Risk Management Plan (RMP) for Erbitux® (Cetuximab)

Active substance(s) (INN/Trade Name):	Cetuximab / Erbitux®
Name of Company:	**Merck Healthcare KGaA** **Frankfurter Straße 250** **D-64293 Darmstadt** **Germany** **Telephone +49 61 51-72 0** **Telefax +49 61 51-72 69 14** **e-mail: GlobalDrugSafety@merckgroup.com**

RMP version to be assessed as part of this application:

RMP version number:	22.0
Data lock point for this RMP:	30 Sep 2025
Date of final sign off:	Document signed electronically, see date of eSignature at the end of the document
Rationale for submitting an updated RMP:	Inclusion of the indication for the treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer in combination with encorafenib and mFOLFOX6 and in combination with encorafenib in patients who have received prior systemic therapy. Scientific review of Version 21.1 was endorsed by EMA. Version number of the RMP updated to integer number 22.0 for closing sequences (Procedure No. EMA/VR/0000326978 and Procedure No. EMA/VR/0000327014). No changes in content compared to Version 21.1.

Summary of significant changes in this RMP:

Part I	Product(s) Overview	• Proposed indication(s) in the EEA has been updated with the indication for the treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer in combination with encorafenib and mFOLFOX6, and in combination with encorafenib in patients who have received prior systemic therapy. • Proposed dosage in the EEA has been updated accordingly.
Part II	Module SI Epidemiology of the Indication(s) and Target Population(s) Module SIII Clinical Trial Exposure Module SV Post Authorization Experience Module SVII Identified and Potential Risks	• Updated to latest information and aligned with PBRER with reporting period 01 Oct 2024 to 30 Sep 2025 (including exposure data [both clinical and post-authorization] and details of safety concerns [frequency and number of cases]). • Added “Hypophosphatemia” to the list of “Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP”.

Other RMP versions under evaluation: Not applicable

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[redacted]

Signatures

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Document signed electronically by the EU QPPV

EU QPPV oversight declaration: The content of this RMP has been reviewed and approved for use in the EEA by the Marketing Authorization Holder's EU QPPV. The electronic signature is available on file.

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Global Patient Safety, [redacted] - Cetuximab

(Contact person for this RMP)

Signature: **Document signed electronically**

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List of Abbreviations

ACE-27	Adult Comorbidity Evaluation-27 items
ADCC	Antibody-Dependent Cell Mediated Toxicity
BMS	Bristol-Myers Squibb
BRAF	V-Raf Murine Sarcoma Viral Oncogene Homolog B, Serine/Threonine Kinase
BSA	Body Surface Area
BSC	Best Supportive Care
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal Cancer
CRT	Chemoradiotherapy
CT	Chemotherapy
CTD	Common Technical Document
DLP	Data Lock Point
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
DSUR	Development Safety Update Report
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FOLFIRI	Folinic Acid (Leucovorin), 5-Fluorouracil, Irinotecan
FOLFOX	Folinic Acid (Leucovorin), 5-Fluorouracil, Oxaliplatin
GI	Gastrointestinal
GPS	Global Patient Safety
HPV	Human Papilloma Virus
IBD	Inflammatory Bowel Disease
IMRT	Intensity Modulated Radiation Therapy
ICSRs	Individual Case Safety Reports
Ig	Immunoglobulin
IRR	Infusion-Related Reaction
KRAS	V-Ki-Ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog
LA SCCHN	Locally Advanced Squamous Cell Cancer of Head and Neck
Lilly	Eli Lilly and Company
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
Merck	Merck Healthcare KGaA, Merck KGaA
mCRC	Metastatic Colorectal Cancer
NCCN	National Comprehensive Cancer Network
NRAS	Neuroblastoma RAS Viral [v-ras]
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PI	Product Information
PBRER	Periodic Benefit-Risk Evaluation Report

[redacted]

PE	Pulmonary Embolism
PL	Package Leaflet
PPE	Palmar-Plantar Erythrodysesthesia Syndrome
PRES	Posterior Reversible Encephalopathy Syndrome
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Report Single Assessment
Q1W	Once a week, Every 1 week
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QPPV	Qualified Person Responsible for PharmacoVigilance
RAS	Rat Sarcoma Proto-Oncogene
RMP	Risk Management Plan
R/M SCCHN	Recurrent and/or Metastatic Squamous Cell Carcer of Head and Neck
RT	Radiotherapy
SCCHN	Squamous Cell Cancer of Head and Neck
SEER	Surveillance Epidemiology and End Results
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
TEN	Toxic Epidermal Necrolysis
TSE	Transmissible Spongiform Encephalopathies
TTP	Thrombotic Thrombocytopenic Purpura
US, USA	United States, United States of America
VEGF	Vascular Endothelial Growth Factor
XELIRI	Xeloda® [capecitabine] and Irinotecan
XELOX	Xeloda [capecitabine] and Oxaliplatin

[redacted]

Part I: Product(s) Overview

Table 1 Product(s) Overview

Active substance(s) (INN)	Cetuximab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies (L01FE01)
Marketing Authorization Holder	Merck Europe B.V. Gustav Mahlerplein 102 Toyo Ito Toren, 20th Floor, 1082 MA, Amsterdam The Netherlands
Medicinal products to which this RMP refers	Erbitux®
Invented name(s) in the European Economic Area (EEA)	Erbitux
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Cetuximab is a chimeric monoclonal IgG1 antibody that is specifically directed against the epidermal growth factor receptor (EGFR).
	Summary of mode of action: • EGFR-signaling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion (metastases). • Cetuximab binds to the EGFR with an affinity that is approximately 5- to 10-times 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 internalization of EGFR, which could lead to down-regulation of EGFR. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumor cells (antibody-dependent cell mediated cytotoxicity, ADCC). Cetuximab does not bind to other receptors belonging to the HER family.
	Important information about its composition: Cetuximab is a chimeric monoclonal immunoglobulin (Ig) G1 antibody, manufactured from a recombinant mammalian cell line.
Hyperlink to the Product Information	Erbitux Product Information (Module 1.3.1)
Indication(s) in the EEA	Current: ►Colorectal cancer. Erbitux is indicated for the treatment of patients with EGFR-expressing, Rat Sarcoma Proto-Oncogene (RAS) wild-type metastatic colorectal cancer (CRC): • in combination with irinotecan-based chemotherapy • in first-line in combination with folinic acid (leucoverin), 5-fluorouracil, oxaliplatin (FOLFOX) • as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

	►Squamous cell cancer of head and neck. Erbitux is indicated for the treatment of patients with squamous cell cancer of head and neck (SCCHN): • in combination with radiation therapy for locally advanced disease • in combination with platinum-based chemotherapy for recurrent and/or metastatic disease
	Proposed: ►Colorectal cancer. Erbitux is indicated for the treatment of patients with EGFR-expressing, Rat Sarcoma Proto-Oncogene (RAS) wild-type metastatic colorectal cancer (CRC): • in combination with irinotecan-based chemotherapy • in first-line in combination with folinic acid (leucoverin), 5-fluorouracil, oxaliplatin (FOLFOX) • as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. • • Erbitux is indicated for the treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer • in combination with encorafenib and mFOLFOX6, • in combination with encorafenib in patients who have received prior systemic therapy. ►Squamous cell cancer of head and neck. Erbitux is indicated for the treatment of patients with SCCHN: • in combination with radiation therapy for locally advanced disease in combination with platinum-based chemotherapy for recurrent and/or metastatic disease
Dosage in the EEA	Current: In all indications, cetuximab is administered Q1W. The Initial dose is 400 mg cetuximab per m^2 body surface area (BSA). All subsequent doses are 250 mg/m^2 each. Erbitux may be administered in a weekly or every other week dose regimen. *Weekly dose regimen* Erbitux is administered Q1W. The initial dose is 400 mg cetuximab per m^2 BSA. All subsequent weekly doses are 250 mg/m^2 each. *Biweekly dose regimen* Erbitux is administered Q2W. Each dose is 500 mg cetuximab per m^2 BSA.
	Proposed: <u>Colorectal cancer – wt mCRC</u> Erbitux may be administered in a weekly or every other week dose regimen. *Weekly dose regimen* Erbitux is administered Q1W. The initial dose is 400 mg cetuximab per m^2 BSA. All subsequent weekly doses are 250 mg/m^2 each. *Biweekly dose regimen* Erbitux is administered Q2W. Each dose is 500 mg cetuximab per m^2 BSA. <u>Colorectal cancer - BRAF V600E mutant metastatic colorectal cancer</u> *In combination with encorafenib and mFOLFOX6* Erbitux is administered Q2W. Each dose is 500 mg cetuximab per m^2 BSA.

	In combination with encorafenib in patients who received prior systemic therapy Erbitux is administered Q1W. The very first dose is 400 mg cetuximab per m^2 BSA. All subsequent weekly doses are 250 mg/m^2 each. Squamous cell cancer of the head and neck *In combination with radiation therapy* Erbitux is administered Q1W. The initial dose is 400 mg cetuximab per m^2 BSA. All subsequent weekly doses are 250 mg/m^2 each. *In combination with platinum-based chemotherapy* Erbitux may be administered in a weekly or every other week dose regimen. *Weekly dose regimen* Erbitux is administered Q1W. The initial dose is 400 mg cetuximab per m^2 BSA. All subsequent weekly doses are 250 mg/m^2 each. *Biweekly dose regimen* Erbitux is administered Q2W. Each dose is 500 mg cetuximab per m^2 BSA.
Pharmaceutical form(s) and strengths	Current: Erbitux is available as 5 mg/mL solution for infusion
	Proposed: NA
Is/will the product be subject to additional monitoring in the EU?	No

ATC=anatomical therapeutic chemical code; BSA=body surface area; CRC=colorectal cancer: EEA=European Economic Area; EGFR=epidermal growth factor receptor; EU=European Union; FOLFOX=folinic acid (leucovorin), 5 fluorouracil, oxaliplatin; INN=international nonproprietary names; NA=not applicable; PI=Prescribing Information; RAS=rat sarcoma proto-oncogene; RMP=Risk Management Plan; SCCHN=squamous cell cancer of head and neck; SmPC=Summary of Product Characteristics.

Part II Safety Specification

Part II Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Incidence

SI.1.1 Colorectal Cancer (CRC)

According to GLOBOCAN 2022 estimates, CRC is the third most common form of cancer in males and in females, with 1.9 million new cases and 904,019 deaths estimated to have occurred in 2022 worldwide (Ferlay 2024).

Globally, the regional incidence of CRC varies widely. According to data from the GLOBOCAN database (Ferlay 2024), age-standardized (world) incidence rates of CRC ranged from 5.5 per 100,000 cases in South-Central Asia and Middle Africa to 35.3 per 100,000 in Australia-New Zealand. In Europe, the age-standardized (world) incidence rate was 30.5 per 100,000, 27.2 per 100,000 in Northern America and 15.6 per 100,000 in Asia. Globally, the world age-standardized incidence rate for CRC was estimated at 19.3 new cases per 100,000 population. Age-standardized incidence rates for colorectal in different continents in 2022 are detailed in Table 2.

In the USA, CRC is the second most common cause of cancer-related deaths. Most recent data from the USA suggest that 160,186 new CRC cases along with 54,614 deaths were reported in 2022 (Ferlay 2024).

Table 2 Age-standardized (World) Incidence Rates per 100,000 of CRCs by Continent (2022)

Regions	Males	Females	Total
Africa	9.1	7.5	8.2
Latin America and Caribbean	18.9	15.2	16.9
Asia	19.0	12.4	15.6
Europe	37.7	24.8	30.5
Northern America	30.5	24.2	27.2
Oceania	34.9	27.7	31.1

From the Cancer today GLOBOCAN database (Ferlay 2024) (http://globocan.iarc.fr/) accessed 11 Nov 2025.
CRC=colorectal cancer

BRAF V600E mutations occur in approximately 8% to 12% of patients with mCRC and confer a poor prognosis (Tabernero 2022). BRAF V600 mutations lead to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signaling, resulting in increased cell proliferation and survival (Corcoran 2012). This disease remains a high unmet medical need.

SI.1.2 Squamous Cell Cancer of the Head and Neck (SCCHN)

For SCCHN data, the following locations were included: lip, oral cavity, (oro- and hypo-) pharynx and larynx.

Worldwide, head and neck cancer accounts for more than 771,000 cases and 385,000 deaths reported in 2022 according to the GLOBOCAN database (Ferlay 2024). In the United States, head and neck cancer accounts for 3% of malignancies, with approximately 56,000 Americans developing head and neck cancer annually and 12,000 dying from the disease (Ferlay 2024). In Europe, there were approximately 148,000 new cases and 65,000 deaths, both sexes in 2022 (Ferlay 2024).

Males are affected significantly more than females, with a ratio ranging from 2:1 to 4:1. The incidence rate in males exceeds 20 per 100,000 in regions of France, Hong Kong, the Indian subcontinent, Central and Eastern Europe, Spain, Italy, and Brazil, and among African Americans in the United States (Lambert 2011).

Age-standardized incidence rates for lip, oral cavity, (oro- and hypo-) pharynx and larynx cancers, from the GLOBOCAN database (Ferlay 2024), in different continents in 2022 are detailed in Table 3.

Table 3 Age-standardized (World) Incidence Rates per 100,000 of Lip, Oral Cavity, Larynx and Oro- and Hypo- pharynx Cancers by Continent (2022)

Regions	Males	Females	Total
Africa	5.5	2.0	3.6
Latin America and Caribbean	10.0	2.4	5.9
Northern America	14.7	4.4	9.4
Asia	12.8	3.5	8.1
Europe	17.7	3.9	10.3
Oceania	16.2	5.8	10.9

From the Cancer today GLOBOCAN database (Ferlay 2024) (http://globocan.iarc.fr/) accessed 11 Nov 2025.

SI.2 Prevalence

SI.2.1 Prevalence CRC

In 2022, the worldwide 5-year prevalence of CRC was 5,767,781cases. The 5-year prevalence rates, from the GLOBOCAN database (Ferlay 2024), for the continents in 2022 are described in Table 4.

Table 4 5-year Prevalence Counts and Rates (per 100,000) for CRC by Continent (2022)

Regions	Males	Females	Total
Africa	83,804 (11.9)	82,655 (11.8)	166,459 (11.8)
Latin America and Carribean	206,055 (63.0)	206,078 (60.9)	412,133 (61.9)
Northern America	332,234 (179.8)	299,546 (158.9)	631,780 (169.2)
Europe	911,092 (252.2)	786,922 (203.7)	1,698,014 (227.2)
Oceania	39,091 (178.5)	35,916 (164.4)	75,007 (171.4)
Asia	1,611,480 (67.9)	1,172,908 (51.6)	2,784,388 (59.9)

From the Cancer today Globocan database (Ferlay 2024) (http://globocan.iarc.fr/) accessed 11 Nov 2025.
CRC=colorectal cancer

SI.2.2 Prevalence SCCHN

In 2022, the worldwide 5-year prevalence of lip, oral cavity, larynx, and oro- and hypo- pharynx cancers, both sexes and all ages, was 504,617 cases in 2022 worldwide. The 5-year prevalence figures, from the GLOBOCAN database (Ferlay 2024), for the continents in 2022 are described in Table 5.

Table 5 5-year Prevalence Counts and Rates (per 100,000) for Lip, Oral Cavity, Larynx and Oro- and Hypo- pharynx Cancers by Continent (2022)

Regions	Males	Females	Total
Africa	50,600 (7.2)	22,305 (3.2)	72,905 (5.2)
Latin America and Carribean	107,625 (32.9)	31,756 (9.4)	139,381 (21.0)
Northern America	157,741 (85.4)	54,781 (29.1)	212,522 (56.69)
Europe	366,549 (101.5)	109,196 (28.3)	475,745 (63.6)
Oceania	15,085 (68.9)	5,885 (26.9)	20,970 (47.9)
Asia	942,327 (39.7)	280,694 (12.3)	1,223,021 (26.3)

From the Cancer today GLOBOCAN database (Ferlay 2024) (http://globocan.iarc.fr/) accessed 11 Nov 2025.

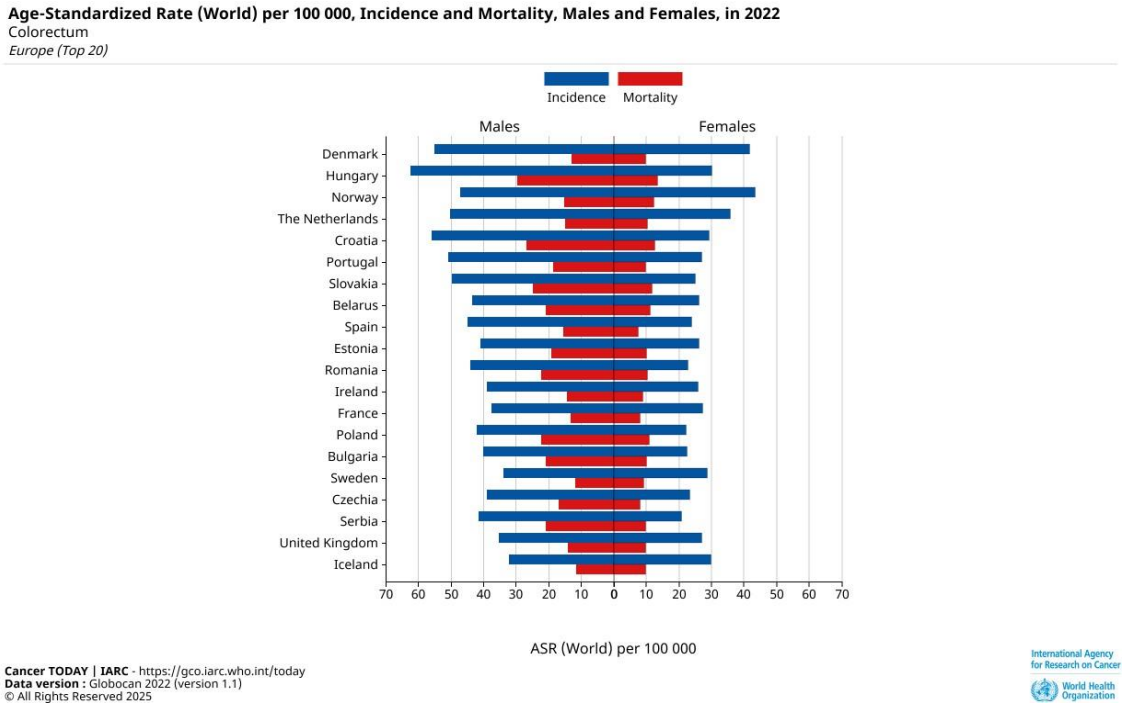
SI.3 Demographics of the Population in the Authorized Indications-age and Gender and Risk Factors for the Disease

SI.3.1 Demographics of the Population in the Authorized Indication CRC

The incidence rates of CRC are higher in men than in women (Figure 1). Increasing age carries an increased likelihood of CRC in the general population, in particular after the age of 40 years.

In the US, declines in CRC incidence and mortality have slowed from 3% to 4% per year during the 2000s to 1% per year and 2% per year, respectively, during the past decade. Declining incidence is confined to ages 65 years and older; since 2011, rates have been stable in ages 50 to 64 years and increasing by 2% per year in people younger than 50 years of age, as well as in people aged 50 to 54 years. These incidence trends are rapidly shifting towards a younger patient population; 20% (1 in 5) of CRCs in 2019 were in people 54 years or younger, up from 11% (1 in 10) in 1995. Incidence rates for advanced disease have increased by about 3% annually in people younger than 50 years of age and 0.5% to 2% annually in people 50 to 64 years of age since around 2010. As a result, diagnosis have also shifted to more advanced disease; the proportion of regional- or distant-stage cancer increased from 52% in the mid-2000s to 60% in 2019 (American Cancer Society, "Colorectal cancer Facts and Figures 2023-2025").

Figure 1 Age-standardized Incidence and Mortality Rates of CRC by Gender and Country (top 20) in Europe 2022



ASR=age-standardized rate; CRC=colorectal cancer

Risk factors for the disease (Potential health risk and risk factors)

Both environmental and genetic factors can increase the risk of developing CRC. Familial CRC is thought to account for approximately 20% of all CRC cases (Gandomani 2017) and is an important risk factor when considered outside genetic predisposition: having a single affected first-degree relative with CRC increases the risk approximately 2-fold over that of the general population (Tuohy 2014).

There is evidence indicating that the risk of CRC increases exponentially around the age of 50 years (Marley 2016), though recent data from the US suggest that CRC incidence is increasing in the under 50 years age group; while it is decreasing in older age groups (Siegel 2017a, Davis 2011).

The role of gender in CRC is still unclear: while incidence rates are approximately 30% higher in men than in women, the reason for this disparity is not fully understood and could be partly reflected by differences in exposures to risk factors (Murphy 2011). Furthermore, there appears to be a delay in the occurrence of CRC in women compared to men (Gandomani 2017) but the overall life-threatening risk of CRC in both sexes is numerically identical (Lin 2009, Zisman 2006). Regarding race, African Americans have the highest CRC rates of all ethnic groups in the US (Siegel 2017a). However, it is possible the cause of this difference is related to the etiological factors (smoking, diabetes mellitus), and lower access to screening for African Americans in the US (Wong 2010).

Some medical history is also thought to be associated with CRC. Inflammatory bowel disease (IBD) is a recognized risk factor with a well-documented association between CRC and the extent, duration, and activity of the IBD (Yashiro 2014). Various studies have shown that diabetes mellitus subjects are at a higher risk for CRC compared to non diabetic subjects, a meta-analysis study showed that the risk of CRC in people who have diabetes mellitus is 35% higher than in non diabetic subjects (Luo 2016). Cholecystectomy, ureterocolic anastomosis and pelvic radiotherapy (RT) are procedures for which an association with CRC has been found (Gandomani 2017), though the mechanisms could be linked to the underlying diseases.

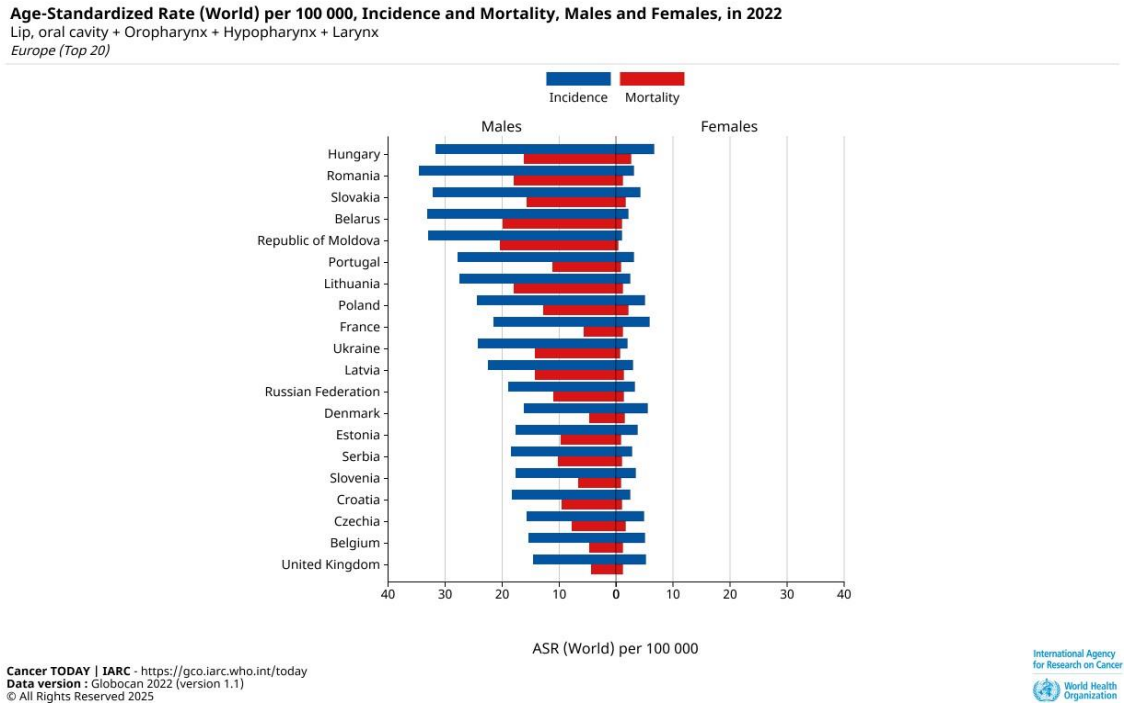
Modifiable risk factors include reduced physical activity and increased body mass index which can significantly increase the risk of CRC (Gandomani 2017). Diet is also an important factor linked to disease prevention and CRC risk: reduced legume intake and increased intake of meat are associated with an increased risk of CRC which can partly explain geographic variations of the disease (Aran 2016). Smoking and alcohol consumption are important risk factors in CRC: a meta-analysis estimated that the risk of developing CRC was increased by 18% among cigarette smokers compared with those who never smoked and the risk of dying from CRC increased by 25% (Botteri 2008). Moderate alcohol drinkers (2-3 drinks per day) and heavy drinkers (≥4 drinks per day) had an increased risk of 21% and 52%, respectively, of developing CRC according to a meta-analysis (Fedirko 2011).

SI.3.2 Demographics of the Population in the Authorized Indication SCCHN

In Europe, 98% and 50% of patients diagnosed are over 40 and 60 years of age, respectively (Mehanna 2010). The incidence rates of SCCHN are higher in men than in women (Figure 2).

Research suggests that 4-6% of oral and oropharyngeal cancers now occur at ages below 40 years. This is recent trend of increasing incidence in younger populations is thought to be associated with an increased incidence of SCCHN risk factors in these populations: Human Papilloma Virus (HPV) infections, early use of tobacco (in numerous forms), alcohol and other drug abuse, all known risk factors for SCCHN (Gupta 2016).

Figure 2 Age-standardized Incidence and Mortality Rates of SCCHN by Gender and Country (top 20) in Europe 2022



ASR=age-standardized rate; SCCHN=squamous cell cancer of head and neck

Risk factors for the disease (Potential health risk and risk factors)

The risk factors most frequently associated with SCCHN include smoking, alcohol consumption, and HPV infections for oropharyngeal cancers (Sankaranarayanan 1998, Gupta 2016).

Tobacco and alcohol consumption are major etiological factors involved in the onset of SCCHN accounting for about 75% of cases and have a multiplicative combined effect (Sturgis 2004, Mehanna 2010). There is 5- to 25-fold increased risk of head and neck cancer in heavy cigarette smokers compared to nonsmokers, and there is a significant increase in risk associated with pipe and cigar smoking as well (Blot 1988, Wyss 2013). The association between tobacco use and SCCHN appears to follow a dose-response trend: in a case-control study, the relative risk of current tobacco users was 6.5 and relative risk increased with the duration of smoking and gradually declined after smoking cessation, with no excess risk at 20 years (Lewin 1998). Smokeless tobacco (both chewing tobacco and snuff) is associated with an increased risk of cancer of the oral cavity and pharynx (Wyss 2016, Gupta 2016). Alcohol consumption independently increases the risk of cancer in the upper aerodigestive tract, although it is difficult to clearly separate the effects of smoking and alcohol and derive precise risk estimates. The risk of developing SCCHN due to

alcohol appears to be dose-dependent. Common intake of alcohol and cigarette appear to have an interactive and multiplicative effect on the risk (Blot 1988, Hashibe 2007, Ansary-Moghaddam 2009).

Viral infections, mostly HPV, but also the hepatitis C virus, are associated with an increased risk of SCCHN (Gupta 2016, Mahale 2016). Sustained infections by HPV are a well-documented risk factor for SCCHN: high risk genotypes, particularly HPV-16 and HPV-18, are thought to be a causal factor for neoplasms originating in the tonsils, base of the tongue and elsewhere in the oropharynx (Anantharaman 2013). Recent studies suggest that HPV could account for 70 to 80% of oropharynx cancer cases in North America and Europe (O'Sullivan 2016). Previous findings suggested a small association with the Herpes Simplex virus, however, this infection is now thought to be a modifier for other risk factors (tobacco, alcohol and HPV infection) (Parker 2006).

Familial inheritance has been noted and the risk for SCCHN seems to increase in individuals with cancer susceptibility syndromes (e.g. hereditary non polyposis CRC, Li-Fraumeni syndrome, Fanconi's anemia, and ataxia telangiectasia) (Argiris 2008). Other risk factors include dietary habits: cooking of salt-cured food, consumption of preserved or fermented foods with high level of added nitrites, and more generally diets deficient in antioxidants (Gupta 2016). Ultraviolet radiation is a risk factor for cancer of the lip. Trauma to the oral mucosa as well as poor oral hygiene are emerging as significant risk factors (Gupta 2014, Hashim 2016).

SI.4 The Main Existing Treatment Options

SI.4.1 The Main Existing Treatment Options for Metastatic CRC

Most patients have metastatic disease that is not initially suitable for potentially curative resection. It is, however, important to select patients with resectable metastases and those with initially unresectable disease in whom resection may be possible after a major response with systemic therapy. The aim of treatment here should be to convert initially unresectable disease to resectable (Osterlund 2021).

The addition of a targeted agent to a cytotoxic doublet or triplet is the most effective treatment in mCRC. Treatment of potentially resectable mCRC: anti-EGFR mAbs in left-sided RAS-wt patients should be used as conversion therapy, when complete resection is the aim (II, A) (Cervantes 2023). Anti-EGFR mAbs in RAS-wt patients with left-sided primary tumors are more effective than bevacizumab-based combinations (Stintzing 2016, Lenz 2014).

In the management of advanced and metastatic disease without potential conversion, several factors were established in the 2016 ESMO Consensus guideline (Cervantes 2023) such as clinical presentation (impending symptoms at diagnosis, primary tumor location), histology and molecular biology of the tumor, the patient characteristics (age, performance status, comorbidities, socioeconomic factors), the goal of treatment and treatment-related issues (toxicity, quality of life etc.) (Van Cutsem 2016).

Patients are usually treated in the first-line with chemotherapy (CT), commonly consisting of a fluoropyrimidine and either irinotecan or oxaliplatin. The most common regimens include FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, irinotecan) and FOLFOX (folinic acid

[leucovorin], 5-fluorouracil, oxaliplatin) and also XELIRI (Xeloda® [capecitabine] and irinotecan) and XELOX (Xeloda [capecitabine] and oxaliplatin), which are using capecitabine instead of 5-FU as the fluoropyrimidine-component. Recently, triplet CT regimens consisting of all 3 chemotherapies (irinotecan, oxaliplatin and fluoropyrimidine) are being used more often, especially in patients with poor prognosis e.g. due to BRAF proto-oncogene, serine/threonine kinase (BRAF) mutated disease. Clinical treatment guidelines recommend the addition of a targeted agent to CT, e.g. a monoclonal antibody targeting either the epidermal groth factor receptor (EGFR, e.g. Cetuximab and panitumumab) or the vascular endothelial growth factor (VEGF, e.g. bevacizumab) (Cervantes 2023).

For the second line therapy of mCRC, the same treatments are being used, often switching between agents, e.g. using FOLFIRI in second line, if FOLFOX has been used in first-line, but also regimens that are better tolerated are being used in patients who can no longer tolerate intensive therapy.

Additional agents, like regorafenib, TAS 102 and ramucirumab are usually used for third and later line treatment but also the above mentioned agents are being used in these setttings, depending on the preference of the treating physician, patient condition and the previously received therapies.

Specific treatments for patients with BRAF V600E-mutant mCRC are limited. The encorafenib-cetuximab (EC) combination was approved in 2020 for the treatment of patients with BRAF V600E-mutant mCRC after prior therapy (Kopetz 2019). Until the recent US FDA accelerated approval in December 2024 for EC + mFOLFOX6, no treatments were indicated specifically for patients with BRAF V600E-mutant mCRC in the first-line setting and thus, these patients receive systemic therapy that is recommended for mCRC in general. The common regimens used in patients with mCRC include mFOLFOX6, FOLFIRI, FOLFOXIRI, and CAPOX, each with or without bevacizumab (Cervantes 2023, NCCN 2024).

SI.4.2 The Main Existing Treatment Options for SCCHN

Patients with locally advanced SCCHN (LA SCCHN) are usually treated with curative intent. Therapy for resectable disease consists of surgery and postoperative radiotherapy (RT), resulting in 5-year survival rates of 10-40% (Laramore 1992). Patients with high risk LA SCCHN disease, e.g. with inadequate resection margins, extranodal spread, or multiple involved lymph nodes, surgery is usually followed by postoperative adjuvant RT or chemoradiotherapy (CRT), resulting in a median overall survival (OS) of 72 months (Bernier 2004). Recently, peri-operative pembrolizumab has demonstrated EFS benefit when added to SOC surgery followed by RT ± CT in patients with resectable LA SCCHN CPS≥1 (Uppaluri 2025). Peri-operative pembrolizumab is recommended by the NCCN guidelines with a category 2A for resectable LA SCCCHN.

RT is the cornerstone in the treatment of LA SCCHN. Various combinations of RT and concomitant CT have been investigated, whereby concomitant CT resulted in improved survival and logo-regional control rates compared to RT alone. In the MACH-NC meta-analysis, the absolute benefit of CRT at 5 years was 6.5% for OS and about 13% for the logo-regional control (Pignon 2009).

Results from several randomized studies have been published that compared concomitant CRT (cisplatin 100 mg/m² Q3W and carboplatin + 5-FU) with RT alone, both regimens are recommended with a Category 1 evidence by the National Comprehensive Cancer Network (NCCN) guidelines. Weekly cisplatin (40 mg/m^2) and carboplatin/paclitaxel are other recommended regimen with Category 2A and 2B rate of evidence, respectively (NCCN Clinical Practice Guidelines, Head and Neck Cancers Version 1 2024). An increase in the survival rate of approximately 10% to 20% with CRT at 2 and 3 years compared to RT alone was reported in most of the studies (Adelstein 2003, Budach 2005). However, in several trials, CRT was associated with low compliance and a substantial increase in acute and late toxicity (Argiris 2008, Machtay 2008).

In recurrent and/or metastatic SCCHN (R/M SCCHN), patients who are not suitable for surgery or reirradiation are usually offered a palliative treatment options (Cohen 2004), including single agent chemotherapy, combination chemotherapy, targeted therapy + chemotherapy (Vermorken 2008) or immunotherapy ± chemotherapy
(NCCN Clinical Practice Guidelines, Head and Neck Cancers Version 5 2025; Machiels 2020).

Immune checkpoint inhibitor e.g. pembrolizumab has been approved in EU as a monotherapy or in combination with platinum + 5-FU CT as a first-line treatment of R/M SCCHN in adults whose tumor express PD-L1 with Combined Positive Score (CPS) ≥1. In the US, pembrolizumab in combination with platinum + 5-FU CT is approved for all patients and pembrolizumab monotherapy is approved for patients whose tumors expressed PD-L1 with CPS≥1. Approvals were based on the KEYNOTE-048 study results (Burtness 2019).

Immune checkpoint inhibitor e.g. nivolumab monotherapy has been approved for the treatment of SCCHN in adults progressing on or after platinum-based therapy. In the randomized Phase 3 CheckMate-141 study, nivolumab monotherapy increased significantly median OS versus Investigator's choice (methotrexate, docetaxel or cetuximab monotherapy) in patients with R/M SCCHN whose disease had progressed within 6 months after platinum-based CT (HR 0.70; 97.73% CI, 0.51 to 0.96; p=0.01). The median progression-free survival was not significantly improved (HR 0.89; 95% CI, 0.70 to 1.13; p=0.32) and response rate with nivolumab was low (13.3% vs 5.8% in the standard-therapy arm). Treatment-related adverse events of Grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard-therapy arm (Ferris 2016).

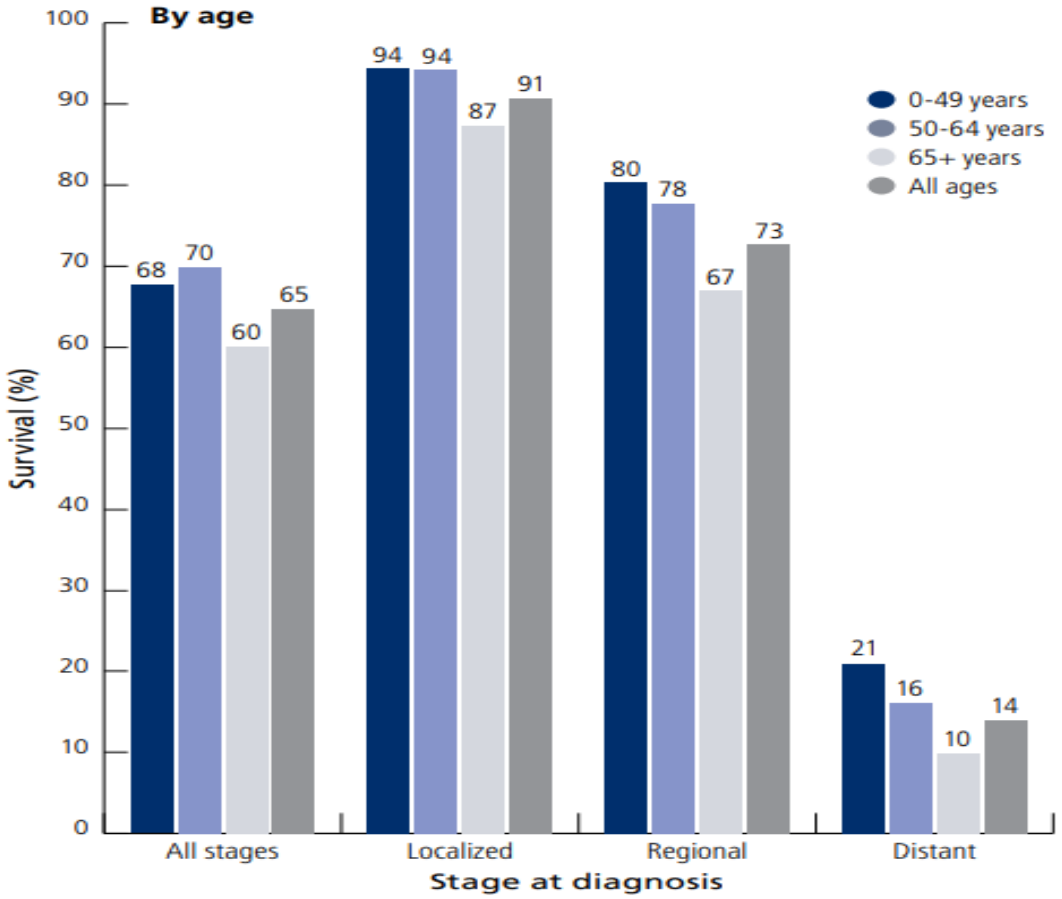
SI.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

SI.5.1 Natural History of the Indicated Condition in the CRC Population, Including Mortality and Morbidity

In population-based studies, 20% to 30% of patients diagnosed with localized or regional CRC will develop metastatic disease. The vast majority of patients (>80%) moving to metastatic stage, will do so within a 3-year period (Luo 2016, Elferink 2015, van Gestel 2014, Leporrier 2006). Histology is associated with both the risk of metastasis and poor prognosis: mucinous adenocarcinoma and signet ring cell carcinoma are associated with increased risk for metastasis and worsened prognosis (Hugen 2014).

Survival rates do not vary substantially by gender and are considered overall. Based on the US Surveillance Epidemiology and End Results (SEER) data, the 5-year relative survival rate for CRC has increased from 50% in the mid-1970s to 65% during 2012-2018. Furthermore, stage at diagnosis plays a vital role in predicting survival for example, the 5-year survival rate is highest for patients diagnosed with localized stage disease, but declines for those diagnosed with regional and distant stages, respectively. (see Figure 3) (American Cancer Society, "Colorectal cancer Facts and Figures 2023-2025").

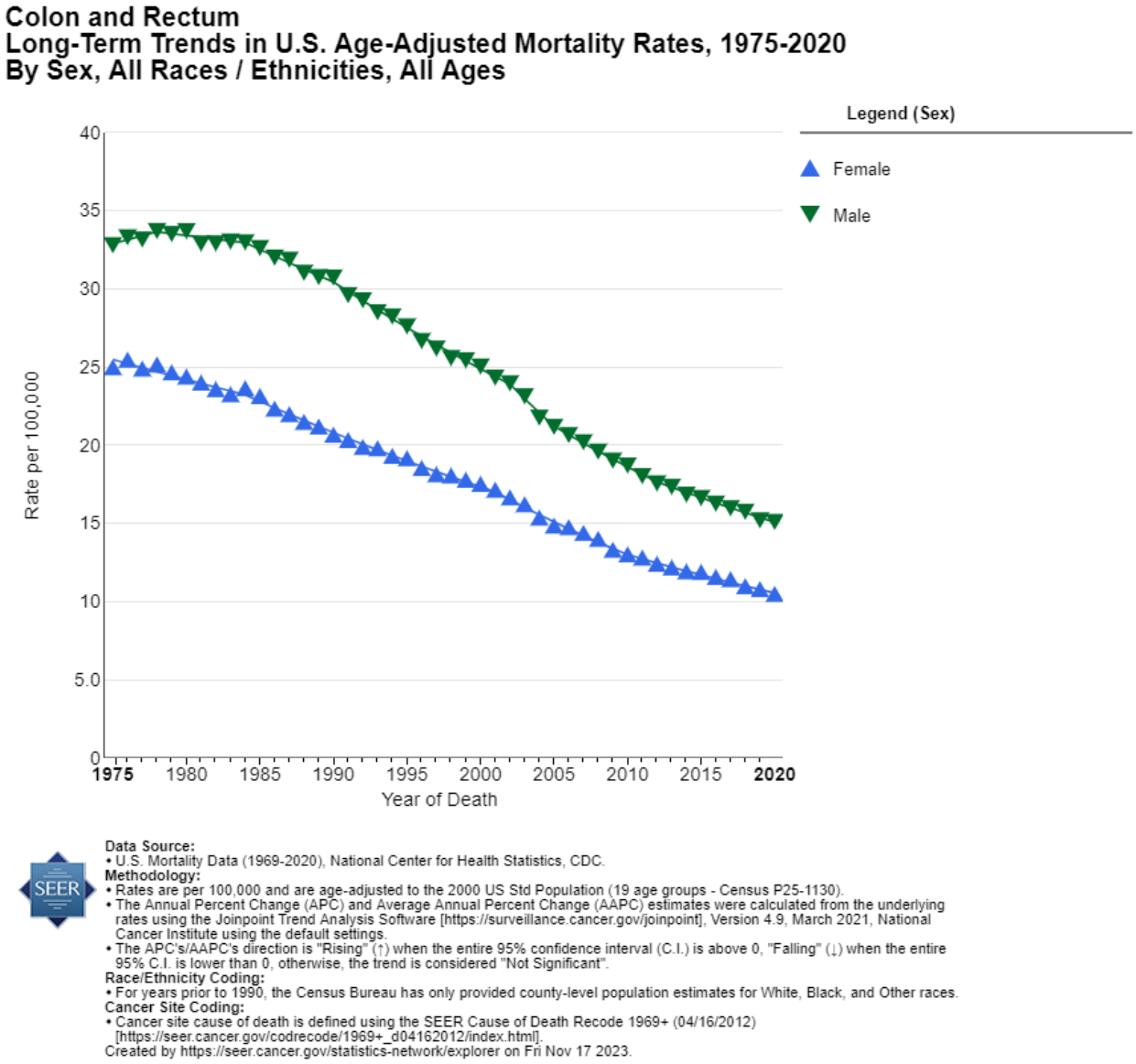
Figure 3 Colorectal Cancer 5-year Survival (%) by Age, 2012-2018, US



Source: Surveillance, Epidemiology, and End Results Program, 2022

From the same SEER data, there is a clear decline in CRC mortality and the death rate has dropped by 51% from its peak of 28.6 per 100,000 in 1976 to 14.1 per 100,000 in 2014. Recent mortality reductions are attributed to improvement of treatments, changing patterns in CRC risk factors and screening uptake (Siegel 2017a).

Figure 4 Long-Term Trend in CRC Mortality: United States, 1975-2020



Worldwide, in 2022, about 904,019 CRC deaths, both sexes, all ages were recorded, accounting for 9.4% of all cancer deaths (Ferlay 2024).

In Europe in 2022, CRC was the second most common cause-of-death from cancer; 538,262 new cases and 247,842 deaths, both sexes, respectively (Ferlay 2024).

SI.5.2 Natural History of the Indicated Condition in the SCCHN Population, Including Mortality and Morbidity

About one-thirds of patients with SCCHN present with early-stage disease, while a little less than half present with advanced disease commonly involving regional lymph nodes. Distant metastasis at initial presentation is uncommon, arising in 10% to 20% of patients (Siegel 2017b). Analysis of SEER data for the period 2018-2021 revealed that 1-yr and 3-yr OS were 84.0% and 68.9%, respectively. OS was significantly higher in Whites than Blacks. OS was highest for lip and oral cavity (3-yr OS: 72.2%), followed by larynx (65.3%), oropharynx (62.9%), and lowest for hypopharynx (39.3%). By AJCC8 stage, the 3-yr OS was 87.8%, 77.1%, 66.7%, and 53.1% for Stages 1, 2, 3, and 4, respectively (Ma 2025).

In Europe, the mean age-standardized 5-year relative survival rates for several primary sites of head and neck cancer are detailed in Table 6. 15-year relative survival for head and neck cancers was 30% for men and 40% for women. Five-year relative survival significantly improved over the period (2002-2013), the major increases for oropharyngeal epithelial tumors and for salivary type glands tumor of head and neck. Across European countries discrepancies remained, with poorer survival outcomes in Baltic and Eastern European countries (Gatta 2025).

Table 6 Head and Neck Cancer Epithelial Cancer Entities, Number of Cases, 5-year Relative Survival (in % Points) Overall and by Sex, Europe 2008-2013.

HNC epithelial cancer entities, number of cases, 5-year relative survival (in % points) overall and by sex, Europe 2008–2013.

	Male and Female				Male				Female			
	no cases	rel surv	lower and upper 95 % CI		no cases	rel surv	lower and upper 95 % CI		no cases	rel surv	lower and upper 95 % CI	
Squamous cell carcinoma with variants of nasal cavity and sinuses	6421	**52.7**	51.0	54.4	4207	**49.5**	47.4	51.6	2214	**58.8**	55.8	61.6
Lymphoepithelial carcinoma of nasal cavity and sinuses	53	**58.0**	40.2	72.2	34	**59.3**	36.9	76.1	19	**56.3**	26.2	78.2
Undifferentiated carcinoma of nasal cavity and sinuses	364	**31.7**	25.2	38.3	228	**31.1**	22.9	39.6	136	**32.8**	22.8	43.2
Intestinal type adenocarcinoma of nasal cavity and sinuses	251	**69.3**	59.8	77.0	231	**67.6**	57.6	75.7	20	**91.2**	34.8	99.2
Squamous cell carcinoma with variants of nasopharynx	6272	**52.4**	50.8	53.9	4594	**49.7**	47.8	51.6	1678	**59.5**	56.4	62.3
Papillary adenocarcinoma of nasopharynx[d]	14	**93.5**	18.4	99.7	-	n.e.	-	-	-	n.e.	-	-
Epithelial tumour of major salivary glands	16,320	**62.0**	60.9	63.0	9210	**54.8**	53.3	56.3	7110	**70.9**	69.4	72.4
Salivary gland type tumour of head and neck	7156	**71.7**	70.2	73.2	3891	**64.1**	61.9	66.2	3265	**80.7**	78.6	82.6
Squamous cell carcinoma with variants of hypopharynx	21,689	**27.4**	26.6	28.2	18,686	**26.7**	25.8	27.5	3003	**31.8**	29.7	33.9
Squamous cell carcinoma with variants of larynx	73,560	**61.0**	60.5	61.5	64,347	**60.8**	60.2	61.3	9213	**62.8**	61.4	64.1
Squamous cell carcinoma with variants of oral cavity	62,993	**50.5**	50.0	51.0	41,187	**47.7**	47.1	48.3	21,806	**55.9**	55.0	56.8
Squamous cell carcinoma with variants of oropharynx	63,696	**47.9**	47.4	48.4	49,163	**45.9**	45.3	46.4	14,533	**54.7**	53.6	55.7
Squamous cell carcinoma of oropharynx TRA[a]	39,102	**53.7**	53.1	54.4	30,018	**51.9**	51.1	52.6[a,b,c]	9084	**60.0**	58.7	61.4
Squamous cell carcinoma of oropharynx nTRA[b]	7516	**43.8**	42.3	45.3	5612	**42.4**	40.7	44.1	1904	**48.2**	45.2	51.2
Total Head & Neck epithelial cancers[c]	265,198	**51.9**	51.7	52.2	200,565	**49.9**	49.6	50.2	64,633	**58.2**	57.7	58.7

[a] Oropharyngeal Tonsil Related Areas: Localisation C019, C024, C090, C091, C099; Morphologies 8051–8052, 8070–8076, 8082–8084.
[b] Oropharyngeal non Tonsil Related Areas: Localisation: C051, C052, C102, C103 Morphologies 8051–8052, 8070–8076, 8082–8084.
[c] Total H&N epithelial cancers include also morphology codes 8000–8003.
[d] Small number of cases.

HNC=head and neck cancer

Due to the nature of several risk factors for SCCHN such as smoking or alcohol intake, , patients with these cancers face important risks of death from competing causes.

A study using SEER data found that cardiac disease (26.3%), chronic obstructive pulmonary disease (8.9%), and lung cancer (6.3%) accounted for the majority of the competing risks of death for SCCHN patients. Deaths due to secondary malignancies accounted for 11.7% of deaths in this

study. Compared to the general population, SCCHN patients' mortality rates from chronic obstructive pulmonary disease were 16 times higher, 10 times higher for cardiovascular disease and nearly 40 times higher for chronic liver disease, reflecting the impact of risk factors on the risk of death incurred by these patients (Massa 2017). Gatta (2025) also estimated the risk of dying from causes other than head and neck cancer, using cause-of-death data from of a selection of cancer registries. Head and neck cancer patients were 2.1 times more likely to die from other causes compared to the general population. The higher risk of death from non-head and neck cancer causes may be due to poorer overall health and greater levels of comorbidity associated with tobacco and alcohol use.

SI.6 Important Comorbidities

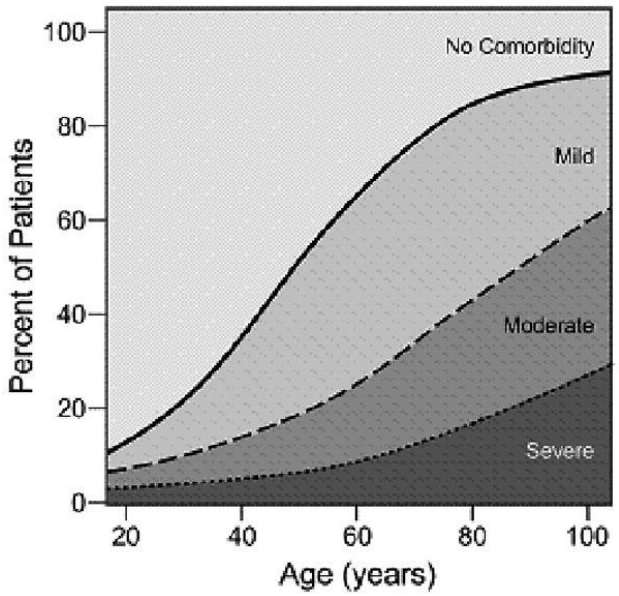
The patients with cancer can suffer from a number of comorbidities potentially leading to frequent administration of concomitant medications in these patients.

Other anticancer drugs are often used to treat the malignancy. Sedatives, antiemetics, antibiotics, analgesics, antihistamines, steroids, granulocyte-colony stimulating factor erythropoietin, or other medications as well as red blood cells, platelets or fresh frozen plasma transfusions may be given to assist in the management of pain, infection, and other complications of the malignancy and/or to manage toxicities related to oncologic treatment.

The importance of comorbidities is that they influence OS and frequently influence treatment options for individual patients. With increasing age, the number of comorbid illnesses increases. In a study of 7,600 patients older than 55 years with cancer, those aged 55 to 64 years had an average of 2.9 comorbid conditions compared with patients aged ≥75 years, who had an average of 4.2 comorbid conditions (Yancik 1997).

A prospective study conducted between 1998 and 2003 in 8 US cancer care facilities on a cohort of patients with newly diagnosed cancer aimed to describe the prevalence and severity of individual comorbid ailments across age groups of patients with cancer using the Adult Comorbidity Evaluation-27 item (ACE-27; scale reporting on 27 different comorbid ailments, each graded into a 3-category severity system) index (Piccirillo 2008). The study included 23,650 patients with newly diagnosed cancer, including 10.0% of CRC patients and 5.5% of oral cavity/larynx cancer patients. In this cohort, 11% of the population had a severe level of comorbidity, and 54% had either mild or moderate level of comorbidity. The overall comorbidity score severity increased with age (Figure 5) as did the average number of conditions per patient: from 0.7 in the youngest age group (18-53 years) to 1.8 in the oldest (≥74 years). The different comorbid ailments showed different prevalence patterns across the age spectrum (Table 7).

Figure 5 **Prevalence of Overall Comorbidity by Severity (Assessed by ACE-27) Across the Age Spectrum for Patients with Newly Diagnosed Cancer in Cancer Care Facilities in the US**



ACE-27: Adult Comorbidity Evaluation 27 (scale reporting on 27 different comorbid ailments, each graded into a 3-category severity system) Source: Piccirillo 2008
ACE=adult comorbidity evaluation

Table 7 **Prevalence of the 10 most Frequent Comorbid Ailments Across Various Age Groups in Patients with Newly Diagnosed Cancer in Cancer Care Facilities in the US**

Comorbid Ailment	18-53 years N (%)	54-64 years N (%)	65-73 years N (%)	≥74 years N (%)
Hypertension	1,349 (18.9)	2,588 (35.2)	2,959 (44.3)	2,946 (46.4)
Previous Solid Tumor(s)	438 (6.1)	659 (9.0)	939 (14.1)	1,284 (20.2)
Angina/ Artery Disease	148 (2.1)	560 (7.6)	924 (13.8)	1,129 (17.8)
Respiratory Disease	429 (6.0)	758 (10.3)	996 (14.9)	1,075 (16.9)
Diabetes Mellitus	403 (5.7)	824 (11.2)	1,033 (15.5)	958 (15.1)
Arrhythmias	69 (1.0)	204 (2.8)	363 (5.4)	760 (12.0)
Myocardial Infarct	113 (1.6)	346 (4.7)	524 (7.8)	673 (10.6)
Stroke	54 (0.8)	162 (2.2)	277 (4.1)	502 (7.9)
Congestive Heart Failure	54 (0.8)	150 (2.0)	200 (3.0)	487 (7.7)
Gastrointestinal Disease	171 (2.4)	256 (3.5)	299 (4.5)	348 (5.5)

Source: Piccirillo 2008

Regarding prognosis, studies show that the severity of comorbidities affects OS in a dose-dependent fashion, independent of cancer stage (Pal 2010). Observational studies of patients with colon cancer have reported 1.2- to 4.8-fold higher 5-year mortality for patients with

comorbidity versus without comorbidity. The negative impact of comorbidities in cancer survival may be due to the comorbidity itself, the impact of the comorbidity on cancer detection, choice of treatment and adherence, or a higher rate of treatment-related complications, such as infections and cardiovascular events (Janssen-Heijnen 2005, Søgaard 2013).

SI.6.1 Important Comorbidities in CRC Patients

Several etiological factors for the development of CRC can translate into prevalent comorbidities for patients with such cancer. Most notably, IBD, diabetes mellitus and alcohol appear to play a significant role in CRC (Yashiro 2014, Luo 2016, Botteri 2008, Qiu 2023). Consequently, diabetes mellitus, IBD, impaired liver function, malnutrition and other complications as a consequence of extensive alcohol consumption are comorbidities to consider.

CRC also predominantly occurs in older patients. Thus, diseases typical for this age group, such as cardiovascular and cerebrovascular illnesses are among the most relevant comorbidities. A study in the UK reported that the total number of comorbid conditions in CRC patients increased sharply with age (Mounce 2017). A study in the US based on the SEER data linked to Medicare described the comorbidity burden of people living with any cancer, CRC or free of cancer among those aged 66 years or more (Edwards 2014). Among the selected comorbidities, the most frequent in CRC patients were diabetes, chronic obstructive pulmonary disease, congestive heart failure and cerebrovascular disease (Table 10). Compared with people without cancer, patients with CRC had a higher overall prevalence of comorbid conditions (at least 1 or 2 or more).

Table 8 Comorbidities in Early and Advanced Stages of CRC in Females, Older Than Age 50 Years

1a Females – Early stages		1b Females – Advanced stages	
Comorbidities	**Prevalence**	**Comorbidities**	**Prevalence**
Essential hypertension	0.63	Essential hypertension	0.60
Anemia	0.33	Hyperlipidemia	0.41
Hyperlipidemia	0.32	Personal history of tobacco use	0.38
History of malignant Neo of large bowel	0.30	History of malignant Neo of large bowel	0.33
Urinary tract infection	0.26	Anemia	0.33
Hypopotassemia	0.24	Diabetes mellitus Type 2	0.27
Diabetes mellitus Type 2	0.23	Coronary atherosclerosis	0.26
Esophageal reflux	0.22	Paralytic ileus	0.23

Source: Ljubic 2020
CRC=colorectal cancer

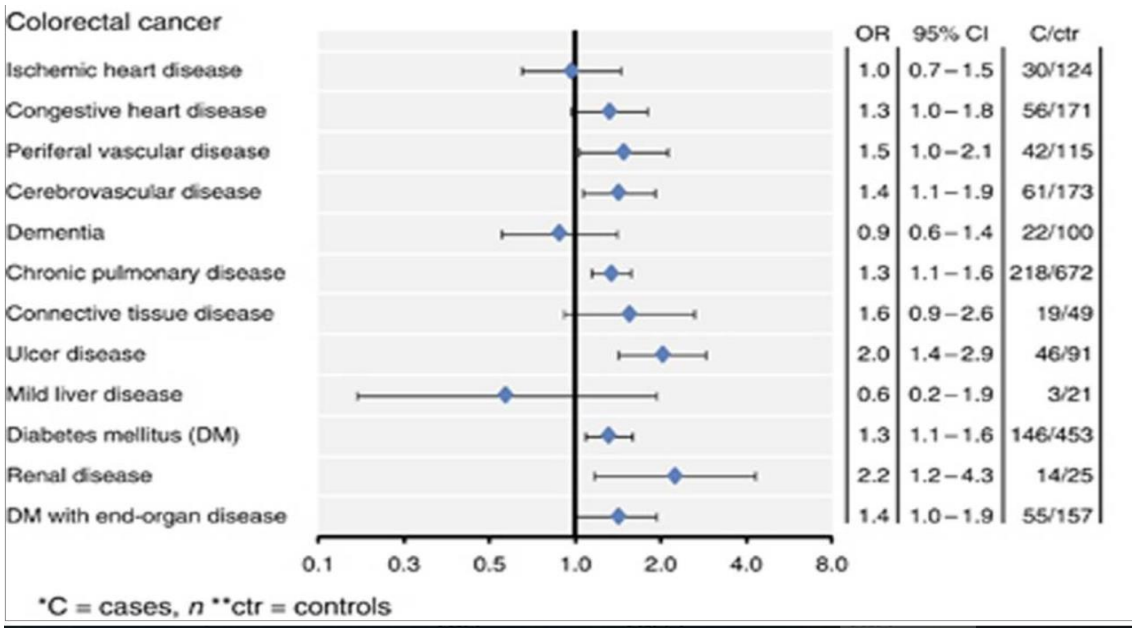
Table 9 Comorbidities in Early and Advanced Stages of CRC in Males, Older Than Age 50 Years

2a Males – Early stages		2b Males – Advanced stages	
Comorbidities	**Prevalence**	**Comorbidities**	**Prevalence**
Essential hypertension	0.60	Essential hypertension	0.58
Anemia	0.34	History of malignant Neo of large bowel	0.38
History of malignant Neo of large bowel	0.31	Anemia	0.37
Personal history of tobacco use	0.30	Hyperlipidemia	0.33
Hyperlipidemia	0.29	Personal history of tobacco use	0.32
Pneumonia	0.26	Diabetes mellitus Type 2	0.25
Diabetes mellitus Type 2	0.24	Acute kidney failure	0.25
Paralytic ileus	0.24	Dehydration	0.25

Source: Ljubic 2020
CRC=colorectal cancer

A study based on Danish population registers reported on the increased risk of selected comorbidities for CRC patients aged 70 years or more compared to controls (matched on age and gender, free of cancer). There was an increased risk for cerebrovascular disease (odds ratio of 1.4), chronic pulmonary disease (odds ratio of 1.3), ulcer disease (odds ratio of 2.0), diabetes mellitus (odds ratio of 1.3) and renal disease (odds ratio of 2.2) (Jørgensen 2012). See Figure 6.

Figure 6 Odds Ratios of the Prevalence of Charlson Comorbidity Score Items of CRC Cases and Matched Controls in Danish Patients Aged 70 Years or More



Source: Jørgensen 2012
C=cases; ctr=control; CRC=colorectal cancer; OR=odds ratio.

Another population-based study examined in more details the comorbidities in patients suffering from CRC and reported that cardiovascular diseases, hypertension and previously diagnosed cancers were the most common chronic diseases associated to this type of cancer in patients of all ages considered (de Marco 2000).

Below the age of 70 years, 37% of male and 59% of female diagnosed with CRC did not suffer from any serious comorbid condition. In contrast, only 27% of male and 34% of female patients aged 70 years and older who were diagnosed with CRC were without serious comorbid conditions (de Marco 2000). In line with that, a recent population-based study among patients aging 66 or more identified in SEER-Medicare database, reported that 40% of patients had no recorded comorbid conditions at the time of diagnosis (Noone 2025). Among the CRC patients with comorbidities, the most prevalent comorbidities were diabetes (29%), chronic obstructive pulmonary disease (COPD) (19%), Congestive heart failure (15%), and peripheral vascular disease (15%).

Table 10 Prevalence of Comorbidity in % Patients Diagnosed with CRC (Modified From de Marco 2000 and Noone 2025)

Comorbidity	De Marco (2000)			Noone (2025)	
	Male		Female	Both Sexes	
	Age (years)		Age (years)	Age (years)	
	<70	≥70	<70	≥70	>66
None	37.2	26.5	59.0	33.9	40
Previous cancers	9.7	23.2	8.9	16.9	NR
Cardiovascular	14.6	26.5	5.1	16.9	30% (Congestive heart failure 15% + peripheral vascular disease 15%)
Hypertension	10.9	11.8	11.0	12.8	NR
Chronic obstructive pulmonary disease	6.2	15.6	3.6	8.0	19
Diabetes	8.7	9.1	4.3	13.8	29
Cerebrovascular	2.2	6.6	1.2	5.0	10
Other	4.2	9.9	3.5	8.0	NR
Unknown	11.4	7.0	9.7	7.4	NR

CRC=colorectal cancer; NR=Not Reported

In a prospective, observational study in China, Qiu (2023) found that 75.5% of patients (22,369/29,610) had at least 1 comorbidity. The most prevalent comorbidities were hypertension (8,581/29,610, 29.0%; 95% CI 28.5%-29.5%), hyperplasia of the prostate (3,816/17,426 [male participants], 21.9%; 95% CI 21.3%-22.5%), and COPD; 4,199/29,610, 14.2%; 95% CI 13.8%-14.6%). The prevalence of single comorbidities was different in each subgroup in most cases. Comorbidities were closely associated, with disorders of lipoprotein metabolism and hyperplasia of the prostate mediating correlations between other comorbidities. Males and females shared 58.3% (141/242) of disease pairs, whereas male-female disparities occurred primarily in diseases coexisting with COPD, cerebrovascular diseases, atherosclerosis, heart failure, or renal failure

among males and with osteoporosis or gonarthrosis among females. Urban patients generally had more comorbidities with higher prevalence and more complex disease coexistence relationships, whereas rural patients were more likely to have coexisting severe diseases, such as heart failure comorbid with the sequelae of cerebrovascular disease or COPD.

SI.6.2 Important Comorbidities in SCCHN Patients

SCCHN is primarily caused by smoking, alcohol and HPV infection. Besides having a carcinogenic effect, smoking also leads to other diseases and thus, contributes to a high prevalence of comorbidities among patients with SCCHN. Most studies demonstrate that approximately 60% of patients with head and neck cancer have concurrent illnesses, and 20% carry a severe comorbid burden, and the prevalence can be higher in elderly patients. In a study of comorbidity in 180 patients with laryngeal cancer, the cardiovascular and respiratory systems were the most frequent body systems affected. Over 25% of patients had comorbid illnesses in more than 1 body system (Paleri 2010). A systematic literature review aiming to describe comorbidities and their impact on prognosis in patients with head and neck cancer report the prevalence rates of comorbid ailments from different studies, that are summarized in Table 11.

Table 11 Prevalence of Comorbidity in Patients With Head and Neck Cancer.

Country	Patients	Index	Comorbidity prevalence (%)	Prevalence of moderate/severe comorbidity (%)
USA	70 (<45 years)	ACE 27	-	30
Brazil	110 (oral cavity only)	CI	53.6	8.2
UK	182 (larynx only)	ACE27	64.5	55.1
Brazil	530 (oral cavity and oropharynx)	CI	39.1	-
USA	1,086	ACE 27	53.9	24.1
Finland	221	CI	48.4	48.4
Brazil	90 (larynx only)	ACE27	88.9	16.7
		CI	65.6	18.9
Brazil	310 (>70 years)	ACE 27	75	29.4
The Netherlands	1,282	ACE 27	36.4	19

Source: Paleri 2010
ACE 27=Adult Comorbidity Evaluation 27 (scale reporting on 27 different comorbid ailments, each graded into a 3-category severity system); CI=Charlson index; UK=United Kingdom; USA=United States of America

A Danish study also showed that comorbidities have a negative prognostic impact on OS (Boje 2013). In this study, comorbidity was present in 36% of the patients, the most common vascular, pulmonary and metabolic diseases. The study showed that survival significantly decreased with increasing level of comorbidity. In patients without comorbidities, 50% were alive after 5-years, whereas only 33% of patients with severe comorbidity were alive.

A second primary cancer can also develop in these patients, the most common places being head and neck, lung, and esophagus, all of which related to smoking (Hall 2000).

Part II: Module SII - Nonclinical Part of the Safety Specification

SII.1 Key Safety Findings (from Nonclinical Studies)

The potential systemic toxicity of intravenously administered cetuximab was investigated in mice, rats and Cynomolgus monkeys. These studies comprised single dose toxicity testing in mice and rats, and repeat-dose toxicity testing in rats (up to 28 days) and Cynomolgus monkeys (39 weeks).

The genotoxic potential of cetuximab has been investigated both in vitro and in vivo. The in vitro study was an Ames test using *Salmonella typhimurium* and *Escherichia coli* as test strains. The in vivo test was a rat micronucleus test involving single iv injection of cetuximab.

In order to determine the potential reproductive toxicity of cetuximab, effects of cetuximab on male and female fertility were investigated within the chronic repeat-dose toxicity study by vaginal cytology in female and evaluation of testosterone data and sperm analysis in male Cynomolgus monkeys as well as by histopathology of the sexual organs. Furthermore, a dedicated study on embryo-fetal development was performed in Cynomolgus monkeys.

Local tolerance testing of cetuximab drug product has been performed in rabbits.

Supporting data came from evaluation of toxicokinetic and immunogenicity parameters in repeat-dose studies in rats and monkeys. Investigations on immunoreactivity in mouse, rat, dog, primate and goat tissues guided the selection of relevant species for nonclinical safety testing. Moreover, limited safety relevant data can be deduced from 2 comparative single dose pharmacokinetic studies in Cynomolgus monkeys.

Safety pharmacology parameters relevant for cardiovascular and respiratory functions were evaluated within the chronic repeat-dose toxicity study in Cynomolgus monkeys as well as in a separate safety pharmacology study with single administration of cetuximab to anesthetized male Cynomolgus monkeys.

Table 12 Key Safety Findings from Cetuximab Nonclinical Studies

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
• Dose-dependent skin alterations, starting at dose levels equivalent to those used in humans, were the major findings observed in toxicity studies with Cynomolgus monkeys.	• Also in the clinical context, main adverse reactions of cetuximab are skin reactions.
• Skin alterations in primates caused secondary bacterial superinfections with subsequent involvement of inner organs due to septicemia.	• The risk for secondary infections (mainly bacterial) is also valid for the human usage and has been found to be increased under cetuximab treatment. Superinfections of skin lesions and subsequent complications are an identified risk.

Key Safety findings (from nonclinical studies)	Relevance to human usage
• Diarrhea respectively liquid or soft feces were observed in primates treated with cetuximab within repeat-dose toxicity, embryo-fetal toxicity and pharmacokinetic studies at all dose groups with incidences in the majority of cases not significantly differing from those observed in controls respectively in the predose phase.	• In humans, diarrhea is a common undesirable effect of cetuximab.
• Primates treated chronically with high doses of cetuximab essentially showed increases in serum enzymes (gamma-glutamyl transferase [GGT], glutamate dehydrogenase, alanine aminotransferase [ALT]) and globulin levels and decreases in albumin and albumin/globulin ratio (A/G ratio). The changes observed for GGT, albumin, A/G ratio and globulin were observed in the intermediate and low dose groups as well and showed in the majority of cases a dose-dependency.	• Increased liver enzyme levels (AST, ALT, ALP) have been observed as very common undesirable effects in humans treated with cetuximab.
• The embryo-fetal development study in Cynomolgus monkeys revealed no signs of teratogenicity. However, dependent on the dose, an increased incidence of abortions was observed. • Nonclinical data on genotoxicity and local tolerance, including accidental administration by routes other than the intended iv infusion, revealed no special hazard for humans.	• It is strongly recommended that cetuximab is only be given during pregnancy or to any woman not employing adequate contraception, if the potential benefit for the mother justifies a potential risk to the fetus.
Safety pharmacology	
• Safety pharmacological evaluations of cardiovascular and respiratory parameters in Cynomolgus monkeys yielded no concerns. • Clinical observations within the chronic repeat-dose toxicity study in Cynomolgus monkeys revealed no findings indicative of cetuximab-related CNS effects.	No signal of concern for human use.
Mechanisms for drug interactions	
• A formal clinical interaction study showed that the pharmacokinetic characteristics of cetuximab remain unaltered after coadministration of a single dose of irinotecan (350 mg/m^2 body surface area). Similarly, the pharmacokinetics of irinotecan were unchanged when cetuximab was coadministered. • No other formal interaction studies with cetuximab have been performed in humans.	No signal of concern for human use.

ALT=alanine transaminase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; CNS=central nervous system; GGT=gamma-glutamyl transferase

No nonclinical safety data have been established in juvenile animals. Clinically, no new safety signals were identified in pediatric patients as reported from a Phase 1 study.

No formal animal studies have been performed to establish the carcinogenic potential of cetuximab. However, the results of the genotoxicity assays and the chronic repeat-dose toxicity study raised no concerns regarding carcinogenicity.

No formal animal studies have been performed to determine the effects of cetuximab on male and female fertility. Limited data from the chronic repeat-dose toxicity study suggest a tendency for an impairment of menstrual cyclicity in cetuximab-treated female monkeys, whereas evaluation of testosterone data and sperm analysis did not show any toxicologically significant differences among the males in cetuximab-treated groups when compared to controls.

Toxicity studies with coadministration of cetuximab and chemotherapeutic agents have not been conducted. However, a formal clinical interaction study has been performed to investigate the potential for pharmacokinetic interactions between cetuximab and irinotecan (refer to study EMR 62202-012 included in the initial CRC submission). This study showed that the pharmacokinetic characteristics of cetuximab remains unaltered after coadministration of a single dose of irinotecan. Similarly, the pharmacokinetics of irinotecan was unchanged when cetuximab was coadministered.

In preclinical wound healing models with EGFR, selective tyrosine kinase inhibitors were shown to retard wound healing. No nonclinical data on the effect of cetuximab on wound healing are available to date. However, clinical safety data that have been reviewed so far did not reveal any reasonable suspicion that cetuximab may promote impaired wound healing.

In conclusion, based on the available nonclinical safety information and considering the target indications of cetuximab in life-threatening diseases, the target patient population and the extensive clinical safety data available from several randomized, controlled Phase 3 studies, no need for further collection of nonclinical safety data is presently identified.

Part II: Module SIII - Clinical Trial Exposure

Cetuximab has been investigated in the following indications: mCRC, LA SCCHN, R/M SCCHN and Non-Small Cell Lung Cancer (NSCLC). The development program comprised 10 randomized controlled studies, 4 in mCRC (CO17 NCT00079066, NCT00063141, NCT00154102, NCT125034), 2 in SCCHN (NCT00122460, EMR 62202006) and 4 in NSCLC (EMR 62202-11, NCT00148798, NCT00112294, NCT00112346) with a total of 6,193 patients (3,102 patients exposed to cetuximab).

Further, patients have been enrolled in other clinical trials conducted by the Marketing Authorization Holder (MAH) or by cooperative groups and Investigator-sponsors, in approved and nonapproved indications.

Cumulative data have been calculated until 30 September 2025 and include patients from completed trials (safety population as described in Clinical Study Reports) and ongoing trials (based on recruitment status as provided by the license partners Bristol-Myers Squibb [BMS] [until 31 January 2016] and Eli Lilly and Company [Lilly] and the Merck Healthcare KGaA [Merck] clinical trial database) as follows:

- **From 2003-2012 (Periodic Safety Update Report [PSUR] 1-11):** Patients in interventional clinical studies from the cetuximab project by BMS, Lilly or Merck from the start of PSUR 1 period onwards (IBD) and from Merck-sponsored studies from non cetuximab projects in which cetuximab is an investigational drug from 01 October 2010 [start of cetuximab Development Safety Update Report (DSUR) 2011] onwards.
- **Since 2013 (Periodic Benefit-Risk Evaluation Report [PBRER] 2013-2025):** Patients in interventional clinical studies in the cetuximab project by BMS, Lilly or Merck from the developmental international birth date of cetuximab onwards, patients in interventional Merck-sponsored studies from non cetuximab projects in which cetuximab is an investigational drug from 01 October 2010 (start of cetuximab DSUR 2011) onwards and patients in interventional BMS- and Lilly-sponsored studies from non cetuximab projects in which cetuximab is an investigational drug ongoing or completed from the reporting period of PBRER 2013 onwards. Patients in BMS interventional clinical studies in the cetuximab project, and patients in interventional BMS-sponsored studies from non cetuximab projects in which cetuximab is an investigational drug, were included until 31 January 2016.

Between 01 December 2003 (international birth date) and 30 September 2025 (data lock point [DLP] of this Risk Management Plan [RMP]), the cumulative number of patients exposed to cetuximab in clinical studies, irrespective of the treatment indication, was estimated to be about 12,259.

The estimated cumulative subject exposure until 30 September 2025, based upon actual exposure data from ongoing and completed clinical trials by indication is provided in the Table 13 below.

Table 13 Estimated Cumulative Subject Exposure from Ongoing and Completed Clinical Trials Sponsored by Merck, Lilly or Former License Partners by Indication Until 30 Sep 2025

Treatment	Number of subjects			
	CRC	SCCHN	Other indications	All indications
Medicinal Product	5,994	2,076	4,189	12,259
Comparator	1,968	755	1,954	4,677

CRC=colorectal cancer; SCCHN=squamous cell carcinoma of head and neck

Additional patients have been exposed to cetuximab during clinical trials sponsored by investigators, but the exact number of such patients is not available to Merck.

Exposure data and demographics (gender, age) by indication are presented for the target indication studies that were the basis for the marketing authorization approval in CRC and SCCHN.

CRC

- Initial CRC submission (uncontrolled studies)
- CRC indication enlargement (randomized controlled studies)

SCCHN

- Initial SCCHN submission
- LA SCCHN (randomized controlled study)
- R/M SCCHN (uncontrolled study)
- R/M SCCHN (controlled study)

SIII.1 Duration of Exposure

Indication CRC

Table 14 Duration of Exposure to Cetuximab in Pivotal Studies Included in the Initial CRC Submission*

Characteristic	Statistic	Pooled combination therapy (N=350)	Pooled monotherapy (N=172)
Duration of treatment, weeks			
≤6 weeks	% patients	31.1	46.5
>6 to 12 weeks	% patients	16.3	18.6
>12 to 18 weeks	% patients	12.3	10.5
>18 to 24 weeks	% patients	10.0	8.7
>24 weeks	% patients	30.3	15.7

CRC=colorectal cancer
* EMR 62202-007, IMCL CP02-9923, IMCL CP02-0141; Erbitux: CTD 2.7.4.1.2, 2.7.4.1.3

Table 15 Duration of Exposure to Cetuximab in Pivotal Studies Included in the CRC Indication Enlargement Application*

Characteristic	Statistic	CA225025 N=288 (+ BSC)	CA225006 N=638 (+irinotecan)	EMR 62 202-013 N=600 (+FOLFIRI)	EMR 62202-47 N=170 (+FOLFOX)
Duration of treatment, weeks	Median	8.0	14.0	25.0	24.0
	Range	1 to 60	1 to 98	1 to 159	1 to 644

BSC=best supportive care; CRC=colorectal cancer
* Erbitux: CTD 2.5.5.3 CRC2, 5.3.5.1.4-CRC2, 2.7.4 CRC2A-6, 5.3.5.1.6-CRC2 Table 14.1.8, 14.3.0-7

Indication SCCHN

Table 16 LA SCCHN: Duration of Exposure to Cetuximab in the Pivotal Study Included in the Initial SCCHN Submission (EMR 62202-006)*

Characteristic	Statistic	RT + cetuximab (N=208)
No. of infusions per patient	Median	8.0
	Q1 – Q3**	8.0 -8.0
≤6 infusions	% patients	9.1
≥7 to 12 infusions	% patients	90.9
>12 infusions	% patients	0
Duration of treatment, weeks	Median	8.0
	Q1 – Q3	7.7 - 8.0

LA=locally advanced; RT=radiotherapy; SCCHN=squamous cell carcinoma of head and neck

* Erbitux: CTD 2.7.4.1.2A HN1, 2.7.4.1.3A HN1

** Q1 – Q3: lower quartile – upper quartile

Table 17 R/M SCCHN: Duration of Exposure to Cetuximab, in the Pivotal Study Included in the Initial SCCHN Submission (EMR 62202-016)*

Characteristic	Statistic	Monotherapy (N=103)
No. of infusions per patient	Median	11.0
	Q1 – Q3**	6.0-19.0
≤6 infusions	% patients	33.0
7 to 12 infusions	% patients	22.3
13 to 18 infusions	% patients	19.4
19 to 24 infusions	% patients	9.7
25 to 30 infusions	% patients	7.8
>30 infusions	% patients	7.8
Duration of treatment, weeks	Median	11.0
	Q1 – Q3	6.0-19.9

R/M=recurrent and/or metastatic; SCCHN=squamous cell carcinoma of head and neck

* Erbitux: CTD 2.7.4.1.2B HN1, 2.7.4.1.3B HN1

** Q1 – Q3: lower quartile – upper quartile

Table 18 Duration of Exposure to Cetuximab in the Pivotal Study Included in the SCCHN Indication Enlargement Application (EMR 62202-002)*

Characteristic	Statistic	Cetuximab N=219
Number of infusions, No. subjects (%)		
1-20	% patients	61.6
21-30	% patients	20.1
31-50	% patients	11.9
>50	% patients	6.4
Duration of treatment, weeks	Median (Range)	17 (1-89)
	Median (Q1 – Q3)**	18 (8–29)

SCCHN=squamous cell carcinoma of head and neck
* Erbitux: CTD 2.7.4.1.2.3 HN2
** Q1 – Q3: lower quartile – upper quartile

SIII.2 Exposure by Gender and Age

Indication CRC

Table 19 Summary of Exposure to Cetuximab by Gender and Age; in Pivotal Studies Included in the Initial CRC Submission*

Characteristic	Statistic	Pooled combination therapy (N=350)	Pooled monotherapy (N=172)
Gender			
Male	% patients	61.1	59.3
Female	% patients	38.9	40.7
Age (years)			
	Median	59.0	58.0
	Range	26-83	28-84
<65	% patients	66.0	72.7
≥65	% patients	34.0	27.3

CRC=colorectal cancer
* EMR 62202-007, IMCL CP02-9923, IMCL CP02-0141; Erbitux: CTD 2.7.4.1.2, 2.7.4.1.3

Table 20 Gender and Age in Pivotal Studies Included in the CRC Indication Enlargement*

Characteristic	Statistic	CA225025 N=288 (+ BSC)	CA225006 N=638 (+irinotecan)	EMR 62 202-013 N=600 (+FOLFIRI)	EMR 62202-47 N=170 (+FOLFOX)
Gender					
Male	% patients	64.8	62.5	61.6	52.7
Female	% patients	35.2	37.5	38.4	47.3

Characteristic	Statistic	CA225025 N=288 (+ BSC)	CA225006 N=638 (+irinotecan)	EMR 62 202-013 N=600 (+FOLFIRI)	EMR 62202-47 N=170 (+FOLFOX)
Age (years)					
	Median	63.0	61.0	61.0	62.0
	Range	29-88	23-85	22-82	24-82
<65	% patients	61.7	60.6	62.4	56.8
≥65	% patients	38.3	39.4	37.4	43.2

BSC=Best Supportive Care; CRC=colorectal cancer

* Erbitux: CTD 2.5.5.3 CRC2, 5.3.5.1.4-CRC2, 2.7.4 CRC2A-6, 5.3.5.1.6-CRC2 Table 14.1.8, 14.3.0-7

Indication SCCHN

Table 21 LA SCCHN: Gender and Age in the Pivotal Study Included in the Initial SCCHN Submission (EMR 62202-006)*

Characteristic	Statistic	RT + cetuximab (N=208)
Gender		
Male	% patients	79.2
Female	% patients	20.8
Age (years)		
	Median (Range)	57.5 (35-83)
<65	% patients	69.8
≥65	% patients	26.2

LA=locally advanced; SCCHN=squamous cell carcinoma of head and neck

* Erbitux: CTD 2.7.4.1.2A HN1, 2.7.4.1.3A HN1

Table 22 R/M SCCHN: Gender and Age in the Pivotal Study Included in the Initial SCCHN Submission (EMR 62202-016)*

Characteristic	Statistic	Monotherapy (N=103)
Gender		
Male	% patients	81.6
Female	% patients	18.4
Age (years)		
	Median (Range)	57.0 (23-77)
<65	% patients	76.7
≥65	% patients	23.3

R/M=recurrent and/or metastatic; SCCHN=squamous cell carcinoma of head and neck

* Erbitux: CTD 2.7.4.1.2B HN1, 2.7.4.1.3B HN1

Table 23 Gender and Age in the Pivotal Study Included in the SCCHN Indication Enlargement Application (EMR 62202-002)*

Characteristic	Statistic	Cetuximab N=219
Gender		
Male	% patients	88.6
Female	% patients	11.4
Age (years)		
	Median (Range)	56 (37-80)
<65	% patients	82.6
≥65	% patients	17.4

SCCHN=squamous cell carcinoma of head and neck

* Erbitux: CTD 2.7.4.1.2.3 HN2

SIII.3 Dose

Indication CRC

Table 24 Dose of Cetuximab in Pivotal Studies Included in the Initial CRC Submission*

Characteristic	Statistic	Pooled combination therapy (N=350)	Pooled monotherapy (N=172)
Cumulative dose, mg/m²	Median	3,255.8	1,839.3
	Range	7.1-20,575.0	3.5-15,882.7
Dose intensity, mg/m²/week	Median	238.90	243.56
	Range	126.2-264.7	140.6-268.4
Relative dose intensity ≥80%	% patients	86.3	86.6

CRC=colorectal cancer

* EMR 62202-007, IMCL CP02-9923, IMCL CP02-0141; Erbitux: CTD 2.7.4.1.2, 2.7.4.1.3

Table 25 Dose of Cetuximab in Pivotal Studies Included in the CRC Indication Enlargement Application*

Characteristic	Statistic	CA225025 N=288 (+ BSC)	CA225006 N=638 (+irinotecan)	EMR 62 202-013 N=600 (+FOLFIRI)	EMR 62202-47 N=170 (+FOLFOX)
Cumulative dose per subject, mg/m²	Median	2,156	3,170	5,912	5,412
	Range	391 to 15,216	3 to 22,086	8 to 39,243	5 to 15,890
Dose intensity per subject, mg/m²/week	Median	247	234	234	225
	Range	117 to 283	67 to 293	59 to 381	67 to 262
Subjects with ≥80% of planned dose intensity	% patients	86.5	77.7	81.0	83.8

BSC=Best Supportive Care; CRC=colorectal cancer

* Erbitux: CTD 2.5.5.3 CRC2, 5.3.5.1.4-CRC2, 2.7.4 CRC2A-6, 5.3.5.1.6-CRC2 Table 14.1.8, 14.3.0-7

Indication SCCHN

Table 26 LA SCCHN: Dose of Cetuximab in the Pivotal Study Included in the Initial SCCHN Submission (EMR 62202-006)*

Characteristic	Statistic	RT + cetuximab (N=208)
Cumulative dose, mg/m²	Median	2,163.7
	Q1 – Q3**	1,987.7 – 2,198.6
Dose intensity, mg/m²/week	Median	251.1
	Q1 – Q3**	247.0 - 254.8
Relative dose intensity ≥80%	% patients	90.4

LA=locally advanced; SCCHN=squamous cell carcinoma of head and neck
* Erbitux: CTD 2.7.4.1.2A HN1, 2.7.4.1.3A HN1
** Q1 – Q3: lower quartile – upper quartile

Table 27 R/M SCCHN: Dose of Cetuximab in the Pivotal Study Included in the Initial SCCHN Submission (EMR 62202-016)*

Characteristic	Statistic	Monotherapy (N=103)
Cumulative dose, mg/m²	Median	2,904.2
	Q1 – Q3**	1,653.6-4,690.4
Dose intensity, mg/m²/week	Median	249.6
	Q1 – Q3**	243.1-251.1
Relative dose intensity ≥80%	% patients	94.1
Gender		
Male	% patients	81.6
Female	% patients	18.4
Age (years)		
	Median (Range)	57.0 (23-77)
<65	% patients	76.7
≥65	% patients	23.3

R/M=recurrent and/or metastatic; SCCHN=squamous cell carcinoma of head and neck
* Erbitux: CTD 2.7.4.1.2B HN1, 2.7.4.1.3B HN1
** Q1 – Q3: lower quartile – upper quartile

Table 28 Dose of Cetuximab in the Pivotal Study Included in the SCCHN Indication Enlargement Application (EMR 62202-002)*

Characteristic	Statistic	Cetuximab N=219
Cumulative dose, mg/m²	Median (Range)	4,139 (2,077–7,053)
Dose intensity, mg/m²/week	Median (Range)	241(225–249)
Relative dose intensity, ≥80%	% patients	89.8

SCCHN=squamous cell carcinoma of head and neck
* Erbitux: CTD 2.7.4.1.2.3 HN2

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 29 Exclusion Criteria in the Pivotal Clinical Studies Across the Development Program

Exclusion criterion	Reason for exclusion	Missing information Yes/No (if no rationale)
Administrative and ethical exclusion criteria and general precautionary exclusion criteria to minimize potential risks such as evidence of brain metastasis, alcohol or drug abuse, severe pulmonary disease	Standard exclusion criteria for clinical trials	No/ Not relevant for the treatment of the target population in clinical practice and not considered as contraindication
Patients with unacceptable hematological, renal or hepatic function were not included, e.g. hemoglobin <9 g/dL, leukocyte count <3,000/mm³, absolute neutrophil count <1,500/mm³, platelet count <100,000/mm³; serum creatinine >1.5 fold; transaminases >5 fold and bilirubin >1.5 fold the upper limit of normal	Standard exclusion criteria for clinical trials related to CT combination partner and to ensure homogeneity of trial populations	No/ Clinical impact of the combination with CT was manageable. Pharmacokinetic characteristics of cetuximab are not influenced by renal or hepatic status. Exclusion criteria not considered as contraindication
Previous exposure to EGFR targeting therapy	Ensure homogeneity of target population and any impact of previous therapy	No/ Not assumed that pharmacokinetic characteristics of cetuximab are influenced by previous exposure to EGFR targeting therapy Exclusion criterion not considered as contraindication
Known hypersensitivity to any study drugs or their components	Cetuximab is contraindicated in patients with known Grade 3 or 4 hypersensitivity to cetuximab as preventive measure for serious and potentially life-threatening hypersensitivity reactions	No/ Exclusion criterion is considered as contraindication
Patients with mutant RAS mCRC	Cetuximab in combination with oxaliplatin-containing CT is contraindicated for patients with mutant RAS mCRC or for whom RAS mCRC status is unknown to prevent lack of efficacy and even negative effects	No/ Exclusion criterion is considered as contraindication

CRC=colorectal cancer; CT=chemotherapy; EGFR=epidermal growth factor receptor

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions or those caused by prolonged or cumulative exposure.

Table 30 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare (i.e. frequency ≥1/10,000 - <1/1,000)	6,193 patients were exposed over the whole CT program	Only ADRs with a frequency greater than 1 in 2,000 could be detected if there were no background incidence
Due to prolonged exposure	Number of patients with prolonged exposure is low due to target populations with advanced and/or metastatic cancer	N/A
Due to cumulative effects	N/A	N/A

ADR=adverse drug reaction; CT=clinical trial; N/A=not applicable

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 31 Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of special population	Exposure
Children	Not included in the clinical development program There is no relevant use of cetuximab in the pediatric population in the granted indications.
Elderly	No dose adjustment is required in the elderly.
Pregnant or breast-feeding women	Not included in the clinical development program Cetuximab is not recommended during pregnancy and lactation, as information in this population is not available.
Patients with hepatic impairment	Not included in the clinical development program An integrated analysis across all clinical studies showed that the pharmacokinetic characteristics of cetuximab are not influenced by hepatic status. However, only patients with adequate hepatic function have been investigated to date (transaminases ≤5-fold and bilirubin ≤1.5 fold the upper limit of normal).
Patients with renal impairment	Not included in the clinical development program An integrated analysis across all clinical studies showed that the pharmacokinetic characteristics of cetuximab are not influenced by renal status. However, only patients with adequate renal function have been investigated to date (serum creatinine ≤1.5-fold).
Patients with pre-existing hematological disorders	Not included in the clinical development program

Type of special population	Exposure
	Cetuximab has not been studied in patients with pre-existing hematological disorders, i.e. in patients presenting with 1 or more of the following laboratory parameters: hemoglobin <9 g/dL leukocyte count <3,000/mm³ absolute neutrophil count <1,500/mm³ platelet count <100,000/mm³
Patients with cardiovascular comorbidity and reduced performance status	An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed in the treatment of non-small cell lung cancer, squamous cell carcinoma of the head and neck and colorectal carcinoma. In some studies, association with age ≥65 years or performance status has been observed. When prescribing cetuximab, the cardiovascular and performance status of the patients and concomitant administration of cardiotoxic compounds such as fluoropyrimidines should be taken into account. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease with regard to the occurrence of severe infusion-related reactions.
Subpopulations carrying known and relevant polymorphisms	The V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) status was in 2008 recognized as predictive factor for the treatment with cetuximab and had been analyzed in 7 of the 8 randomized controlled studies (EMR 62 202-013, EMR 62 202-047, FIRE-3, CALGB/SWOG 80405, COIN [OxFP and OxFP + cetuximab groups only], CA225025 and CA225006) mentioned above. KRAS wild-type tumor status was confirmed for 3,239 patients in these 7 studies. Furthermore, analyses of RAS mutational status for 4 of these studies (EMR 62 202-013, EMR 62 202-047, FIRE-3, CALGB/SWOG 80405) became available in 2014. In these analyses 1,380 patients were confirmed to have RAS wild-type status.

Part II: Module SV - Post Authorization Experience

SV.1 Post Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Due to updates in the distribution of the indication (CRC versus SCCHN) and in the method of administration (Q1W versus Q2W), the method of calculation varied slightly per period.

Method of calculation for PBRER reference period of 01 October 2020 to 30 September 2025

Method of calculation for period of 01 October 2020 to 30 September 2021

The sales were provided in mg Erbitux sold (2 mg/mL and 5 mg/mL strengths).

The patient exposure estimate was made using the following assumptions for the PBRER reference period of 01 October 2020 to 30 September 2021:

- [redacted]% of sales in the USA (Lilly) were attributed to the treatment of CRC ([redacted]% every 1 week [Q1W], [redacted]% every 2 weeks [Q2W]) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W).
- [redacted]% of sales in Canada (Lilly) were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W).
- From 01 October 2020 to 30 September 2021, [redacted]% of sales from the rest of the world (non USA/Canada), except Japan, were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W). Percentage of Q2W administration was calculated based on Ipsos Oncology Monitor data 2021 from 5 European countries (France, Germany, Italy, Spain, UK).
- In Japan, [redacted]% of sales were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W). Percentage of Q2W administration was calculated based on Ipsos Oncology Monitor data 2021 from Japan.

Method of calculation for period of 01 October 2021 to 30 September 2022

The sales were provided in mg Erbitux sold (2 mg/mL and 5 mg/mL strengths).

The patient exposure estimate was made using the following assumptions for the PBRER reporting period of 01 October 2021 to 30 September 2022:

- [redacted]% of sales in the USA (Lilly) were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W).
- [redacted]% of sales in Canada (Lilly) were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W).
- From 01 October 2021 to 30 September 2022, [redacted]% of sales from the rest of the world (non USA/Canada), except Japan, were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W). Percentage of Q2W

administration was calculated based on Ipsos Oncology Monitor data 2022 from 5 European countries (France, Germany, Italy, Spain, UK).

- In Japan, [redacted]% of sales were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W). Percentage of Q2W administration was calculated based on Ipsos Oncology Monitor data 2022 from Japan.

Method of calculation for period of 01 October 2022 to 30 September 2025

The sales were provided in mg Erbitux sold (2 mg/mL strength in US/Canada, 5 mg/mL strength in the rest of the world except US/Canada).

The patient exposure estimate was made using the following assumptions for the PBRER reporting period of 01 October 2022 to 30 September 2025:

- [redacted]% of sales in the USA (Lilly) were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W).
- [redacted]% of sales in Canada (Lilly) were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W).
- From 01 October 2022 to 30 September 2025, [redacted]% of sales from the rest of the world (non USA/Canada), except Japan, were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W). Percentage of Q2W administration was calculated based on Ipsos Oncology Monitor data 2022 from 5 European countries (France, Germany, Italy, Spain, UK).
- In Japan, [redacted]% of sales were attributed to the treatment of CRC ([redacted]% Q1W, [redacted]% Q2W) and [redacted]% to the treatment of SCCHN ([redacted]% Q1W, [redacted]% Q2W). Percentage of Q2W administration was calculated based on Ipsos Oncology Monitor data 2022 from Japan.

Dosage of Erbitux

Q1W: The dosage of Erbitux is calculated per m² BSA based on an initial dose of 400 mg/m² and subsequent weekly doses of 250 mg/m². An average BSA of 1.8 m² was assumed for calculations, which was the average BSA of 329 patients in the pivotal study EMR 62202-007 for CRC (the "average patient" in the tables below in this Section).

Q2W: The dosage of Erbitux is calculated per m² BSA based on an initial dose of 500 mg/m² and subsequent Q2W doses of 500 mg/m². An average BSA of 1.8 m² was assumed for calculations, which was the average BSA of 329 patients in the pivotal study EMR 62202-007 for CRC (the "average patient" in the tables below in this Section).

Duration of treatment with Erbitux

Treatment duration for Q1W and Q2W is calculated with the same assumptions.

CRC

Worldwide excluding USA, Canada. From 01 October 2020 to 30 September 2023, patient exposure was calculated using the average of 20 weeks' treatment for first-, second- and third-line CRC. From 01 October 2023 to 30 September 2025, patient exposure was calculated using the average of 25 weeks' treatment for first-, second- and third-line CRC.

USA and Canada (Lilly territories). From 01 October 2020 to 30 September 2022, patient exposure was calculated using the average of 17.33 weeks' treatment for first-, second- and third-line CRC. From 01 October 2022 to 30 September 2025, patient exposure was calculated using the average of 23.6 weeks' treatment for first-, second- and third-line CRC.

SCCHN

Worldwide excluding USA and Canada. From 01 October 2020 to 30 September 2023, patient exposure was calculated using the average of 13 weeks' treatment for SCCHN. From 01 October 2023 to 30 September 2025, patient exposure was calculated using the average of 14 weeks' treatment for SCCHN.

The duration of treatment for LA SCCHN in combination with RT is 8 weeks (about 50% of patients). The average duration for R/M SCCHN in combination with CT is 18 weeks (also about 50% of patients). 13 weeks is the midpoint between 8 and 18 weeks.

USA and Canada (Lilly territories). From 01 October 2020 to 30 September 2022, patient exposure was calculated using the average of 8 weeks' treatment for SCCHN. From 01 October 2022 to 30 September 2025, patient exposure was calculated using the average of 14.5 weeks' treatment for SCCHN.

The average amount of Erbitux (mg) per patient and treatment for CRC and SCCHN for Q1W and Q2W treatment schedule based on the above assumptions for treatment duration is given in Table 32, Table 33 and Table 34.

Table 32 Average Amount of Erbitux (mg) for Initial and Subsequent Doses in the Average Patient for Q1W and Q2W Treatment Schedule

Dose	Dose based on BSA	Average amount (mg) in the average patient
Initial dose (Q1W)	400 mg/m²	720
Subsequent doses (Q1W)	250 mg/m²	450
Dose (Q2W)	500 mg/m²	900

BSA=body surface area

Table 33 Amount of Erbitux (mg) Given for Average Treatment Duration per Indication for Q1W and Q2W Treatment Schedule from 01 Oct 2020 until 30 Sep 2022

Indication and area (average treatment duration)	Method of calculation[a]	Average amount (mg) for the average treatment duration in the average patient
CRC (Q1W)		
Total worldwide except USA and Canada (20 weeks)	**(1 x 720 mg)** + *(19 x 450 mg)*	9,270
USA + Canada (17.33 weeks)	**(1 x 720 mg)** + *(16.33 x 450 mg)*	8,068.5
CRC (Q2W)		
Total worldwide except USA and Canada (20 weeks)	**10.5 x 900 mg**	9,450
USA + Canada (17.33 weeks)	**9.165 x 900 mg**	8,248.5
SCCHN (Q1W)		
Total worldwide except USA and Canada (13 weeks)	**(1 x 720 mg)** + *(12 x 450 mg)*	6,120
USA and Canada (8 weeks)	**(1 x 720 mg)** + *(7 x 450 mg)*	3,870
SCCHN (Q2W)		
Total worldwide except USA and Canada (13 weeks)	**7 x 900 mg**	6,300
USA and Canada (8 weeks)	**4.5 x 900 mg**	4,050

CRC=colorectal cancer; SCCHN=squamous cell carcinoma of the head and neck; USA=United States of America

[a] For Q1W first dose is given in bold type and subsequent weekly doses in italics, for Q2W every dose is given in bold type

Table 34 Amount of Erbitux (mg) Given for Average Treatment Duration per Indication for Q1W and Q2W Treatment Schedule from 01 Oct 2022 until 30 Sep 2023

Indication and area (average treatment duration)	Method of calculation[a]	Average amount (mg) for the average treatment duration in the average patient
CRC (Q1W)		
Total worldwide except USA and Canada (20 weeks)	**(1 x 720 mg)** + *(19 x 450 mg)*	9,270
USA + Canada (23.6 weeks)	**(1 x 720 mg)** + *(22.6 x 450 mg)*	10,890

Indication and area (average treatment duration)	Method of calculation[a]	Average amount (mg) for the average treatment duration in the average patient
CRC (Q2W)		
Total worldwide except USA and Canada (20 weeks)	**10.5 x 900 mg**	9,450
USA + Canada (23.6 weeks)	**12.3 x 900 mg**	11,070
SCCHN (Q1W)		
Total worldwide except USA and Canada (13 weeks)	**(1 x 720 mg)** + *(12 x 450 mg)*	6,120
USA and Canada (14.5 weeks)	**(1 x 720 mg)** + *(13.5 x 450 mg)*	6,795
SCCHN (Q2W)		
Total worldwide except USA and Canada (13 weeks)	**7 x 900 mg**	6,300
USA and Canada (14.5 weeks)	**7.75 x 900 mg**	6,975

CRC=colorectal cancer; SCCHN=squamous cell carcinoma of the head and neck; USA=United States of America

[a] For Q1W first dose is given in bold type and subsequent weekly doses in italics, for Q2W every dose is given in bold type

Table 35 Amount of Erbitux (mg) Given for Average Treatment Duration per Indication for Q1W and Q2W Treatment Schedule from 01 Oct 2023 until 30 Sep 2025

Indication and area (average treatment duration)	Method of calculation[a]	Average amount (mg) for the average treatment duration in the average patient
CRC (Q1W)		
Total worldwide except USA and Canada (25 weeks)	**(1 x 720 mg)** + *(24 x 450 mg)*	11,520
USA + Canada (23.6 weeks)	**(1 x 720 mg)** + *(22.6 x 450 mg)*	10,890
CRC (Q2W)		
Total worldwide except USA and Canada (25 weeks)	**13 x 900 mg**	11,700
USA + Canada (23.6 weeks)	**12.3 x 900 mg**	11,070
SCCHN (Q1W)		
Total worldwide except USA and Canada (14 weeks)	**(1 x 720 mg)** + *(13 x 450 mg)*	6,570
USA and Canada (14.5 weeks)	**(1 x 720 mg)** + *(13.5 x 450 mg)*	6,795

Indication and area (average treatment duration)	Method of calculation[a]	Average amount (mg) for the average treatment duration in the average patient
SCCHN (Q2W)		
Total worldwide except USA and Canada (14 weeks)	**7.5 x 900 mg**	6,750
USA and Canada (14.5 weeks)	**7.75 x 900 mg**	6,975

CRC=colorectal cancer; SCCHN=squamous cell carcinoma of the head and neck

[a] For Q1W first dose is given in bold type and subsequent weekly doses in italics, for Q2W every dose is given in bold type

For the method of calculation used in PSURs 1–11, PBRER 2013-2020 please see the respective Marketing Experience Section in each PSUR or PBRER.

SV.1.2 Exposure

The provision of post authorization exposure data stratified by age and gender is not possible due to privacy protection regulations.

Between 01 December 2003 (international birth date) and 30 September 2025 (DLP of this RMP), the cumulative number of patients exposed to commercially available cetuximab worldwide was estimated to be 1,601,551 (976,830 in the indication CRC and 624,721 in the indication SCCHN, refer to PBRER 2025, Section 5.2.1).

Table 36 Cumulative Exposure From the Marketing Experience to Cetuximab

Indication	Region				Total
	[redacted]	[redacted]	[redacted]	[redacted]	
CRC	[redacted]	[redacted]	[redacted]	[redacted]	976,830
SCCHN	[redacted]	[redacted]	[redacted]	[redacted]	624,721
Total	[redacted]	[redacted]	[redacted]	[redacted]	**1,601,551**

CRC=colorectal cancer; [redacted]; SCCHN=squamous cell carcinoma of head and neck; [redacted]

Note: Due to rounding, the number of patients given for each region and each indication may differ from the total number of patients.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Based on the mode of action of cetuximab as an antineoplastic agent, its known side effects and the absence of effects or side effects such as analgesia/anesthesia, psychoanaleptic effects or performance improvement, the potential of cetuximab to cause misuse for illegal purposes is regarded as low.

Potential transmission of infectious agents

The active cetuximab drug substance is produced in a culture medium containing bovine serum albumin. The only animal derived material added during fermentation of cetuximab is bovine lipoprotein, tested for viruses. This minimizes a possible contamination for adventitious viruses. The cells used and animal products used for the production of cetuximab have been screened for viruses. All batches of the drug product are tested for sterility and bacterial endotoxins during release of the drug product (Scientific discussion for the approval of cetuximab in the European Community, 2004). A transmissible spongiform encephalopathies (TSE) risk assessment of the materials used in the production of cetuximab and the manufacture of the cell banks was conducted for raw materials that utilize animal derived components in their manufacturing process. The assessment of risk was on the basis of the European Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev.02). The Company has selected suppliers who have obtained Certification of Suitability to the TSE monograph of the European Pharmacopeia (Ph. Eur. 5.2.8).

The raw materials included in the risk assessment were the currently used materials of biological origin: bovine serum albumin, EX-CYTE® (medium component/supplement for routine manufacturing and working cell bank establishment), Fetal bovine serum (component of the working cell bank establishment and freezing medium). The sourcing of raw material of bovine origin is strictly controlled. Biological raw material is, in addition, routinely tested for non viral adventitious agents. In addition, measurements have been implemented to control potential viral adventitious agents during the manufacture of cetuximab. All bovine raw materials are tested for in vitro adventitious virus according to 9 CFR 113. The Master, Working and Postproduction Cell Banks are tested for sterility, mycoplasma, and endogenous and potential adventitious virus. In the production process, robust purification steps are included designed to inactivate and remove potential viral contamination.

Based on the performed risk assessment, it can be concluded that treatment with cetuximab poses no risk of transmitting infectious agents to patients.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable as this is not the initial RMP version.

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following **potential risks** are not included in the list of safety concerns in the RMP as these are adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- [redacted]

- [redacted]
- [redacted]
- [redacted]

  [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1 Important Identified Risks

Not applicable.

SVII.1.2.2 Important Potential Risks

Reason for considering a potential risk as important for inclusion in the list of safety concerns in the RMP:

- **(Acute) renal failure**

Almost all cases of (acute) renal failure reported with cetuximab are serious (809/817). Cetuximab can cause diarrhea and dehydration, which may potentially increase the risk of (acute) renal failure. (Acute) renal failure is a severe medical condition in which the kidneys fail to adequately filter waste products from the blood. (Acute) renal failure may result in a number of complications including changes in body fluid balance and high blood levels of potassium.

- **Gastrointestinal (GI) perforation**

Almost all cases of GI perforation reported with cetuximab are serious (701/707). GI perforation 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 GI perforations.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks

Not applicable.

Important Potential Risks

Table 37 Important Potential Risk

Important Potential Risk: (Acute) Renal Failure		
Frequency	**Number of cases:**	**817**
	Reporting rate up to 30 Sep 2025:	
	• 817 cases/1,613,810 total exposure=0.0506%	
Seriousness/outcomes	**Number of cases:**	**817**
	• Serious:	809
	• Non serious:	8
	Outcome:	
	• Fatal	160
	• Not recovered	121
	• Recovered with sequelae	38

Important Potential Risk: (Acute) Renal Failure		
	• Recovered/Recovering	355
	• Unknown/not reported	143
Severity	(Acute) Renal failure is a severe, life-threatening condition characterized by rapid decline in glomerular filtration rate, retention of nitrogenous waste products, oliguria, extracellular fluid overload, electrolyte and acid-base abnormalities and is potentially fatal.	
Background incidence/prevalence	Cumulative incidence rate of acute kidney failure among newly diagnosed patients with cancer: 1 year after diagnosis 4.5% (95%CI:4.3-4.7%) 5 years after diagnosis: 7.6% (95%CI: 7.3-7.8%) (Christiansen 2011)	
Risk factors and risk groups	Unknown	
Potential mechanisms	(Acute) renal failure was observed in the context of, or secondary to fluid loss (e.g. due to diarrhea, vomiting, and reduced oral intake) and dehydration.	
Preventability	Unknown	
Impact on individual patient	Impairs everyday activities, may result in sequelae (e.g. chronic dialysis-dependency).	
Impact on the risk-benefit balance of the product	NA	
Public health impact	No public health implications are expected.	
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)	
MedDRA terms	SMQ Narrow: acute renal failure Out of these, ICSRs reporting the specific PTs renal failure and acute kidney injury were selected for further evaluation.	

MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable; PBRER=Periodic Benefit-Risk Evaluation Report; PT=preferred term; SMQ=Standardised MedDRA Query

Important Potential Risk: Gastrointestinal (GI) Perforation	
Frequency	**Number of cases*: 707** Subgroup 1 GI perforation and Subgroup 2 pneumatosis intestinalis **Number of cases in Subgroup 1 GI perforation: 638** Reporting rate up to 30 Sep 2025: • 638 cases/1,613,810 total exposure=0.0395% **Number of cases in Subgroup 2 pneumatosis intestinalis: 69** Reporting rate up to 30 Sep 2025: • 69 cases/1,613,810 total exposure=0.0043% (PBRER reporting period 01 Oct 2024 - 30 Sep 2025). Safety database analyses revealed no increased frequency of

Important Potential Risk: Gastrointestinal (GI) Perforation	
	"Gastrointestinal (GI) perforation" in randomized controlled clinical trials and no evidence that Erbitux increased the incidence adjusted for person-years based on incidence rate ratios in all studies pooled or by indication.
Seriousness/outcomes	**Number of cases*:** **707** Subgroup 1 GI perforation and Subgroup 2 pneumatosis intestinalis • Serious: 701 • Non serious: 6 **Number of cases in Subgroup 1 GI perforation:** **638** • Serious: 633 • Non serious: 5 • **Outcome:** • Fatal 121 • Not recovered 76 • Recovered with sequelae 51 • Recovered/Recovering • 256 • Unknown/not reported 134 **Number of cases in Subgroup 2 pneumatosis intestinalis:** **69** • Serious: 68 • Non serious: 1 **Outcome:** • Fatal 3 • Not recovered 4 • Recovered with sequelae 1 • Recovered/Recovering 39 • Unknown/not reported 22
Severity	Gastrointestinal (GI) perforation is a rare, severe and life-threatening condition involving complete penetration of the wall of the stomach, small intestine or large bowel and is potentially fatal. **Number of Pneumatosis intestinalis cases with severity until 30 Sep 2025:** Mild AE 2 Moderate AE 2 Severe AE 8 Life-threatening AE (including life-threatening or disabling) 1 Fatal AE 0 Unknown/not reported 56
Background incidence/prevalence	In 2 population-based studies from USA and Australia, among mCRC patients cumulative incidence of GI perforation after initiation bevacizumab treatment was 1.5% (Meyerhardt 2012) and 2.4% (Lee 2017).
Risk factors and risk groups	Unknown

Important Potential Risk: Gastrointestinal (GI) Perforation	
Potential mechanisms	Gastrointestinal (GI) perforation can be caused by a variety of illnesses, including appendicitis, diverticulitis, ulcer disease, gallstones or gallbladder infection and inflammatory bowel disease. In patients with CRC, perforation occurs most often at the site of the tumor because of necrosis. Various causes of fistula include medical conditions, medical treatment or trauma, e.g. inflammatory bowel disease, complications from surgery or radiation therapy. Cetuximab may impair mucosal integrity and therefore might play a contributory role in the development of events of Gastrointestinal (GI) perforation.
Preventability	Unknown
Impact on individual patient	Immediately life-threatening with potentially fatal outcome.
Impact on the risk-benefit balance of the product	NA
Public health impact	No public health implications are expected.
Evidence source and strength of evidence	The wall of the stomach, small intestine or large bowel can lose integrity (Gastrointestinal [GI] perforation). It can occur in patients with colorectal cancer 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 (GI) perforation.
MedDRA terms	• Subgroup 1: SMQ Gastrointestinal perforation with PTs of the MedDRA SMQ Narrow: 20000107 GI perforation and of the MedDRA HLT gastrointestinal fistula (10017952) • Subgroup 2: pneumatosis intestinalis with MedDRA PTs pneumatosis intestinalis, pneumatosis, portal venous gas and gastric pneumatosis.

AE=adverse event; CRC=colorectal cancer; GI=gastrointestinal; HLT=High Level Term, ICSR=individual case safety report; MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable; PBRER=Periodic Benefit-Risk Evaluation Report; PT=Preferred Term; SMQ=Standardised MedDRA Query

* 7 ICSRs reported PTs in both subgroups and were included in both subgroups

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 38 Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Not applicable
Important potential risks	• (Acute) renal failure • Gastrointestinal (GI) perforation
Missing information	• Not applicable

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Important potential risks

Table 39 Safety Concerns and Overview of Routine Pharmacovigilance Actions: Important Potential Risks

(Acute) renal failure		
Area requiring confirmation or further investigation	**PhV activities**	**Objectives**
Assess reporting rate in post-marketing use, and evaluate possible causal relationship	Routine pharmacovigilance, including close monitoring, e.g. cumulative reanalysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available).	To monitor the reporting rate and severity of reports of (acute) renal failure following the use of cetuximab and the circumstances in which they occur in patients, to elucidate whether they are related to cetuximab treatment and to be vigilant regarding any change in risk-benefit assessment.

PBRER=Periodic Benefit-Risk Evaluation Report; PhV=pharmacovigilance; PSUR=Periodic Safety Update Report

Gastrointestinal (GI) perforation		
Area requiring confirmation or further investigation	**PhV activities**	**Objectives**
Assess reporting rate in post-marketing use, and evaluate possible causal relationship	Routine pharmacovigilance, including close monitoring, e.g. cumulative reanalysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available).	To monitor the reporting rate and severity of reports of gastrointestinal (GI) perforation following the use of cetuximab and the circumstances in which they occur in patients, to elucidate whether they are related to cetuximab treatment and to be vigilant regarding any change in risk-benefit assessment.

PBRER=Periodic Benefit-Risk Evaluation Report; PhV=pharmacovigilance; PSUR=Periodic Safety Update Report

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post Authorization Efficacy Studies

Not applicable.

Part V: Risk Minimization Plan (Including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1 Routine Risk Minimization Measures

Table 40 Description of Routine Risk Minimization Measures by Safety Concern: Important Potential Risks

Safety Concern	Routine Risk Minimization Measures
(Acute) renal failure	No risk minimization activities are needed at this stage
Additional risk minimization measures	None proposed

Safety Concern	Routine Risk Minimization Measures
Gastrointestinal (GI) perforation	No risk minimization activities are needed at this stage
Additional risk minimization measures	None proposed

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Table 41 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
(Acute) renal failure	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures: None proposed	Routine pharmacovigilance, including close monitoring
Gastrointestinal (GI) perforation	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures: None proposed	Routine pharmacovigilance, including close monitoring

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 (PL) 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 PL 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 42 Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Not applicable
Important potential risks	• (Acute) renal failure • Gastrointestinal (GI) perforation
Missing information	• Not applicable

II.B Summary of Important Risks

Table 43 Summary of Important Potential Risks

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 [GI] 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 (GI) perforation.

Important Potential Risk: Gastrointestinal (GI) 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 of Erbitux.

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

There are no studies required for Erbitux.

Part VII Annexes

Annex 1 [redacted]

(Not applicable)

Annex 2 [redacted]

Annex 3 [redacted]

(Not applicable)

Annex 4 **Specific Adverse Drug Reaction Follow-up Forms**

(Not applicable)

Annex 5 [redacted]

Annex 6 **Details of Proposed Additional Risk Minimization Activities (if applicable)**

(Not applicable)

Annex 7 **Other Supporting Data (including Referenced Material)**

Annex 8 [redacted]

[redacted]

Signature Page for VV-PVG-055083 v3.0

Approval Task	[redacted] Pharmacovigilance 02-Jun-2026 14:10:09 GMT+0000

Approval Task	Elke Sylvester Pharmacovigilance 02-Jun-2026 15:47:45 GMT+0000

Signature Page for VV-PVG-055083 v3.0

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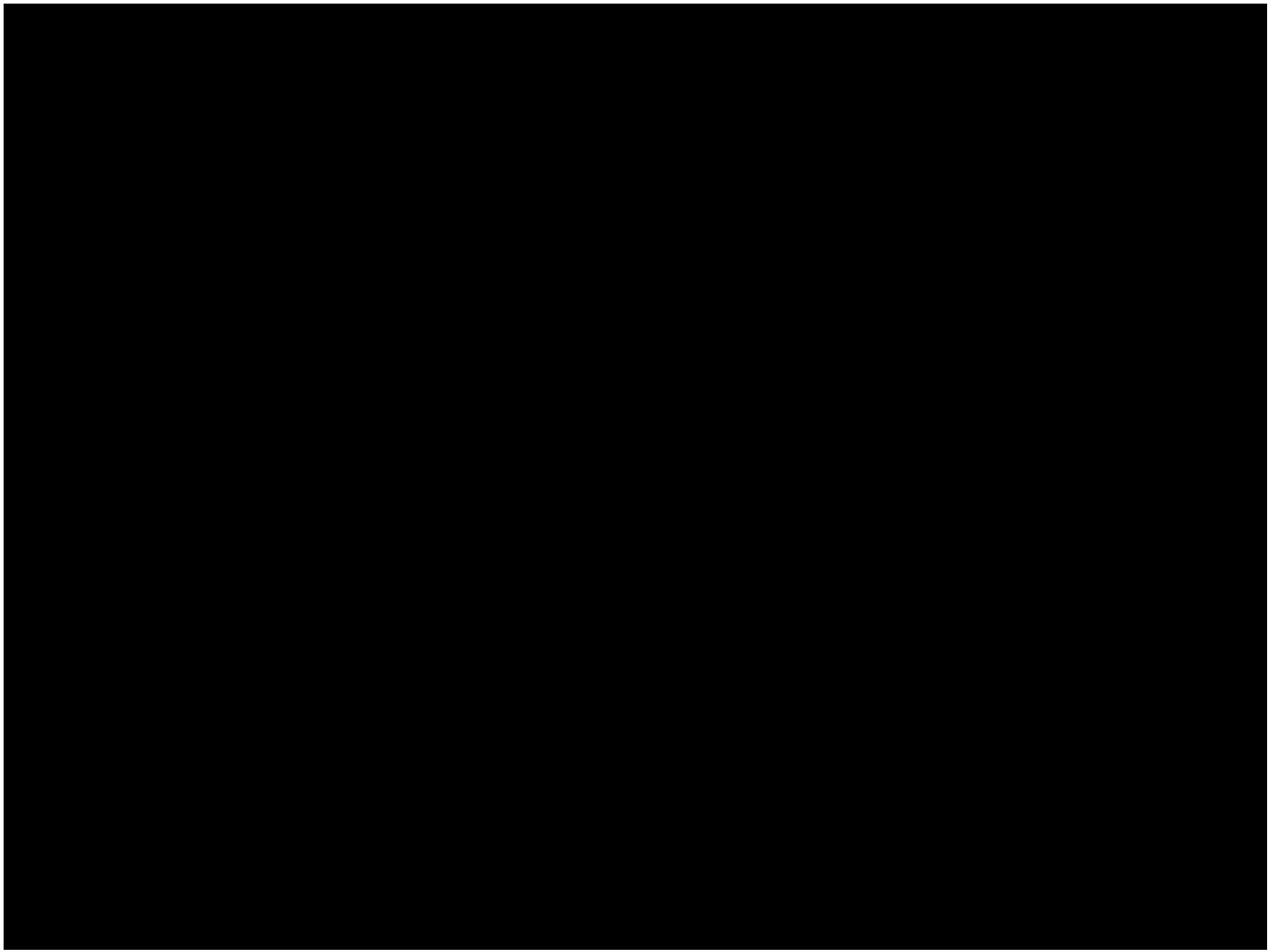

Annex 7 Other Supporting Data (including Referenced Material)

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