m^2 body surface area. In clinical studies with doses up to 700 mg/m^2 given every 2 weeks the safety profile was consistent with that described in section 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC06

Mechanism of action

Cetuximab is a chimeric monoclonal IgG_1 antibody that is specifically directed against the epidermal growth factor receptor (EGFR).

EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis.

Cetuximab binds to the EGFR with an affinity that is approximately 5- to 10-fold higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands resulting in inhibition of the function of the receptor. It further induces the internalisation of EGFR, which can lead to down-regulation of EGFR. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells (antibody dependent cell-mediated cytotoxicity, ADCC).

Cetuximab does not bind to other receptors belonging to the HER family.

The protein product of the proto-oncogene RAS (rat sarcoma) is a central down-stream signal-transducer of EGFR. In tumours, activation of RAS by EGFR contributes to EGFR-mediated increased proliferation, survival and the production of pro-angiogenic factors.

RAS is one of the most frequently activated family of oncogenes in human cancers. Mutations of RAS genes at certain hot-spots on exons 2, 3 and 4 result in constitutive activation of RAS proteins independently of EGFR signalling.

Pharmacodynamic effects

In both *in vitro* and *in vivo* assays, cetuximab inhibits the proliferation and induces apoptosis of human tumour cells that express EGFR. *In vitro* cetuximab inhibits the production of angiogenic factors by tumour cells and blocks endothelial cell migration. *In vivo* cetuximab inhibits expression of angiogenic factors by tumour cells and causes a reduction in tumour neo-vascularisation and metastasis.

Immunogenicity

The development of human anti-chimeric antibodies (HACA) is a class effect of monoclonal chimeric antibodies. Current data on the development of HACAs is limited. Overall, measurable HACA titres were noted in 3.4% of the patients studied, with incidences ranging from 0% to 9.6% in the target indication studies. No conclusive data on the neutralising effect of HACAs on cetuximab is available to date. The appearance of HACA did not correlate with the occurrence of hypersensitivity reactions or any other undesirable effect to cetuximab.

Colorectal cancer

A diagnostic assay (EGFR pharmDx) was used for immunohistochemical detection of EGFR expression in tumour material. A tumour was considered to be EGFR-expressing, if one stained cell could be identified. Approximately 75% of the patients with metastatic colorectal cancer screened for clinical studies had an EGFR-expressing tumour and were therefore considered eligible for cetuximab treatment. The efficacy and safety of cetuximab have not been documented in patients with tumours where EGFR was not detected.

Study data demonstrate that patients with metastatic colorectal cancer and activating RAS mutations are highly unlikely to benefit from treatment with cetuximab or a combination of cetuximab and chemotherapy and as add-on to FOLFOX4 a significant negative effect on progression-free survival time (PFS) was shown.

Cetuximab as a single agent or in combination with chemotherapy was investigated in 5 randomised controlled clinical studies and several supportive studies. The 5 randomised studies investigated a total of 3734 patients with metastatic colorectal cancer, in whom EGFR expression was detectable and who had an ECOG performance status of ≤ 2. The majority of patients included had an ECOG performance status of ≤ 1. In all studies, cetuximab was administered as described in section 4.2.

The KRAS exon 2 status was recognised as predictive factor for the treatment with cetuximab in 4 of the randomised controlled studies (EMR 62 202-013, EMR 62 202-047, CA225006, and CA225025). KRAS mutational status was available for 2072 patients. Further post-hoc analyses were performed for studies EMR 62 202-013 and EMR 62 202-047, where also mutations on RAS genes (NRAS and

KRAS) other than KRAS exon 2 have been determined. Only in study EMR 62 202-007, a post-hoc analysis was not possible.

In addition, cetuximab was investigated in combination with chemotherapy in an investigator-initiated randomised controlled phase-III study (COIN, COntinuous chemotherapy plus cetuximab or INtermittent chemotherapy). In this study EGFR expression was not an inclusion criterion. Tumour samples from approximately 81% of patients were analysed retrospectively for KRAS expression.

FIRE-3, an investigator-sponsored clinical phase-III study, compared the treatment of FOLFIRI in combination with either cetuximab or bevacizumab in the first-line treatment of patients with KRAS exon 2 wild-type mCRC. Further post-hoc analyses on mutations on RAS genes other than KRAS exon 2 have been evaluated.

Cetuximab in combination with chemotherapy

- EMR 62 202-013: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and irinotecan plus infusional 5-fluorouracil/folinic acid (FOLFIRI) (599 patients) to the same chemotherapy alone (599 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 63%. For the assessment of the RAS status, mutations other than those on exon 2 of the KRAS gene were determined from all evaluable tumour samples within the KRAS exon 2 wild-type population (65%). The RAS mutant population consists of patients with known KRAS exon 2 mutations as well as additionally identified RAS mutations.

  The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	RAS wild-type population		RAS mutant population	
	Cetuximab plus FOLFIRI (N=178)	FOLFIRI (N=189)	Cetuximab plus FOLFIRI (N=246)	FOLFIRI (N=214)
OS				
months, median	28.4	20.2	16.4	17.7
(95% CI)	(24.7, 31.6)	(17.0, 24.5)	(14.9, 18.4)	(15.4, 19.6)
Hazard Ratio (95% CI)	0.69 (0.54, 0.88)		1.05 (0.86, 1.28)	
p-value	0.0024		0.6355	
PFS				
months, median	11.4	8.4	7.4	7.5
(95% CI)	(10.0, 14.6)	(7.4, 9.4)	(6.4, 8.0)	(7.2, 8.5)
Hazard Ratio (95% CI)	0.56 (0.41, 0.76)		1.10 (0.85, 1.42)	
p-value	0.0002		0.4696	
ORR				
%	66.3	38.6	31.7	36.0
(95% CI)	(58.8, 73.2)	(31.7, 46.0)	(25.9, 37.9)	(29.6, 42.8)
Odds Ratio (95% CI)	3.1145 (2.0279, 4.7835)		0.8478 (0.5767, 1.2462)	
p-value	<0.0001		0.3970	

CI = confidence interval, FOLFIRI = irinotecan plus infusional 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), OS = overall survival time, PFS = progression-free survival time

- EMR 62 202-047: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and oxaliplatin plus continuous infusional 5-fluorouracil/folinic acid (FOLFOX4) (169 patients) to the same chemotherapy alone (168 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 57%. For the assessment of the RAS status, mutations other than those on exon 2 of the KRAS gene were determined from all evaluable tumour samples within the KRAS exon 2 wild-type population.

The RAS mutant population consists of patients with known KRAS exon 2 mutations as well as additionally identified RAS mutations.

The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	RAS wild-type population		RAS mutant population	
	Cetuximab plus FOLFOX4	FOLFOX4	Cetuximab plus FOLFOX4	FOLFOX4
	(N=38)	(N=49)	(N=92)	(N=75)
OS				
months, median	19.8	17.8	13.5	17.8
(95% CI)	(16.6, 25.4)	(13.8, 23.9)	(12.1, 17.7)	(15.9, 23.6)
Hazard Ratio (95% CI)	0.94 (0.56, 1.56)		1.29 (0.91, 1.84)	
p-value	0.8002		0.1573	
PFS				
months, median	12.0	5.8	5.6	7.8
(95% CI)	(5.8, NE)	(4.7, 7.9)	(4.4, 7.5)	(6.7, 9.3)
Hazard Ratio (95% CI)	0.53 (0.27, 1.04)		1.54 (1.04, 2.29)	
p-value	0.0615		0.0309	
ORR				
%	57.9	28.6	37.0	50.7
(95% CI)	(40.8, 73.7)	(16.6, 43.3)	(27.1, 47.7)	(38.9, 62.4)
Odds Ratio (95% CI)	3.3302 (1.375, 8.172)		0.580 (0.311, 1.080)	
p-value	0.0084		0.0865	

CI = confidence interval, FOLFOX4 = oxaliplatin plus continuous infusional 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), OS = overall survival time, PFS = progression-free survival time, NE = not estimable

In particular a negative effect of cetuximab add-on in the RAS mutant population was observed.

- COIN: This was an open-label, 3-arm, randomised study in 2445 patients with inoperable metastatic or locoregional colorectal cancer who had not received prior treatment for metastatic disease and compared oxaliplatin plus fluoropyrimidines (infusional 5-fluorouracil/folinic acid [OxMdG] or capecitabine [XELOX]) in combination with cetuximab to the same chemotherapy regimen alone. The third experimental arm used an intermittent OxMdG or XELOX regimen without cetuximab. Data for the XELOX regimen and the third experimental arm are not presented.

  Tumour samples from approximately 81% of patients were analysed retrospectively for KRAS expression, of which 55% were KRAS wild-type. Of these, 362 patients received cetuximab and oxaliplatin plus fluoropyrimidines (117 patients OxMdG and 245 patients XELOX) and 367 patients received oxaliplatin plus fluoropyrimidines alone (127 patients OxMdG and 240 patients XELOX). Of the KRAS mutant population, 297 patients received cetuximab and oxaliplatin plus fluoropyrimidines (101 patients OxMdG and 196 patients XELOX) and 268 patients received oxaliplatin plus fluoropyrimidines alone (78 patients OxMdG and 190 patients XELOX).

The efficacy data on the OxMdG regimen generated in this study are summarised in the table below:

Variable/ statistic	KRAS wild-type population		KRAS mutant population	
	Cetuximab plus OxMdG	**OxMdG**	**Cetuximab plus OxMdG**	**OxMdG**
	(N=117)	**(N=127)**	**(N=101)**	**(N=78)**
OS				
months, median	16.3	18.2	13.1	14.6
(95% CI)	(10.3, 32.2)	(9.8, 27.5)	(8.0, 23.9)	(9.5, 22.0)
Hazard Ratio (95% CI)	0.93 (0.72, 1.19)		0.99 (0.75, 1.30)	
p-value	0.617		0.931	
PFS				
months, median	9.0	9.2	6.8	8.5
(95% CI)	(5.8, 15.5)	(5.8, 12.7)	(5.0, 10.7)	(3.4, 10.8)
Hazard Ratio (95% CI)	0.77 (0.59, 1.01)		1.05 (0.77, 1.41)	
p-value	0.056		0.78	
Best overall response rate				
%	68	59	47	51
(95% CI)	(58, 76)	(50, 68)	(37, 57)	(40, 63)
Odds Ratio (95% CI)	1.44 (0.85, 2.43)		0.83 (0.46, 1.49)	
p-value	0.171		0.529	

CI = confidence interval, OxMdG = oxaliplatin plus infusional 5-FU/FA, OS = overall survival time, PFS = progression-free survival time

In time related endpoints no trends indicating clinical benefit could be shown for patients who received cetuximab in combination with the XELOX regimen.

There were significant dose reductions and delays of capecitabine or oxaliplatin administration mainly due to higher frequency of diarrhoea in the cetuximab containing arm. In addition, significantly fewer patients treated with cetuximab received second-line therapy.

FIRE-3 (First-line combination of cetuximab with FOLFIRI): The FIRE-3 study was a multicentre randomised phase-III study investigating head-to-head 5-FU, folinic acid and irinotecan (FOLFIRI) combined with either cetuximab or bevacizumab in patients with KRAS exon 2 wild-type metastatic colorectal cancer (mCRC). RAS status was evaluable in tumour samples of 407 KRAS exon 2 wild-type patients reflecting 69% of the overall KRAS exon 2 wild-type patient population (592 patients). Of these, 342 patients had RAS wild-type tumours while RAS mutations were identified in 65 patients. The RAS mutant population comprises these 65 patients together with 113 patients with KRAS exon 2 mutant tumours treated before study enrolment was restricted to patients with KRAS exon 2 wild-type mCRC.

The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	RAS wild-type population		RAS mutant population	
	Cetuximab plus FOLFIRI (N=171)	**Bevacizumab plus FOLFIRI (N=171)**	**Cetuximab plus FOLFIRI (N=92)**	**Bevacizumab plus FOLFIRI (N=86)**
OS				
months, median	33.1	25.6	20.3	20.6
(95% CI)	(24.5, 39.4)	(22.7, 28.6)	(16.4,23.4)	(17.0, 26.7)
Hazard Ratio (95% CI)	0.70 (0.53, 0.92)		1.09 (0.78, 1.52)	
p-value	0.011		0.60	
PFS				
months, median	10.4	10.2	7.5	10.1
(95% CI)	(9.5, 12.2)	(9.3, 11.5)	(6.1, 9.0)	(8.9, 12.2)
Hazard Ratio (95% CI)	0.93 (0.74, 1.17)		1.31 (0.96, 1.78)	
p-value	0.54		0.085	
ORR				
%	65.5	59.6	38.0	51.2
(95% CI)	(57.9, 72.6)	(51.9, 67.1)	(28.1, 48.8)	(40.1, 62.1)
Odds Ratio (95% CI)	1.28 (0.83, 1.99)		0.59 (0.32, 1.06)	
p-value	0.32		0. 097	

CI = confidence interval, FOLFIRI = irinotecan plus infusional 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), OS = overall survival time, PFS = progression-free survival time

In the KRAS wild-type population of the CALGB/SWOG 80405 study (n=1137), superiority of cetuximab plus chemotherapy over bevacizumab plus chemotherapy was not shown based on an interim analysis. Analyses on the RAS wild-type population are required to appropriately evaluate these data

- CA225006: This randomised study in patients with metastatic colorectal cancer who had received initial combination treatment with oxaliplatin plus fluoropyrimidine for metastatic disease compared the combination of cetuximab and irinotecan (648 patients) with irinotecan alone (650 patients). Following disease progression, treatment with EGFR-targeting agents was initiated in 50% of patients in the irinotecan-alone arm.

  In the overall population, irrespective of KRAS status, the results reported for cetuximab plus irinotecan (648 patients) vs. irinotecan alone (650 patients) were: median overall survival time (OS) 10.71 vs. 9.99 months (HR 0.98), median progression free survival time (PFS) 4.0 vs. 2.6 months (HR 0.69), and objective response rate (ORR) 16.4% vs. 4.2%.

  With respect to the KRAS status, tumour samples were only available from 23% of the patients (300 of 1298). From the KRAS evaluated population 64% of the patients (192) had KRAS wild-type tumours and 108 patients KRAS mutations. On the basis of this data and since no independent review of imaging data was conducted, results in relation to mutation status are considered non-interpretable.

- EMR 62 202-007: This randomised study in patients with metastatic colorectal cancer after failure of irinotecan-based treatment for metastatic disease as the last treatment before study entry compared the combination of cetuximab and irinotecan (218 patients) with cetuximab monotherapy (111 patients).

  The combination of cetuximab with irinotecan compared to cetuximab alone reduced the overall risk of disease progression by 46% and significantly increased objective response rate. In the randomised trial, the improvement in overall survival time did not reach statistical significance; however, in the follow-up treatment, nearly 50% of the patients of the cetuximab alone arm received a combination of cetuximab and irinotecan after progression of disease, which may have influenced overall survival time.

Cetuximab as a single agent

- CA225025: This randomised study in patients with metastatic colorectal cancer who had received prior oxaliplatin-, irinotecan- and fluoropyrimidine-based treatment for metastatic disease compared the addition of cetuximab as a single agent to best supportive care (BSC) (287 patients) with best supportive care (285 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 58%.

  The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	KRAS wild-type population		KRAS mutant population	
	Cetuximab plus BSC (N=117)	BSC (N=113)	Cetuximab plus BSC (N=81)	BSC (N=83)
OS				
months, median	9.5	4.8	4.5	4.6
(95% CI)	(7.7, 10.3)	(4.2, 5.5)	(3.8, 5.6)	(3.6, 5.5)
Hazard Ratio (95% CI)	0.552 (0.408, 0.748)		0.990 (0.705, 1.389)	
p-value	<0.0001		0.9522	
PFS				
months, median	3.7	1.9	1.8	1.8
(95% CI)	(3.1, 5.1)	(1.8, 2.0)	(1.7, 1.8)	(1.7, 1.8)
Hazard Ratio (95% CI)	0.401 (0.299, 0.536)		1.002 (0.732, 1.371)	
p-value	<0.0001		0.9895	
ORR				
%	12.8	0	1.2	0
(95% CI)	(7.4, 20.3)	(-)	(0.0, 6.7)	(-)
p-value	<0.001		0.314	

BSC = best supportive care, CI = confidence interval, ORR = objective response rate (patients with complete response or partial response), OS = overall survival time, PFS = progression-free survival time

Squamous cell cancer of the head and neck

Immunohistochemical detection of EGFR expression was not performed since more than 90% of patients with squamous cell cancer of the head and neck have tumours that express EGFR.

Cetuximab in combination with radiation therapy for locally advanced disease

- EMR 62 202-006: This randomised study compared the combination of cetuximab and radiation therapy (211 patients) with radiation therapy alone (213 patients) in patients with locally advanced squamous cell cancer of the head and neck. Cetuximab was started one week before radiation therapy and administered at the doses described in section 4.2 until the end of the radiation therapy period.

  The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	Radiation therapy + cetuximab (N=211)		Radiation therapy alone (N=213)	
Locoregional control				
months, median (95% CI)	24.4	(15.7, 45.1)	14.9	(11.8, 19.9)
Hazard Ratio (95% CI)	0.68 (0.52, 0.89)			
p-value	0.005			
OS				
months, median (95% CI)	49.0	(32.8, 69.5+)	29.3	(20.6, 41.4)
Hazard Ratio (95% CI)	0.73 (0.56, 0.95)			
p-value	0.018			
median follow-up, months	60.0		60.1	

1-year OS rate, % (95% CI)	77.6 (71.4, 82.7)	73.8 (67.3, 79.2)
2-year OS rate, % (95% CI)	62.2 (55.2, 68.4)	55.2 (48.2, 61.7)
3-year OS rate, % (95% CI)	54.7 (47.7, 61.2)	45.2 (38.3, 51.9)
5-year OS rate, % (95% CI)	45.6 (38.5, 52.4)	36.4 (29.7, 43.1)

CI = confidence interval, OS = overall survival time, a '+' denotes that the upper bound limit had not been reached at cut-off

Patients with a good prognosis as indicated by tumour stage, Karnofsky performance status (KPS) and age had a more pronounced benefit, when cetuximab was added to radiation therapy. No clinical benefit could be demonstrated in patients with KPS ≤ 80 who were 65 years of age or older.

The use of cetuximab in combination with chemo-radiotherapy has so far not been adequately investigated. Thus, a benefit-risk ratio for this combination has not yet been established.

Cetuximab in combination with platinum-based chemotherapy in recurrent and/or metastatic disease

- EMR 62 202-002: This randomised study in patients with recurrent and/or metastatic squamous cell cancer of the head and neck who had not received prior chemotherapy for this disease compared the combination of cetuximab and cisplatin or carboplatin plus infusional 5-fluorouracil (222 patients) to the same chemotherapy alone (220 patients). Treatment in the cetuximab arm consisted of up to 6 cycles of platinum-based chemotherapy in combination with cetuximab followed by cetuximab as maintenance therapy until disease progression.

  The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	Cetuximab + CTX (N=222)		CTX (N=220)
OS			
months, median (95% CI)	10.1 (8.6, 11.2)		7.4 (6.4, 8.3)
Hazard Ratio (95% CI)		0.797 (0.644, 0.986)	
p-value		0.0362	
PFS			
months, median (95% CI)	5.6 (5.0, 6.0)		3.3 (2.9, 4.3)
Hazard Ratio (95% CI)		0.538 (0.431, 0.672)	
p-value		<0.0001	
ORR			
% (95% CI)	35.6 (29.3, 42.3)		19.5 (14.5, 25.4)
p-value		0.0001	

CI = confidence interval, CTX = platinum-based chemotherapy, ORR = objective response rate, OS = overall survival time, PFS = progression-free survival time

  Patients with a good prognosis as indicated by tumour stage, Karnofsky performance status (KPS) and age had a more pronounced benefit, when cetuximab was added to platinum-based chemotherapy. In contrast to progression free survival time, no benefit in overall survival time could be demonstrated in patients with KPS ≤ 80 who were 65 years of age or older.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with cetuximab in all subsets of the paediatric population in the indications adenocarcinoma of the colon and rectum and oropharyngeal, laryngeal or nasal epithelial carcinoma (excluding nasopharyngeal carcinoma or lymphoepithelioma, see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Cetuximab pharmacokinetics were studied when cetuximab was administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy in clinical studies. Intravenous

infusions of cetuximab exhibited dose-dependent pharmacokinetics at weekly doses ranging from 5 to 500 mg/m^2 body surface area.

When cetuximab was administered at an initial dose of 400 mg/m^2 body surface area, the mean volume of distribution was approximately equivalent to the vascular space (2.9 L/m^2 with a range of 1.5 to 6.2 L/m^2). The mean C_{max} (± standard deviation) was 185±55 microgram per mL. The mean clearance was 0.022 L/h per m² body surface area. Cetuximab has a long elimination half-life with values ranging from 70 to 100 hours at the target dose.

Cetuximab serum concentrations reached stable levels after three weeks of cetuximab monotherapy. Mean peak cetuximab concentrations were 155.8 microgram per mL in week 3 and 151.6 microgram per mL in week 8, whereas the corresponding mean trough concentrations were 41.3 and 55.4 microgram per mL, respectively. In a study of cetuximab administered in combination with irinotecan, the mean cetuximab trough levels were 50.0 microgram per mL in week 12 and 49.4 microgram per mL in week 36.

Several pathways have been described that may contribute to the metabolism of antibodies. All of these pathways involve the biodegradation of the antibody to smaller molecules, i.e. small peptides or amino acids.

Pharmacokinetics in special populations

An integrated analysis across all clinical studies showed that the pharmacokinetic characteristics of cetuximab are not influenced by race, age, gender, renal or hepatic status.

Only patients with adequate renal and hepatic function have been investigated to date (serum creatinine ≤ 1.5fold, transaminases ≤ 5fold and bilirubin ≤ 1.5fold the upper limit of normal).

Paediatric population

In a phase-I study in paediatric patients (1-18 years) with refractory solid tumours, cetuximab was administered in combination with irinotecan. The pharmacokinetic results were comparable to those in adults.

5.3 Preclinical safety data

Dose-dependent skin alterations, starting at dose levels equivalent to those used in humans, were the major findings observed in toxicity studies with Cynomolgus monkeys (a chronic repeat-dose toxicity study and an embryo-foetal development study).

An embryo-foetal toxicity study in Cynomolgus monkeys revealed no signs of teratogenicity. However, dependent on the dose, an increased incidence of abortion was observed.

Non-clinical data on genotoxicity and local tolerance including accidental administration by routes other than the intended infusion revealed no special hazard for humans.

No formal animal studies have been performed to establish the carcinogenic potential of cetuximab or to determine its effects on male and female fertility.

Toxicity studies with co-administration of cetuximab and chemotherapeutic agents have not been performed.

No non-clinical data on the effect of cetuximab on wound healing are available to date. However, in preclinical wound healing models EGFR selective tyrosine kinase inhibitors were shown to retard wound healing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Glycine
Polysorbate 80
Citric acid monohydrate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.

Chemical and physical in-use stability of Erbitux 5 mg/mL has been demonstrated for 48 hours at 25ºC, if the solution is prepared as described in section 6.6.

Erbitux does not contain any antimicrobial preservative or bacteriostatic agent. From a microbiological point of view, the product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless opening has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions after opening, see section 6.3.

6.5 Nature and contents of container

20 mL or 100 mL of solution in a vial (Type I glass) with a stopper (halobutyl rubber) and a seal (aluminium/polypropylen).
Pack size of 1 vial.

Not all vial sizes may be marketed.

6.6 Special precautions for disposal and other handling

Erbitux may be administered via a gravity drip, an infusion pump or a syringe pump. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection at the end of infusion.

Erbitux 5 mg/mL is compatible

- with polyethylene (PE), ethyl vinyl acetate (EVA) or polyvinyl chloride (PVC) bags,
- with polyethylene (PE), polyurethane (PUR), ethyl vinyl acetate (EVA), polyolefine thermoplastic (TP) or polyvinyl chloride (PVC) infusion sets,
- with polypropylene (PP) syringes for syringe pump.

Care must be taken to ensure aseptic handling when preparing the infusion.

Erbitux 5 mg/mL must be prepared as follows:

- For administration with infusion pump or gravity drip (diluted with sterile sodium chloride 9 mg/mL (0.9%) solution): Take an infusion bag of adequate size of sterile sodium chloride 9 mg/mL (0.9%) solution. Calculate the required volume of Erbitux. Remove an adequate volume of the sodium chloride solution from the infusion bag, using an appropriate sterile syringe with a suitable needle. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Transfer the Erbitux into the prepared infusion bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with the diluted Erbitux before starting the infusion. Use a gravity drip or an infusion pump for administration. Set and control the rate as explained in section 4.2.

- For administration with infusion pump or gravity drip (undiluted): Calculate the required volume of Erbitux. Take an appropriate sterile syringe (minimum 50 mL) and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Transfer the Erbitux into a sterile evacuated container or bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with Erbitux before starting the infusion. Set and control the rate as explained in section 4.2.

- For administration with a syringe pump: Calculate the required volume of Erbitux. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Remove the needle and put the syringe into the syringe pump. Connect the infusion line to the syringe, set and control the rate as explained in section 4.2 and start the infusion after priming the line with Erbitux or sterile sodium chloride 9 mg/mL (0.9%) solution. If necessary, repeat this procedure until the calculated volume has been infused.

7. MARKETING AUTHORISATION HOLDER

Merck KGaA
64271 Darmstadt
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/04/281/003
EU/1/04/281/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29/06/2004
Date of latest renewal: 29/06/2009

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Merck KGaA
Frankfurter Straße 250
64293 Darmstadt
Germany

Boehringer Ingelheim Pharma GmbH & Co KG
Birkendorfer Str. 65
88397 Biberach
Germany

Name and address of the manufacturer responsible for batch release

Merck KGaA
Frankfurter Straße 250
64293 Darmstadt
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

An updated RMP shall be submitted by 31 March 2014.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Erbitux 5 mg/mL solution for infusion
Cetuximab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 20 mL contains 100 mg cetuximab (5 mg/mL).
Each vial of 100 mL contains 500 mg cetuximab (5 mg/mL).

3. LIST OF EXCIPIENTS

Sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 vial of 100 mg/20 mL
1 vial of 500 mg/100 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck KGaA
64271 Darmstadt
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/281/003
EU/1/04/281/005

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Erbitux 5 mg/mL solution for infusion
Cetuximab
Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/20 mL
500 mg/100 mL

6. OTHER

Store in a refrigerator.

Merck KGaA
64271 Darmstadt
Germany

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Erbitux 5 mg/mL solution for infusion
Cetuximab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Erbitux is and what it is used for
2. What you need to know before you use Erbitux
3. How to use Erbitux
4. Possible side effects
5. How to store Erbitux
6. Contents of the pack and other information

1. What Erbitux is and what it is used for

What Erbitux is

Erbitux contains cetuximab, a monoclonal antibody. Monoclonal antibodies are proteins that specifically recognise and bind to other unique proteins called antigens. Cetuximab binds to the epidermal growth factor receptor (EGFR), an antigen on the surface of certain cancer cells. EGFR activates proteins called RAS. RAS proteins play an important role in the EGFR pathway – a complex signalling cascade which is involved in the development and progression of cancer. As a result of this binding, the cancer cell can no longer receive the messages it needs for growth, progression and metastasis.

What Erbitux is used for

Erbitux is used to treat two different types of cancer:

- metastatic cancer of the large intestine. In these patients, Erbitux is used alone or in combination with other anticancer medicines.

- a certain type of cancer of the head and neck (squamous cell cancer). In these patients, Erbitux is used in combination with radiation therapy or with other anticancer medicines.

2. What you need to know before you use Erbitux

Do not use Erbitux

Do not use Erbitux if you have ever had a severe hypersensitivity (allergic) reaction to cetuximab.

Before starting treatment for metastatic cancer of the large intestine your doctor will test your cancer cells if they contain the normal (wild-type) or mutant form of RAS. You must not receive Erbitux in combination with other anticancer treatment containing oxaliplatin if your cancer cells contain the mutant form of RAS.

Warnings and precautions

Talk to your doctor before using Erbitux, if any of the following information is not clear.

Erbitux may cause infusion-related side effects. Such reactions may be allergic in nature. Please read 'Infusion-related side effects' in section 4 for details, as they may have serious consequences for you, including life-threatening conditions. These side effects normally occur during the infusion, within 1 hour afterwards, or sometimes also after this period. To recognise early signs of such effects, your condition will be checked regularly while you receive each infusion of Erbitux and for at least 1 hour afterwards.
You are more likely to experience severe allergic reactions if you are allergic to red meat, tick bites or had positive results for certain antibodies (seen in a test). Your doctor will discuss appropriate measures with you.

Erbitux may cause side effects concerning the skin. Your doctor will discuss with you whether you may need any preventive measures or early treatment. Please also read 'Side effects concerning the skin' in section 4 for details, as some skin reactions may have serious consequences for you, including life-threatening conditions.

If you have heart problems, your doctor will discuss with you whether you can receive Erbitux in combination with other anticancer medicines, especially if you are 65 years of age or older.
Erbitux may cause side effects concerning the eyes. Please tell your doctor, if you have acute or worsening eye problems such as blurred vision, eye pain, red eyes and/or severe dry eye, if you have had such problems in the past or if you use contact lenses. Your doctor will discuss with you whether you need to consult a specialist.

If you receive Erbitux in combination with anticancer medicines including platinum, it is more likely that your white blood cell count may be reduced. Your doctor will therefore monitor your blood and general condition for signs of infection (see also 'Side effects in combination with other anticancer treatments' in section 4).

If you receive Erbitux in combination with other anticancer medicines, including fluoropyrimidines, it may be more likely that you experience heart problems which may be life-threatening. Your doctor will discuss with you whether you may need any particular supervision (see also 'Side effects in combination with other anticancer treatments' in section 4).

Children and adolescents

There is no relevant use of Erbitux in children and adolescents.

Other medicines and Erbitux

Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy

Tell your doctor if you are pregnant or if you are not using reliable contraception (speak to your doctor if you are not sure). Your doctor will then discuss with you the risks and benefits of using Erbitux in these situations.

Breast-feeding

Do not breast-feed your baby during the period over which you are being treated with Erbitux and for two months after the last dose.

Driving and using machines

Do not drive or use any tools or machines if you experience treatment-related symptoms that affect your ability to concentrate and react.

3. How to use Erbitux

A doctor experienced in the use of anticancer medicines will supervise your Erbitux therapy. During each infusion and for at least 1 hour afterwards, your condition will be checked regularly for early signs of a possible infusion-related side effect.

Pre-treatment

Before the first dose, you will receive an antiallergic medicine in order to reduce the risk of an allergic reaction. Your doctor will decide whether such pre-treatment is necessary for subsequent doses.

Dosage and administration

Erbitux is usually infused into a vein (given as a drip) once a week. Your doctor will calculate the correct dose of Erbitux for you because it depends on your body surface area. The first dose (400 mg/m² body surface area) is infused over a period of approximately 2 hours with an infusion rate not faster than 5 mg/min. Each subsequent dose (250 mg/m² body surface area) is infused in approximately 1 hour with an infusion rate not faster than 10 mg/min.

Detailed instructions for your doctor or your nurse on how to prepare the Erbitux infusion are included at the end of this package leaflet (see 'Handling instructions').

Duration of treatment

Erbitux is usually infused once a week. The duration of treatment may vary depending on your disease as well as from person to person and your doctor will therefore discuss with you how long you will receive Erbitux.

Combination with other anticancer treatments

If you receive Erbitux in combination with other anticancer medicines, these medicines must be administered at least 1 hour after the end of the Erbitux infusion.

If you receive Erbitux in combination with radiation therapy, treatment with Erbitux is usually started one week before radiation therapy.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The main side effects of Erbitux are infusion-related side effects and side effects concerning the skin:

Infusion-related side effects

More than 10 out of 100 patients are likely to experience infusion-related side effects; in more than 1 out of 100 patients these side effects are likely to be severe. Such reactions may be allergic in nature. They normally occur during the infusion, within 1 hour afterwards, or sometimes also after this period.

Mild or moderate infusion-related side effects include:
- fever
- chills
- dizziness
- breathing difficulties

If such symptoms occur, please inform your doctor as soon as possible. Your doctor may consider reducing the infusion rate of Erbitux to manage these symptoms.

Severe infusion-related side effects include:
- severe breathing difficulties which develop rapidly
- hives
- fainting
- chest pain (a symptom of side effects on your heart)

If such symptoms occur, speak to a doctor immediately. These side effects may have serious consequences, in rare cases including life-threatening conditions, and require immediate attention. Treatment with Erbitux must then be stopped.

Side effects concerning the skin

More than 80 out of 100 patients are likely to experience side effects involving the skin. In about 15 out of 100 patients these skin reactions are likely to be severe. Most of these side effects develop within the first three weeks of treatment. They usually disappear over time after the end of Erbitux therapy.

Main side effects concerning the skin include:
- acne-like skin alterations
- itching
- dry skin
- scaling
- excessive growth of hair
- nail disorders, for example inflammation of the nail bed

In very rare cases (may affect up to 1 in 10,000 people) patients may experience blistering or peeling of the skin, which may indicate a severe skin reaction called "Stevens-Johnson syndrome"**. If you experience these symptoms, please speak to a doctor immediately,** because these signs may have serious consequences including life-threatening conditions.

If you notice other extensive skin alterations, please inform your doctor as soon as possible because the Erbitux dose or the time between infusions may need to be changed. Your doctor will decide whether treatment has to be stopped if skin reactions reappear after several dose reductions.

If you notice that already affected areas of your skin get worse, **speak to a doctor immediately,** especially if you also experience general signs of infection such as fever and tiredness. These signs may indicate a skin infection, which may have serious consequences including life-threatening conditions.

Side effects concerning the lungs

In uncommon cases (may affect up to 1 in 100 people) patients may experience an inflammation of the lungs (called interstitial lung disease), which may have serious consequences including life-threatening conditions.

If you notice symptoms such as occurrence or worsening of breathing difficulties, speak to a doctor immediately, especially if you also experience cough or fever. Your doctor will decide whether treatment has to be stopped.

Other side effects

Very common side effects (may affect more than 1 in 10 people)
- inflammation of the lining of the intestine, mouth, and nose (in some cases severe), which may lead to nose bleeding in some patients
- decrease in blood levels of magnesium
- increase in blood levels of certain liver enzymes

Common side effects (may affect up to 1 in 10 people)
- headache
- tiredness
- irritation and redness of the eye
- diarrhoea
- drying out which may be due to diarrhoea or reduced fluid intake
- feeling sick
- vomiting
- loss of appetite, leading to weight decrease
- decrease in blood levels of calcium

Uncommon side effects (may affect up to 1 in 100 people)
- blood clots in the veins of the legs
- blood clots in the lungs
- inflammation of the eye lid or the front part of the eye

Side effects of which the frequency is not known (cannot be estimated from the available data)
- inflammation of the lining of the brain (aseptic meningitis)

Side effects in combination with other anticancer treatments

If you receive Erbitux in combination with other anticancer medicines, some of the side effects you may experience can also be related to the combination or the other medicines. Therefore, please make sure that you also read the package leaflet for the other medicines.

If you receive Erbitux in combination with anticancer medicines including platinum, it is more likely that your white blood cell count may be reduced. This may lead to infectious complications including life-threatening conditions, especially if you experience skin reactions, inflammation of the lining of the intestine and mouth or diarrhoea. **Therefore, if you experience general signs of infection such as fever and tiredness, please speak to a doctor immediately.**

If you receive Erbitux in combination with an anticancer medicine containing fluoropyrimidines, it is more likely that you experience the following side effects of this other medicine:
- chest pain
- heart attack
- heart failure
- redness and swelling of the palms of the hands or the soles of the feet which may cause the skin to peel (hand-foot syndrome)

If you receive Erbitux with radiation therapy, some of the side effects you may experience can also be related to this combination, such as:
- inflammation of the lining of the intestine and mouth
- skin reactions typical for radiation therapy
- difficulty in swallowing
- reduction in the number of white blood cells

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Erbitux

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Once opened, Erbitux is intended for immediate use.

6. Contents of the pack and other information

What Erbitux contains

- The active substance is cetuximab.
  Each mL of the solution for infusion contains 5 mg cetuximab.
  Each vial of 20 mL contains 100 mg cetuximab.
  Each vial of 100 mL contains 500 mg cetuximab.
- The other ingredients are sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide and water for injections.

What Erbitux looks like and contents of the pack

Erbitux 5 mg/mL solution for infusion is supplied in vials containing 20 mL or 100 mL.
Each pack contains 1 vial.

Not all vial sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Merck KGaA
64271 Darmstadt
Germany

This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for medical or healthcare professionals only:

Handling instructions

Erbitux may be administered via a gravity drip, an infusion pump or a syringe pump. Since Erbitux is only compatible with sterile sodium chloride 9 mg/mL (0.9%) solution for injection, it must not be mixed with other intravenously applied medicinal products. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection at the end of infusion.

Erbitux 5 mg/mL is compatible

- with polyethylene (PE), ethyl vinyl acetate (EVA) or polyvinyl chloride (PVC) bags,
- with polyethylene (PE), polyurethane (PUR), ethyl vinyl acetate (EVA), polyolefine thermoplastic (TP) or polyvinyl chloride (PVC) infusion sets,
- with polypropylene (PP) syringes for syringe pump.

Erbitux 5 mg/mL is chemically and physically stable for up to 48 hours at 25°C, if the solution is prepared as described hereafter. However, since it does not contain any antimicrobial preservative or bacteriostatic agent, it is intended for immediate use. Care must be taken to ensure aseptic handling when preparing the infusion. Erbitux 5 mg/mL must be prepared as follows:

- <u>For administration with infusion pump or gravity drip (diluted with sterile sodium chloride 9 mg/mL (0.9%) solution)</u>: Take an infusion bag of adequate size of sterile sodium chloride 9 mg/mL (0.9%) solution. Calculate the required volume of Erbitux. Remove an adequate volume of the sodium chloride solution from the infusion bag, using an appropriate sterile syringe with a suitable needle. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Transfer the Erbitux into the prepared infusion bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with the diluted Erbitux before starting the infusion. Use a gravity drip or an infusion pump for administration. The first dose (400 mg/m² body surface area) is infused over a period of approximately 2 hours with an infusion rate not faster than 5 mg/min. Each subsequent dose (250 mg/m² body surface area) is infused in approximately 1 hour with an infusion rate not faster than 10 mg/min.

- <u>For administration with infusion pump or gravity drip (undiluted)</u>: Calculate the required volume of Erbitux. Take an appropriate sterile syringe (minimum 50 mL) and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Transfer the Erbitux into a sterile evacuated container or bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with Erbitux before starting the infusion. The first dose (400 mg/m² body surface area) is infused over a period of approximately 2 hours with an infusion rate not faster than 5 mg/min. Each subsequent dose (250 mg/m² body surface area) is infused in approximately 1 hour with an infusion rate not faster than 10 mg/min.

- <u>For administration with a syringe pump</u>: Calculate the required volume of Erbitux. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Remove the needle and put the syringe into the syringe pump. Connect the infusion line to the syringe and start the infusion after priming the line with Erbitux or sterile sodium chloride 9 mg/mL (0.9%) solution. Repeat this procedure until the calculated volume has been infused. The first dose (400 mg/m² body surface area) is infused over a period of approximately 2 hours with an infusion rate not faster than 5 mg/min. Each subsequent dose (250 mg/m² body surface area) is infused in approximately 1 hour with an infusion rate not faster than 10 mg/min.