Summary of the Risk Management Plan (RMP)
for
ERBITUX® (cetuximab)

Dosage strength:	100 mg/20 ml; 500 mg/100 ml
Pharmaceutical Form:	Solution for infusion
Marketing Authorisation Number:	56072
Marketing Authorisation Holder	Merck (Schweiz) AG, Chamerstrasse 174, 6300 Zug
Based on EU RMP:	Version 20.0, sign-off date: 05 December 2024

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Erbitux is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Erbitux in Switzerland is the "Arzneimittelinformation/Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Merck (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Erbitux.

Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for Erbitux (Cetuximab)

This is a summary of the RMP for Erbitux. The RMP details important risks of cetuximab, and how more information will be obtained about Erbitux's risks and uncertainties (missing information).

Erbitux's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Erbitux should be used.

This summary of the RMP for Erbitux should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Erbitux's RMP.

I. The Medicine and What It Is Used For

Erbitux is authorized for the treatment of metastatic cancer of the large intestine. In these patients, Erbitux is used alone or in combination with other anticancer medicines. Erbitux is also used to treat 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 (for both cancer types, see SmPC for the full indication). It contains cetuximab as the active substance and it is given by intravenous route.

Further information about the evaluation of Erbitux's benefits can be found in Erbitux's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/erbitux

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Erbitux, together with measures to minimize such risks are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

II.A List of Important Risks and Missing Information

Important risks of Erbitux are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Erbitux. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

Table 1 Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Infusion-related reactions • Superinfections of skin lesion and subsequent complications
Important potential risks	• Posterior Reversible Encephalopathy Syndrome (PRES) • Hemolytic disorders and Disseminated Intravascular coagulation (DIC) • Thrombotic thrombocytopenic purpura • (Acute) renal failure • Gastrointestinal (GI) perforation
Missing information	• Not applicable

II.B Summary of Important Risks

Table 2 Summary of Important Identified Risks

Important identified Risk: Infusion-Related Reactions (IRRs)	
Evidence source and strength of evidence	Severe IRRs, including anaphylactic reactions, may commonly occur treatment (≥1/100 to <1/10), in some cases with fatal outcome. Occurrence of a severe IRR requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency (Chung [2008][1], O'Neil [2010][2], Mariotte [2011][3]).

Important identified Risk: Infusion-Related Reactions (IRRs)	
Risk factors and risk groups	Patients with a history of allergies, cardiorespiratory disease, elderly patients and patients with reduced performance status are at increased risk. Severe allergy-like reactions may occur as early as within a few minutes of the first infusions e.g., due to preformed IgE antibodies cross-reacting with cetuximab. The risk is much increased in patients with known red meat allergy or tick bites or positive results for preformed IgE antibodies against cetuximab.
Risk minimization measures	Addressed in Sections, 4.2, 4.3, 4.4 and 4.8 of the EU SmPC ***4.2 Posology and method of administration*** • *Supervision of a physician experienced in the use of anti cancer medicinal products.* • *Close monitoring during the infusion and for at least 1 hour after the end of the infusion.* • *Availability of resuscitation equipment* ***Posology**:* • *Premedication with an antihistamine and a corticosteroid at least 1 hour prior to first administration of cetuximab. recommended prior to all subsequent infusions.* ***Method of administration**:* • *Instructions referring to infusion rate* ***4.3 Contraindications**:* • *Patients with known severe (Grade 3 or 4) hypersensitivity reactions to cetuximab.* ***4.4 Warnings and Precautions*** *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.* • *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. 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. 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).* *Description of measures in case of an infusion-related reaction* • *Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.*

Important identified Risk: Infusion-Related Reactions (IRRs)	
	4.8. Adverse reactions *General disorders and administration site conditions* *Very common:* *Mild or moderate infusion-related reactions (see Section 4.4 of the EU SmPC)* *Common:* *Severe infusion-related reactions, in some cases with fatal outcome (see Section 4.4 of the EU SmPC)* Other routine risk minimization measures: • Patient Information Leaflet • Prescription only medicine Additional risk minimization measures: None proposed

Important Identified Risk: Superinfections of Skin Lesion and Subsequent Complications	
Evidence source and strength of evidence	The risk for secondary infections, mainly bacterial, subsequent to skin reaction is increased (frequency not known). Superinfections of skin lesions may have serious consequences including life-threatening conditions.
Risk factors and risk groups	Immunocompromised patients and patients with reduced performance status, patients with diabetes mellitus, liver and kidney disease, vascular insufficiency
Risk minimization measures	Addressed in Sections 4.4. and 4.8 of the EU SmPC: ***4.4 Special warnings and precautions for use*** ***The risk for secondary infections*** *(mainly bacterial) subsequent to skin reactions due to cetuximab is increased and cases of staphylococcal scalded skin syndrome, necrotizing fasciitis and sepsis, in some cases with fatal outcome, have been reported (see Section 4.8 of the EU SmPC).* ***4.8. Adverse reactions*** *Skin and subcutaneous tissue disorders* *Frequency not known:* *Superinfection of skin lesions* Other routine risk minimization measures: • Patient Information Leaflet • Prescription only medicine Additional risk minimization measures: None proposed

1 Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-α-1,3-galactose. New Engl J Med. 2008;358(11):1109-17.

2 O'Neil B.H. Overview of hypersensitivity to cancer therapies. Community Oncol. 2010;7(1):11-6.

3 Mariotte D, Dupont B, Gervais R, et al. Anti cetuximab IgE ELISA for identification of patients at a high risk of cetuximab-induced anaphylaxis. mAbs 2011;3:(4):396-401.

Table 3 Summary of Important Potential Risks

Important Potential Risk: Posterior Reversible Encephalopathy Syndrome (PRES)	
Risk factors and risk groups	Hypertension and exposure to toxic agents (including chemotherapeutic drugs)
Evidence source and strength of evidence	Posterior Reversible Encephalopathy Syndrome is a rare "encephalopathic" condition, where the diagnosis depends on clinical and radiological features. On magnetic resonance imaging of the brain, areas of edema (swelling) are seen. Despite the name 'leukoencephalopathy', lesions can occur in both white and grey areas of the brain. It is also increasingly recognized that it can affect the anterior cerebrum, as well as the anterior and posterior cortex, brainstem, cerebellum or even the spinal cord. PRES comprises usually symptoms like headache, confusion, seizures and visual loss. A very low number of PRES cases have been reported with cetuximab and the causal association to cetuximab has not been established
Risk minimization measures	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures: None proposed

Important Potential Risk: Hemolytic Disorders and Disseminated Intravascular Coagulation (DIC)	
Evidence source and strength of evidence	Disorders due to breaking down of red blood cells with liberation of hemoglobin in the blood (Hemolytic Disorders) and DIC, which is a serious medical condition that develops when the normal balance between bleeding and clotting is disturbed. Hemolytic disorders may cause excessive bleeding. DIC may cause excessive bleeding and clotting which injures body organs, and causes low number of red blood cells (anemia) and may be fatal. Cases of hemolytic disorders and DIC have been reported with cetuximab. A causal association to cetuximab has not been established.
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures: None proposed

Important Potential Risk: Thrombotic Thrombocytopenic Purpura (TTP)	
Evidence source and strength of evidence	Thrombotic Thrombocytopenic Purpura (TTP) is a rare, severe and life-threatening multisystemic condition. TTP is a rare form of thrombotic microangiopathy. It is characterized by microangiopathic haemolysis (breaking down of red blood cells with liberation of hemoglobin in the blood) in very little blood vessels, thrombocytopenia (low number of thrombocytes), neurological abnormalities (e.g., confusion, headache, dysarthria (speech disorder), visual problems, encephalopathy, and coma), fever and renal dysfunction. The diagnosis of TTP should be treated as a medical emergency as the risk to die if untreated is very high. Risk of death can be greatly reduced with prompt treatment with plasma exchange Only a very low number of TTP cases with cetuximab have been reported, A causal association to cetuximab has not been established.

Important Potential Risk: Thrombotic Thrombocytopenic Purpura (TTP)	
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures: None proposed

Important Potential Risk: (Acute) Renal Failure	
Evidence source and strength of evidence	Cetuximab can cause loose stools and loss of fluids, which may potentially increase the risk of failure of kidney function. (Acute) failure of kidney function is a severe life-threatening condition in which the kidneys fail to adequately filter waste products from the blood. Failure of kidney function may result in problems with increased fluid in the body (leading to swelling), raised levels of potassium, decreased levels of calcium and increased levels of phosphate, and in later stages low number of red blood cells (anemia)
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures: None proposed

Important Potential Risk: Gastrointestinal (GI) Perforation	
Evidence source and strength of evidence	The wall of the stomach, small intestine or large bowel can lose integrity (gastrointestinal perforation). It can occur in patients with CRC or when there are tumor metastases in the stomach, the small intestine and large bowel or due to inflammatory disorders. Cetuximab can cause an inflammation of the inner lining in these organs. This may potentially increase the risk of gastrointestinal perforation.
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures: None proposed

II.C Post Authorization Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation Erbitux.

II.C.2 Other Studies in the Post Authorization Development Plan

There are no studies required for Erbitux.