AUSTRALIAN PRODUCT INFORMATION – ERBITUX® (cetuximab (rmc)) solution for injection (intravenous infusion)

1. NAME OF THE MEDICINE

cetuximab (rmc)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 100 mg cetuximab.

Each 100 mL vial contains 500 mg cetuximab.

Each mL solution contains 5 mg cetuximab.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Erbitux is a sterile, preservative-free, clear to slightly opalescent, colourless to yellowish solution that is intended for intravenous infusion.

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 infusional 5-fluorouracil/folinic acid plus irinotecan
- in combination with irinotecan in patients who are refractory to first-line chemotherapy
- in first-line in combination with FOLFOX
- as a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy.

(see Clinical trials)

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. DOSE AND METHOD OF ADMINISTRATION

Erbitux must be administered under the supervision of a physician experienced in the use of antineoplastic agents. 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. If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped.

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

Chemotherapy must not be administered earlier than 1 hour after the end of the cetuximab infusion.

Colorectal cancer

Detection of *RAS* mutational status (K-RAS and N-RAS exons 2, 3 and 4) must be performed prior to the first cetuximab infusion. It is important that a validated test method is used by an experienced laboratory (see Clinical trials and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In patients with metastatic colorectal cancer, cetuximab is used as monotherapy or in combination with chemotherapy, either once a week or every two weeks.

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

Weekly dose regimen

Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m^2 body surface area (BSA); the recommended infusion period is 120 minutes. All subsequent weekly doses are 250 mg/m^2 each; the recommended infusion period is 60 minutes.

Every two weeks dose regimen

For initial and subsequent doses, Erbitux is administered once every two weeks: each dose is 500 mg cetuximab per m^2 BSA. The recommended infusion period is 120 minutes.

Squamous cell cancer of the head and neck

In combination with radiation therapy
In patients with locally advanced squamous cell cancer of the head and neck, cetuximab is used concomitantly with radiation therapy.

Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m^2 BSA; the recommended infusion period is 120 minutes. All subsequent weekly doses are 250 mg/m^2 each; the recommended infusion period is 60 minutes.

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 (see Clinical trials).

In combination with platinum-based chemotherapy
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. Erbitux is administered either once a week or every two weeks.

Weekly dose regimen

Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m^2 BSA; the recommended infusion period is 120 minutes. All subsequent weekly doses are 250 mg/m^2 each; the recommended infusion period is 60 minutes.

Every two weeks dose regimen

For initial and subsequent doses, Erbitux is administered once every two weeks: each dose is 500 mg cetuximab per m^2 BSA. The recommended infusion period is 120 minutes.

Administration

Erbitux is administered intravenously with an infusion pump, gravity drip or a syringe pump (see Instructions for use/handling).

The initial dose should be given slowly to minimise the risk of infusion-related reactions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The recommended infusion period is 120 minutes. For subsequent administration, the infusion rate must not exceed 10 mg/min. If the initial infusion is well tolerated, the recommended infusion period for weekly dose regimen of 250 mg/m^2 is 60 minutes and recommended infusion period for the every two weeks dose regimen of 500 mg/m^2 is 120 minutes.

Special Recommendations

The following measures are to be taken if a patient experiences infusion- related or skin reactions:

Infusion-related reactions

Mild or moderate (symptoms include fever, chills, dizziness or dyspnoea): infusion rate should be decreased. It is recommended that the infusion rate remain at the lower value for all subsequent infusions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Infusion-related, including anaphylactic, reactions).

Severe (symptoms include rapid onset of airway obstruction, urticaria, increase or decrease of blood pressure, loss of consciousness or shock; in rare cases, angina pectoris, myocardial infarction or cardiac arrest have also been observed): immediate and permanent discontinuation of cetuximab therapy. Emergency treatment may be necessary (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Infusion-related, including anaphylactic, reactions).

Skin reactions

First occurrence of severe skin reaction (≥ grade 3; US National Cancer Institute – Common Terminology Criteria for Adverse Events, CTCAE): cetuximab should be ceased for up to 2 consecutive weeks. If the reaction has resolved to grade 2 when the next infusion is due, treatment may be resumed without any change in dose level.

If a second severe skin reaction occurs, cease cetuximab for up to 2 consecutive weeks. If the skin reaction has resolved to grade 2 when the next infusion is due, treatment may be resumed with a dose reduction of 20% (200 mg/m^2 BSA in the weekly dosing regimen or 400 mg/m^2 BSA in the every two weeks dosing regimen).

If a third severe skin reaction occurs at the lower dose, cease cetuximab for up to 2 consecutive weeks. If the skin reaction has resolved to grade 2 when the next infusion is due, treatment may be resumed with a dose reduction of 40% (150 mg/m^2 BSA in the weekly dosing regimen or 300 mg/m^2 BSA in the every two weeks dosing regimen). Dose reductions should continue for the duration of treatment.

If a fourth severe skin reaction occurs or the skin reaction fails to resolve to grade 2 during interruption of treatment, permanent discontinuation of cetuximab is required.

Combination Treatment

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

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.

Before initiation of combination treatment, contraindications for concomitantly used chemotherapeutic agents (refer to their product information documents) or radiation therapy must be considered.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infusion-related, including anaphylactic, reactions

Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab. Similar premedication is recommended for all subsequent infusions. Cetuximab infusion must be carried out in an area where resuscitation equipment and agents are available.

Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 initial infusion and for 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 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 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.

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

If patients develop dyspnoea during the course of cetuximab treatment, it is recommended to investigate them for signs of progressive pulmonary disorders as appropriate. In the event of acute onset or worsening dyspnoea, cetuximab therapy should be interrupted.

Cases of interstitial lung disease (ILD), including fatal cases, have been reported, with the majority of cases arising from a Japanese postmarketing surveillance study in metastatic colorectal cancer. Confounding or contributing factors, such as concomitant chemotherapy known to be associated with ILD, and pre-existing pulmonary diseases were frequent in fatal cases. Such patients should be closely monitored. In the event of symptoms (such as dyspnoea, cough, fever) or radiographic findings suggestive of ILD, prompt diagnostic investigation should occur. Geriatric patients and patients with a history of interstitial lung disease may be at an increased risk of developing this event. If interstitial lung disease is diagnosed, cetuximab must be discontinued and the patient treated appropriately.

Skin Reactions

Skin reactions are very common and treatment interruption or discontinuation may be required. According to clinical practice guidelines, prophylactic use of oral tetracyclines (e.g. doxycycline) for 6-8 weeks and topical application of 1% hydrocortisone cream with moisturiser should be considered. Use of sunscreen should also be considered.

Medium to high-potency topical corticosteroids or oral tetracyclines have been used for the treatment of skin reactions.

If a patient experiences a severe skin reaction (≥ grade 3; US National Cancer Institute – Common Terminology Criteria for Adverse Events, CTCAE), cetuximab therapy must be interrupted. Treatment may be resumed if the reaction has resolved to grade 2 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 4.2 DOSE AND METHOD OF ADMINISTRATION for further information on handling skin reactions).

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 sometimes 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.

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

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 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

Cases of keratitis and ulcerative keratitis have been reported with the use of cetuximab. It is recommended that patients with signs and symptoms suggestive of keratitis consult an ophthalmologist.

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

Special attention is recommended for 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 combination with continuous infusional 5-flurouracil/folinic acid plus oxaliplatin (see Clinical trialsand Section 4.3 CONTRAINDICATIONS)**.**

Combination with Capecitabine and Irinotecan

The benefit-risk balance of cetuximab in combination with XELIRI (capecitabine plus irinotecan) has not been established. This combination is therefore not recommended in the treatment of patients with metastatic colorectal cancer.

Colorectal Cancer Patients with Resectable Liver Metastases

There is insufficient evidence to determine the benefit/risk balance of administering cetuximab as peri-operative therapy to mCRC patients presenting with resectable liver metastases. Accordingly, cetuximab is not recommended for use in this patient population.

Wound Healing

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

Hepatic and Renal Impairment

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

Haematological

Cetuximab has not been studied in patients presenting with an abnormal haematological profile as defined by one or more of the following:

- haemoglobin < 90 g/L
- leukocyte count < 3 x 10^9/L
- absolute neutrophil count < 1.5 x 10^9/L
- platelet count < 100 x 10^9/L

Use in the elderly

No dose adjustment is required in the elderly but experience is limited in patients 75 years of age and above. However, elderly patients, especially those with a history of cardiac disease, are at greater risk of adverse effects than younger patients and patients without a history of cardiac disease (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Paediatric use

The effectiveness 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 (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Physicians are advised to consider the toxicities of the individual components of therapy and to monitor patients receiving cetuximab in combination with other therapies closely.

When cetuximab is used in combination with chemo- or radiotherapy, patients may experience an increased incidence of specific adverse reactions (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)):

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.

When used in combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia is increased compared to use of platinum-based chemotherapy alone, and this may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis. Patients with skin lesions, mucositis or diarrhoea that may facilitate the development of infections are at particular risk.

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

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.

In squamous cell cancer of the head and neck, use of cetuximab in combination with chemoradiotherapy has not been adequately investigated. Therefore benefits and risks of this combination are not known.

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects of fertility

There are no data on the effect of cetuximab on human fertility. Fertility has not been specifically examined in animal studies. However, female cynomolgus monkeys given IV maintenance doses of 7.5 - 75 mg/kg/week (approx. 1-17 times the recommended maintenance dose in humans based on serum AUC values) showed impairment of menstrual cycling.

Use in pregnancy – Pregnancy Category D

The epidermal growth factor receptor (EGFR) is involved in foetal development. Observations in animals are indicative of a placental transfer of cetuximab, and other IgG_1 antibodies have been found to cross the placental barrier. An embryo-foetal toxicity study in cynomolgus monkeys revealed no evidence of teratogenicity at exposures (AUC) up to 16 times that anticipated clinically. However, a dose-dependent, increased incidence of abortion was observed, with a NOAEL of 7.5 mg/kg/week (exposure (AUC) similar to clinical exposure). No data regarding use in pregnant women are available. It is recommended that Erbitux should not be administered during pregnancy. Adequate contraception should be maintained in women of child-bearing potential during treatment with Erbitux and for 2 months after the last dose.

Use in lactation

Studies in animals or sufficient data from lactating women are not available. It is recommended that women do not breast-feed during treatment with Erbitux and for 2 months after the last dose.

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. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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)

A hash symbol (#) indicates that additional information on the respective undesirable effect is provided below.

<u>Nervous system disorders</u>	
Common:	Headache
Frequency not known:	Aseptic meningitis
<u>Eye disorders</u>	
Common:	Conjunctivitis
Uncommon:	Blepharitis, keratitis
<u>Respiratory, thoracic and mediastinal disorders</u>	
Uncommon:	Pulmonary embolism
Rare:	Interstitial lung disease, which may be fatal (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
<u>Gastrointestinal disorders</u>	
Common:	Diarrhoea, nausea, vomiting
<u>Skin and subcutaneous tissue disorders</u>	
Very common:	Skin reactions#
Common:	Hand-foot syndrome in combination with fluoropyrimidines (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
Very rare:	Stevens-Johnson syndrome/toxic epidermal necrolysis
Frequency not known:	Superinfection of skin lesions#

Metabolism and nutrition disorders

Very common:	Hypomagnesaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Common:	Dehydration, in particular, secondary to diarrhoea or mucositis; hypocalcaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE); anorexia which may lead to weight decrease; hypokalaemia (in combination with irinotecan or platinum/fluorouracil combinations)

Vascular disorders

Uncommon:	Deep vein thrombosis

General disorders and administration site conditions

Very common:	Mild or moderate infusion-related reactions[#] (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Infusion-related, including anaphylactic, reactions); 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Infusion-related, including anaphylactic, reactions); fatigue; increased infections in combination with platinum-based regimens and increased radiation-related effects in combination with radiotherapy (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Hepatobiliary disorders

Very common:	Increase in liver enzyme levels (AST, ALT, AP)

Cardiac disorders

Uncommon:	Ischaemia including myocardial infarction and congestive heart failure in combination with fluoropyrimidines, including capecitabine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Haematological disorders

Frequency not known:[1]	Increased severe neutropenia and leukopenia in combination with platinum-based chemotherapy which may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

[1] Not to be estimated from the available data set in patients with recurrent and/or metastatic squamous cell cancer of the head and neck because patient numbers were too small to provide a meaningful frequency estimation.

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 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 or radiation therapy, also refer to the agents' respective product information and to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems

4.9. OVERDOSE

There is limited experience to date with weekly administration of doses higher than 250 mg/m^2 BSA or every two weeks administrations of doses higher than 500 mg/m^2 BSA. In clinical studies with doses up to 700 mg/m^2 given every two weeks the safety profile was consistent with that described in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC Code: L01FE01.

In both *in vitro* and *in vivo* assays, cetuximab inhibits the proliferation and induces apoptosis of human tumour cells that express EGFR, but it has no anti-tumour effects in human tumour xenografts that do not 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.

Cetuximab is a mediator of antibody-dependent cellular cytotoxicity *in vitro*, eliciting increased cytotoxicity of EGFR-expressing tumour cells in the presence of immune effector cells. Therefore, in addition to its inhibitory function on receptor signalling, patients with

EGFR-expressing tumours may also benefit from this immune stimulatory effect of cetuximab.

Mechanism of action

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 induces the internalisation of the EGFR, which could lead to down-regulation of EGFR.

Cetuximab does not bind to other receptors belonging to the HER family (Erb B2, Erb B3, Erb B4).

The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicles. Over-expression of EGFR is also detected in many human cancers, including those of the colon and rectum. The contribution of the EGFR signalling pathways in the development of malignancy of certain tumours has been extensively documented in *in vitro* and *in vivo* studies. EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Expression of EGFR and its cognate ligands in tumours has been correlated with poor prognosis, decreased survival, and/or increased metastases.

RAS is one of the most frequently activated families 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.

The protein products of the proto-oncogene *K-RAS* (Kirsten rat sarcoma 2 viral oncogene homologue) and *N-RAS* (neuroblastoma *RAS* viral [v-rs] oncogene homologue) are central down-stream signal-transducers of EGFR. In tumours, activation of *RAS* by EGFR contributes to EGFR-mediated increased proliferation, survival and the production of pro-angiogenic factors.

Immunogenicity

The development of human anti-chimaeric antibodies (HACA) is a class-specific effect of monoclonal chimaeric antibodies. Measurable HACA titres developed in 3.4% of the patients studied. 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 effects of cetuximab.

Clinical trials

Colorectal Cancer

A diagnostic assay (EGFR pharmDx™) was used for immunohistochemical detection of EGFR expression in tumour material. 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.

In metastatic colorectal cancer, the incidence of *RAS* mutations is in the range of 40-55%. Study data demonstrate that patients with *RAS* wild-type metastatic colorectal cancer have a significantly higher chance of benefiting from treatment with cetuximab or a combination of cetuximab and chemotherapy.

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 DOSE AND METHOD OF ADMINISTRATION.

RAS status was recognised as a predictive factor for treatment with cetuximab in studies EMR 62 202-013 and EMR 62-202 047.

Cetuximab in combination with chemotherapy

- EMR 62 202-013 (CRYSTAL): This randomised, open-label, Phase III 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 fluorouracil/folinic acid (5-FU/FA) (599 patients) to the same chemotherapy alone (599 patients).

  The chemotherapy regimen was the FOLFIRI regimen. The median age of subjects was 61 years (range 19-84), with most being male (61%). The primary endpoint was progression-free survival. Addition of cetuximab to FOLFIRI in the overall population marginally increased progression-free and overall survival.

  RAS status was assessed retrospectively in 69% of randomised subjects. The *RAS* mutant population consisted of subjects with mutations on exons 2, 3 or 4 of the *K-RAS* or *N-RAS* genes. Addition of cetuximab to FOLFIRI significantly increased progression-free and overall survival in *RAS* wild-type but not *RAS* mutant subjects (see Table 1).

TABLE 1. Study EMR 62 202-013: Efficacy Results

	Overall population		RAS wild-type subgroup		RAS mutant subgroup	
Variable/statistic	**Cetuximab + FOLFIRI (n=599)**	**FOLFIRI (n=599)**	**Cetuximab + FOLFIRI (n=178)**	**FOLFIRI (n=189)**	**Cetuximab + FOLFIRI (n=246)**	**FOLFIRI (n=214)**
PFS						
Hazard Ratio (95% CI)	0.85 (0.73, 1.00)		0.56 (0.41, 0.76)		1.10 (0.85, 1.42)	
p-value	0.05		0.0002		0.47	
median (mths, 95% CI)	8.9 (8.0, 9.5)	8.0 (7.6, 9.0)	11.4 (10.0, 14.6)	8.4 (7.4, 9.4)	7.4 (6.4, 8.0)	7.5 (7.2, 8.5)
OS						
Hazard Ratio (95% CI)	0.88 (0.77, 1.00)		0.69 (0.54, 0.88)		1.05 (0.86, 1.28)	
p-value	0.04		0.002		0.64	
median (mths, 95% CI)	19.9 (18.5,21.3)	18.6 (16.7,19.8)	28.4 (24.7,31.6)	20.2 (17.0,24.5)	16.4 (14.9,18.4)	17.7 (15.4,19.6)
ORR						
% (95% CI)	46.9 (42.9,51.0)	38.7 (34.8,42.8)	66.3 (58.8,73.2)	38.6 (31.7,46.0)	31.7 (25.9,37.9)	36.0 (29.6,42.8)

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

Patients with *K-RAS* wild-type tumours and an ECOG performance status of > 2 or who were 65 years of age or older, had no benefit in overall survival time, when cetuximab was added to FOLFIRI.

- EMR 62 202-047 (OPUS): This randomised, open-label 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 fluorouracil/folinic acid (FOLFOX4) (169 patients) to the same chemotherapy alone (168 patients). The chemotherapy regimen was the FOLFOX4 regimen. The median age of subjects was 61 years (range 24-82), with most being male (54%).

  The primary endpoint was objective response rate. Addition of cetuximab to FOLFOX4 in the overall population did not significantly increase objective response rate, overall survival or progression-free survival.

  RAS status was assessed retrospectively in 75% of randomised subjects. The *RAS* mutant population consisted of patients with mutations on exons 2, 3 or 4 of the *K-RAS* or *N-RAS* genes. Addition of cetuximab to FOLFOX4 significantly increased objective response rate in *RAS* wild-type but not *RAS* mutant subjects. Addition of cetuximab to FOLFOX4 showed a trend to increased progression-free and overall survival in *RAS* wild-type subjects but had an adverse effect in *RAS* mutant subjects (see Table 2).

TABLE 2. Study EMR 62 202-047: Efficacy Results

	Overall population		**RAS wild-type subgroup**		**RAS mutant subgroup**	
Variable/statistic	**Cetuximab + FOLFOX4 (n=169)**	**FOLFOX 4 (n=168)**	**Cetuximab + FOLFOX4 (n=38)**	**FOLFOX 4 (n=49)**	**Cetuximab + FOLFOX4 (n=92)**	**FOLFOX 4 (n=75)**
ORR % (95% CI) p-value	46.2 (38.5, 54.0) 0.24	39.9 (32.4, 47.7)	57.9 (40.8, 73.7) 0.008	28.6 (16.6, 43.3)	37.0 (27.1,47.7) 0.09	50.7 (38.9,62.4)
OS Hazard Ratio (95% CI) p-value median (mths, 95% CI)	1.02 (0.79, 1.30) 0.91 18.3 (14.8, 20.4)	18.0 (16.7, 21.8)	0.94 (0.56, 1.56) 0.80 19.8 (16.6, 25.4)	17.8 (13.8, 23.9)	1.29 (0.91, 1.84) 0.16 13.5 (12.1,17.7)	17.8 (15.9,23.6)
PFS Hazard Ratio (95% CI) p-value median (mths, 95% CI)	0.93 (0.70, 1.23) 0.62 7.2 (5.6, 7.7)	7.2 (6.0, 7.8)	0.53 (0.27, 1.04) 0.06 12.0 (5.8, NE)	5.8 (4.7, 7.9)	1.54 (1.04, 2.29) 0.03 5.6 (4.4, 7.5)	7.8 (6.7, 7.9)

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, PFS = progression-free survival, NE = not estimable.

- COIN: This open-label, randomised, investigator-sponsored study compared the addition of cetuximab to first-line chemotherapy (oxaliplatin plus oral or infusional fluoropyrimidine) to the same chemotherapy alone, in patients with advanced colorectal cancer who had not received prior treatment for metastatic disease. Prolonged survival with the addition of cetuximab could not be demonstrated in this study.

Comparison of outcomes in the subgroup of patients with *K-RAS* wild-type tumours given cetuximab plus a FOLFOX-like regimen (modified de Gramont plus oxaliplatin, OxMdG), vs. a group given that chemotherapy alone, was possible. There was no evidence of any survival benefit in the patients given cetuximab. Median overall survival (OS) was 16.3 months in the cetuximab plus chemotherapy group (n=117), vs. 18.2 months in the chemotherapy alone group (n=127), with a hazard ratio of 0.93 (95% CI: 0.72, 1.19), slightly in favour of the cetuximab plus OxMdG combination. OS results may be biased due to imbalances in second-line treatments. Significantly fewer patients treated with cetuximab received second-line therapy. For progression-free survival, a trend towards greater efficacy in the group receiving cetuximab plus OxMdG was suggested based on the hazard ratio of 0.77 (95% CI: 0.59, 1.01), although median progression-free survival was broadly similar across groups: 9.2 months in the cetuximab plus OxMdG group vs. 9.0 months for this chemotherapy alone. However, unlike in the OPUS study, these results did not reach statistical significance. Best overall response rates were not statistically significantly different (68% for cetuximab; 59% for OxMdG; odds ratio, 1.44 [95% CI: 0.85, 2.43]).

- CA225006 (EPIC): This randomised, open-label 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).

  A significant difference in overall survival time could not be shown in this study. Following disease progression, treatment with EGFR-targeting agents was initiated in 50% of patients in the irinotecan-alone arm, which most likely impacted survival results. Objective response rate and progression free survival time were significantly improved with cetuximab. However, as no independent review of imaging data was conducted, these results have to be interpreted with caution. The impact of *K-RAS* status was evaluated retrospectively in 23% of subjects. Unlike in the other trials, cetuximab did not have a significant impact on either progression-free survival or overall survival in wild-type *K-RAS* disease. However, the results should be treated with caution due to the small number of subjects.

- EMR 62 202-007 (BOND): 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).

  Addition of irinotecan to cetuximab increased median progression-free survival from 1.5 months to 4.1 months – hazard ratio 0.54, 95% CI [0.42, 0.71] – and significantly increased the objective response rate. The improvement in overall survival time did not reach statistical significance; however, in the follow-up treatment, nearly 50% of patients in the cetuximab only 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 (NCIC CTG CO.17): This randomised, open-label 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 BSC alone (285 patients). The median age of subjects was 63 years (range 29-88), with most being male (64%).

Addition of cetuximab to BSC (best supportive care) increased overall survival time significantly by 1.5 months from 4.6 to 6.1 months – hazard ratio 0.77, 95% CI [0.64, 0.92]) – while median progression-free survival increased from 1.8 months to 1.9 months – hazard ratio 0.676, 95% CI [0.57, 0.80], in the overall population. The impact of *K-RAS* status was evaluated subsequently in 69% of patients. The benefits of cetuximab were enhanced in the *K-RAS* wild-type population (Table 3).

Table 3: Study CA225025: Efficacy Results

	Overall population		***K-RAS* wild-type population**	
Variable/ statistic	**Cetuximab plus BSC**	**BSC**	**Cetuximab plus BSC**	**BSC**
	(N=287)	**(N=285)**	**(N=117)**	**(N=113)**
OS				
Median (months, 95% CI)	6.1 (5.4, 6.7)	4.6 (4.2, 4.9)	9.5 (7.7, 10.3)	4.8 (4.2, 5.5)
Hazard Ratio (95% CI)	0.77 (0.64, 0.92)		0.55 (0.41, 0.75)	
p-value	0.005		<0.0001	
ORR				
% (95% CI)	6.6 (4.0, 10.2)	0 (-)	12.8 (7.4, 20.3)	0 (-)
p-value	<0.0001		<0.0001	
PFS				
Median (months, 95% CI)	1.9 (1.8, 2.1)	1.8 (1.8, 1.9)	3.7 (3.1, 5.1)	1.9 (1.8, 2.0)
Hazard Ratio (95% CI)	0.68 (0.57, 0.80)		0.40 (0.30, 0.54)	
p-value	<0.0001		<0.0001	

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

Squamous cell cancer of the head and neck

Immunohistochemical detection of EGFR expression was not performed at study entry 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 carcinoma of the head and neck. Cetuximab was started one week before radiation therapy and administered at the doses described in the DOSAGE AND ADMINISTRATION section until the end of the radiation therapy period.

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

Table 4: Study EMR 62 202-006: Efficacy Results

Variable/ statistic	**Radiation therapy alone**		**Radiation therapy + cetuximab**		*Treatment comparison*	
	(N=213)		(N=211)		p-value	Hazard ratio (95% CI)
Locoregional control[§], months						
Median (95% CI)	14.9	(11.8, 19.9)	24.4	(15.7, 45.1)	0.005	0.68 (0.52, 0.89)
Overall Survival time, months						
Median (95% CI)	29.3	(20.6, 42.8)	49.0	(32.8, 62.6+)	0.032	0.74 (0.56, 0.97)

CI = confidence interval; a '+' denotes that the upper bound limit had not been reached at cut-off. [§]Locoregional control = absence of disease recurrence/progression or death.

Subgroup analyses indicated that patients with a good prognosis as indicated by tumour stage (stage II/III vs stage IV), baseline Karnofsky performance status (KPS: 90 – 100% vs 50 – 80%) and age (<65 years vs ≥65 years) had a more pronounced benefit when cetuximab was added to radiation therapy. No clinical benefit could be demonstrated in patients with KPS ≤ 80 and aged 65 years or older.

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

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

- EMR 62 202-002 (EXTREME): This randomised, open-label study in patients with recurrent and/or metastatic squamous cell cancer of the head and neck who had not received prior chemotherapy for recurrent and/or metastatic disease compared the combination of cetuximab and cisplatin or carboplatin plus infusional fluorouracil (222 patients) to the same chemotherapy alone (220 patients). Patients may have received prior chemotherapy for locally advanced disease. The median age of subjects was 56 years (interquartile range 51-62), with most being male (90%). 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.

  Addition of cetuximab to platinum-based chemotherapy significantly increased progression-free and overall survival by a median 2.3 and 2.7 months, respectively (Table 5).

Table 5: Study EMR 62 202-002: Efficacy Results

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)	0.80 (0.64, 0.99)	
p-value	0.036	
PFS		
months, median (95% CI)	5.6 (5.0, 6.0)	3.3 (2.9, 4.3)
Hazard Ratio (95% CI)	0.54 (0.43, 0.67)	
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

Patients with a good prognosis as indicated by tumour stage, baseline Karnofsky performance status (KPS) and age (< 65 years vs ≥ 65 years) 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.

5.2. PHARMACOKINETIC PROPERTIES

Cetuximab pharmacokinetics were studied in clinical studies where cetuximab was administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy. Intravenous infusions of cetuximab exhibited non-linear pharmacokinetics at weekly doses ranging from 5 to 500 mg/m^2 body surface area. Cetuximab clearance decreased with increasing doses to 200 mg/m^2 then appeared to plateau.

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} (± SD) was 185±55 microgram/mL. The mean clearance was 0.022 L/h per m^2 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 3 weeks of cetuximab monotherapy. Mean peak cetuximab concentrations were 155.8 microgram/mL in week 3 and 151.6 microgram/mL in week 8, whereas the corresponding mean trough concentrations were 41.3 and 55.4 microgram/mL, respectively. In a study of cetuximab administered in combination with irinotecan, the mean cetuximab trough levels were 50.0 microgram/mL in week 12 and 49.4 microgram/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.

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. However, only patients with adequate renal and hepatic function have been investigated to

date (serum creatinine ≤ 1.5 fold, transaminases ≤ 5 fold and bilirubin ≤ 1.5 fold 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

Genotoxicity

Cetuximab was not genotoxic in an *in vitro* microbial assay or an *in vivo* rat micronucleus assay.

Carcinogenicity

No long term animal studies have been performed to establish the carcinogenic potential of cetuximab.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

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

6.2. INCOMPATIBILITIES

Erbitux must not be mixed with other intravenously administered medicines, except sterile sodium chloride 9 mg/mL (0.9%) solution. A separate infusion line must be used.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Vials: Store in a refrigerator (2°C to 8°C). Do not freeze.

Chemical and physical in-use stability of Erbitux has been demonstrated for 48 hours at 25°C if the solution is prepared as described in Instructions for use/handling.

In-use storage times and conditions are the responsibility of the user. To reduce microbiological hazard, use as soon as practicable after preparation. If not used immediately and storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

6.5. NATURE AND CONTENTS OF CONTAINER

Erbitux is a sterile, preservative-free solution for intravenous infusion containing 5 mg/mL of cetuximab. It is supplied in clear, colourless glass vials with a fluoropolymer-coated halobutyl rubber stopper and aluminium/polypropylene seal containing 20 mL or 100 mL. Each pack contains 1 single use vial.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

Instructions for use/handling

Erbitux may be administered via a gravity drip, an infusion pump or a syringe pump method. 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.

Product is for single use in one patient only. Discard any residue.

Erbitux is compatible with:
- Polyethylene (PE), ethyl vinyl acetate (EVA) or polyvinyl chloride (PVC) bags,
- PE, polyurethane (PUR), EVA, polyolefine thermoplastic (TP) or PVC infusion sets,
- Polypropylene (PP) syringes for syringe pump.

Since Erbitux does not contain any antimicrobial preservative or bacteriostatic agent, care must be taken to ensure aseptic handling when preparing the infusion.

Erbitux 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 the Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

For administration with infusion pump (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. Use an infusion pump for administration. Set and control the rate as explained in the Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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 the DOSAGE AND ADMINISTRATION section 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.

6.7. PHYSICOCHEMICAL PROPERTIES

The pH of the solution is in the range of 5.3 – 5.7 and the osmolality is between 280 and 350 mOsm/kg.

The molecular weight is approximately 152 kDa.

Chemical structure

Cetuximab is a chimaeric monoclonal antibody of the immunoglobulin G_1 (IgG_1) subclass, produced in mammalian cell culture by mouse myeloma cells (Sp2/0). It is obtained by attaching the variable regions of the murine monoclonal antibody M225 against epidermal growth factor receptor (EGFR) to constant regions of the human IgG_1.

CAS number

205923-56-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Merck Healthcare Pty Ltd
Suite 1, Level 1
Building B
11 Talavera Road
Macquarie Park NSW 2113
Merck Medical Information: 1800 633 463

9. DATE OF FIRST APPROVAL

25 September 2007

10. DATE OF REVISION

1 April 2026

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Summary table of changes

Section changed	Summary of new information
6.5	Updated description of rubber stopper.