PACKAGE INSERT

SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME (AND DOSAGE FORM)

ERBITUX 5 mg/ml Solution for Infusion

COMPOSITION

Each ml of solution for infusion contains 5 mg cetuximab.

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

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

PHARMACOLOGICAL CLASSIFICATION

A.30.2 Biologicals - Antibodies

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 could 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 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.

Colorectal cancer

In assessments 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 non RAS wild type tumours where EGFR was not detected.

The RAS status was recognised as a predictive factor for the treatment with cetuximab in randomised controlled studies.

Study data demonstrated that patients with metastatic colorectal cancer and activating RAS mutations are highly unlikely to benefit from treatment with cetuximub alone or in combination with chemotherapy and as add-on therapy to FOLFOX4 in the KRAS and RAS mutant patient populations. Cetuximab in combination with FOLFOX4 showed a significant negative effect on progression free survival time (PFS) in the KRAS and RAS mutant patient populations.

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. The appearance of HACA did not correlate with the occurrence of hypersensitivity reactions or any other undesirable effect to cetuximab.

Pharmacokinetic properties

Cetuximab pharmacokinetics were studied when cetuximab was administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy 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} ($\pm$ standard deviation) was 185 $\pm$ 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 ≤ 1,5 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.

INDICATIONS

ERBITUX is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer, (see **Contra-indications**):

- In combination with irinotecan-based chemotherapy
- In first-line in combination with continuous infusional 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX)
- As a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

ERBITUX in combination with radiation therapy is indicated for the treatment of patients with locally advanced squamous cell cancer of the head and neck.

ERBITUX as a single agent is indicated for the treatment of patients who have failed chemotherapy for recurrent and/or metastatic squamous cell cancer of the head and neck.

ERBITUX in combination with platinum-based chemotherapy is indicated for treatment of patients with recurrent and/or metastatic squamous cell cancer of the head and neck.

CONTRA-INDICATIONS

ERBITUX is contraindicated in patients with known hypersensitivity reactions to cetuximab.
Mutational status should be determined by an accredited laboratory using validated test methods for detection of KRAS and NRAS (exons 2, 3 and 4) mutations.
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.
Results from clinical studies show a negative benefit-risk balance in patients with tumours bearing RAS mutations. In particular, in these RAS mutant patients negative effects on Progression-Free Survival (PFS) and overall survival (OS) were seen as add-on to FOLFOX4.
Before initiation of combination treatment, contra-indications for concomitantly used chemotherapeutic agents or radiotherapy must be considered.
Pregnancy or during breastfeeding of infants (see **Pregnancy and Lactation**).

WARNINGS AND SPECIAL PRECAUTIONS

Colorectal cancer patients with RAS mutated tumours

ERBITUX 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.

Infusion-related, including anaphylactic, reactions

Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome, (see **Side Effects**).

Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of **ERBITUX** 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 medical practitioner 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 (ILD), including fatal cases, have been reported, with the majority of patients from the Japanese population.

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.

If interstitial lung disease is diagnosed, ERBITUX 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 (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 a severe skin reaction (≥ grade 3; US National Cancer Institute - Common Terminology Criteria for adverse events, CTCAE), **ERBITUX** therapy must be interrupted. Treatment may only be resumed, if the reaction has resolved to grade 2 (see **Side effects**).

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, **ERBITUX** therapy must again be interrupted. Treatment may only be resumed at a lower dose level (200 mg/m² body surface area 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 **ERBITUX** treatment is required.

Electrolyte disturbances

Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia in some patients. Hypomagnesaemia is reversible following discontinuation of ERBITUX.

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 **ERBITUX** treatment. Electrolyte repletion is recommended, as appropriate.

Neutropenia and related infectious complications

Patients who receive **ERBITUX** 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 **Side-Effects**).

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 **ERBITUX**, 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 ERBITUX. It is recommended that patients 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 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 **ERBITUX** 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.

Special populations

Only patients with adequate renal and hepatic function have been investigated (serum creatinine ≤ 1,5 fold, transaminases ≤ 5 fold and bilirubin ≤ 1,5 fold the upper limit of normal).

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

- haemoglobin < 9 g/dl
- leukocyte count < 3 x 10^3/mm³
- absolute neutrophil count < 15 x 10^2/mm^3
- platelet count < 10 x 10^4/mm³

The efficacy of **ERBITUX** in paediatric patients below the age of 18 years has not been established.

There is limited experience in the use of ERBITUX in combination with radiotherapy in colorectal cancer.

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.

INTERACTIONS

There is no evidence that the safety profile of **ERBITUX** is influenced by irinotecan or *vice versa*.

A formal interaction study showed that the pharmacokinetic characteristics of **ERBITUX** 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 **ERBITUX** was co-administered.

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

PREGNANCY AND LACTATION

The use of **ERBITUX** is contra-indicated in pregnancy and lactation. Safety in pregnancy and lactation has not been demonstrated.

The epidermal growth factor receptor (EGFR) is involved in foetal development and other IgG_1 antibodies have been found to cross the placental barrier.

ERBITUX should not be given during pregnancy or to any woman who may become pregnant. Women should not breast-feed during treatment with **ERBITUX** and for 2 months after the last dose. It is not known whether cetuximab is excreted in breast milk.

DOSAGE AND DIRECTIONS FOR USE

ERBITUX 5 mg/ml must be administered under the supervision of a medical practitioner experienced in the use of antineoplastic medicinal products. Close monitoring for adverse reactions including anaphylaxis is required during the infusion and for at least 1 hour after the end of the infusion. (See **Side effects**.) Availability of resuscitation equipment must be ensured.

Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of **ERBITUX 5** mg/ml. This premedication is recommended prior to all subsequent infusions.

In all indications, **ERBITUX** 5 mg/ml is administered once a week. The initial dose is 400 mg cetuximab per m^2 body surface area. The subsequent weekly doses are 250 mg/m^2 each.

Colorectal cancer

In patients with metastatic colorectal cancer, cetuximab is used in combination with chemotherapy or as a single agent in patients who have failed oxaliplatin and irinotecan based therapy and who are intolerant to irinotecan. (See **Indications**). 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 **Warnings and Special Precautions**)

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 **ERBITUX** 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, **ERBITUX** is used concomitantly with radiation therapy. It is recommended to start **ERBITUX** therapy one week before radiation therapy and to continue **ERBITUX** therapy until the end of the radiation therapy period.

In patients with recurrent and/or metastatic squamous cell cancer of the head and neck (SCCHN), **ERBITUX** is used in combination with up to 6 cycles of platinum-based chemotherapy followed by **ERBITUX** as maintenance therapy until disease progression. Chemotherapy must not be administered earlier than 1 hour after the end of the **ERBITUX** infusion.

Administration

ERBITUX 5 mg/ml is administered intravenously with an infusion pump, gravity drip or a syringe pump (for handling instructions, see below).

The initial dose should be given slowly and speed of infusion must not exceed 5 mg/min (see **Warnings and Special Precautions**). 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.

Special populations

Only patients with adequate renal and hepatic function have been investigated to date (see **Warnings and Special Precautions**).

ERBITUX has not been studied in patients with pre-existing haematological disorders (see **Warnings and special Precautions**).

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

Instructions for use and handling

In the absence of compatibility studies, **ERBITUX** must not be mixed with other medicinal products except sterile sodium chloride 9 mg/ml (0,9 %). A separate infusion line must be used.

ERBITUX 5 mg/ml 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, ethyl vinyl acetate or polyvinyl chloride bags,
- with polyethylene, polyurethane, ethyl vinyl acetate, polyolefine thermoplastic or polyvinyl chloride infusion sets.
- With polypropylene 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** 5 mg/ml. 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** 5 mg/ml from a vial. Transfer the **ERBITUX** 5 mg/ml 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** 5 mg/ml before starting the infusion. Use a gravity drip or an infusion pump for administration. Set and control the rate as explained above.

- For administration with a syringe pump (undiluted): Calculate the required volume of **ERBITUX** 5 mg/ml. Take an appropriate sterile syringe and attach a suitable needle.

Draw up the required volume of **ERBITUX** 5 mg/ml 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 above and start the infusion after priming the line with **ERBITUX** 5 mg/ml or sterile sodium chloride 9 mg/ml (0,9 %) solution. If necessary, repeat this procedure until the calculated volume has been infused.

- For administration with a gravity pump or gravity drip (undiluted): Calculate the required volume of **ERBITUX** 5 mg/ml. Take an appropriate sterile syringe (minimum 50 ml) and attach a suitable needle. Draw up the required volume of **ERBITUX** 5 mg/ml from a vial. Transfer the **ERBITUX** into a sterile evacuated container or bag. Repeat this procedure until the calculated volume has been reached. Remove the needle and put the syringe into the syringe pump. Connect the infusion line and prime it with **ERBITUX** 5 mg/ml before starting the infusion. Set and control the rate as explained above.

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

There is no evidence that the safety profile of **ERBITUX** is influenced by irinotecan or *vice versa*.

In combination with irinotecan, additional reported undesirable effects were those expected with irinotecan (such as diarrhoea 72 %, nausea 55 %, vomiting 41 %, mucositis, e.g. stomatitis 26 %, fever 33 %, leukopenia 25 %, alopecia 22 %).

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 **Warnings and Special Precautions**).

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 of a late radiation-therapy-related events were slightly higher in patients receiving radiation therapy in combination with **ERBITUX** than those receiving radiation therapy alone.

Overall, no clinically relevant difference between genders was observed.

The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10)

Common (≥ 1/100, < 1/10)

Uncommon (≥ 1/1 000, < 1/100)

Rare (≥ 1/10 000, < 1/1 000)

Very rare (< 1/10 000, including isolated cases)

Frequency not known (cannot be estimated from the available data)

Metabolism and nutrient disorders

Very common: Progressively decreasing serum magnesium levels which may lead to severe hypomagnesaemia.

Common: Other electrolyte disturbances, mainly hypocalcaemia or hypokalaemia.

Dehydration, in particular secondary to diarrhoea or mucositis. 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,

Rare: interstitial lung disease, which may be fatal (see **Warnings and Special Precautions**).

Gastrointestinal disorders:

Common: Diarrhoea, nausea, vomiting.

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

Very common: 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 cases of skin necrosis. The majority of skin reactions develop within the first three weeks of therapy. These may not resolve without sequelae, following cessation of treatment, even if the recommended adjustments in dose regimen are followed (see **Warnings and Special Precautions**).

Frequency not known: Skin lesions induced by **ERBITUX** may predispose patients to superinfections (e.g. with *S. aureus*), which may lead to subsequent complications, e.g. cellulitis, erysipelas, or, potentially with a fatal outcome, staphylococcal scalded skin syndrome, necrotising fasciitis or sepsis.

Very rare: Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN).

General disorders and administration site conditions

Very common: Mild or moderate infusion-related reactions (see **Warnings and Special Precautions**).

Mucositis which may be severe, has been reported.

Mucositis may lead to epistaxis.

Common: Severe infusion-related reactions which may be fatal. (See **Warnings and Special Precautions**.); fatigue.

For clinical management, see **Warnings and Special Precautions**.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No case of overdose has been reported. 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 '**Side Effects'**

IDENTIFICATION

A clear, colourless solution filled into a colourless vial with a rubber stopper and a grey cap.

PRESENTATION

20 ml or 100 ml of solution in a transparent, colourless glass vial with a rubber stopper and an aluminium seal and a grey flip-off cap.

Pack size of 1.

STORAGE INSTRUCTIONS

Store between 2 - 8 ºC in a refrigerator. Keep out of reach of children.

Chemical and physical in-use stability for **ERBITUX** 5 mg/ml has been demonstrated for 48 hours at 25 ºC, if the solution is prepared as described in section 'Instructions for use and handling'.

ERBITUX 5 mg/ml 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 8 ºC, unless opening has taken place in controlled and validated aseptic conditions.

REGISTRATION NUMBER

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