Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Portrazza (Necitumumab)

This is a summary of the risk management plan (RMP) for Portrazza. The RMP details important risks of Portrazza, how these risks can be minimised, and how more information will be obtained about Portrazza's risks and uncertainties (missing information).

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

This summary of the RMP for Portrazza should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Portrazza's RMP.

I - The Medicine and What It is Used for

Portrazza is authorised for metastatic squamous NSCLC (see SmPC for the full indication). It contains necitumumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Portrazza's benefits can be found in Portrazza'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/portrazza

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Portrazza, together with measures to minimise such risks and the proposed studies for learning more about Portrazza's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Portrazza, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment so that

immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Portrazza is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Portrazza are risks that need special risk management activities to further investigate or minimise 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 Portrazza. 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).

List of important risks and missing information	
Important identified risks	Severe clinical outcomes of venous thromboembolic events Arterial thromboembolic events Severe skin reactions
Important potential risks	Developmental and reproductive toxicity Life-threatening cardiorespiratory disorders
Missing information	Activity in biomarker-defined tumour subtypes (EGFR and KRAS and other downstream markers)

EGFR = epidermal growth factor receptor; KRAS = KRAS = Kirsten Rat Sarcoma.

II.B Summary of Important Risks

Important identified risk: Severe clinical outcomes of venous thromboembolic events	
Evidence for linking the risk to the medicine	Venous thromboembolic events (VTEs) from EGFR mAbs in combination with chemotherapy have been established for other EGFR mAbs (Erbitux® SmPC 2014 [Cetuximab]; Vectibix® [Panitumumab] SmPC 2014). A meta-analysis of 7611 patients investigated the incidence and relative risk of VTEs associated with 2 EGFR mAbs in combination with chemotherapy, including platinum-based doublets (Petrelli et al. 2012). The overall incidence of VTEs for chemotherapy was 3.7% and the overall incidence for the EGFR mAbs in combination with chemotherapy was 5.9%, which in this meta-analysis has been assessed as suggesting a class effect. In completed clinical trials with necitumumab, the incidence of VTEs was 11.6%. In the postmarketing setting, the incidence rate of serious VTEs events was low (0.25%), however, VTEs can result in significant clinical complications.
Risk factors and risk groups	Venous thromboembolic events, including fatal cases, were observed with necitumumab in combination with gemcitabine and cisplatin (see Section 4.8 of the SmPC). Administration of necitumumab should be carefully considered in those patients with a history of thromboembolic events (such as pulmonary embolism, deep vein thrombosis, myocardial infarction, or stroke) or pre-existing risk factors for thromboembolic events (such as advanced age, patients with prolonged periods of immobilisation, severely hypovolemic patients, or patients with acquired or inherited thrombophilic disorders). The relative risk of VTE was approximately 3-fold higher in patients with a reported history of VTE. Necitumumab should not be administered to patients with multiple risk factors for thromboembolic events unless the benefits outweigh the risks to the patient. In patients at high risk for VTE, either because of prior VTE or because of multiple risks, thromboprophylaxis should be considered. Patients who develop VTE should consider discontinuation of necitumumab therapy. In a clinical trial in advanced non-squamous NSCLC, patients experienced an increased rate of serious thromboembolic events (including fatal events) in the necitumumab plus pemetrexed and cisplatin arm as compared to the pemetrexed and cisplatin arm (see also Section 4.8 of the SmPC). The addition of necitumumab did not improve the efficacy outcome over pemetrexed and cisplatin alone in advanced non-squamous NSCLC. Cancer patients account for 20% of all patients with VTEs (Khorana 2010; Horsted et al. 2012). Cancer patients are at risk in general for VTEs due to the general nature of the disease. Overall, the risk of VTE is increased 4-fold in cancer patients (incidence rate ratio = 3.96; 95% CI: 3.68 to 4.27 [Horsted et al. 2012]). Those patients on systemic cytotoxic therapy (that is, cisplatin therapy) appear to have the greatest risk for VTE depending on the cancer type and stage, any comorbidity risk, and time since diagnosis (Moore et al. 2011). Recent surgery is a strong independent transient risk factor for VTE (Glynn and Rosner 2005; Huerta et al. 2007).

Risk minimisation measures	**Routine risk minimisation measures** SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 **Additional risk minimisation measures** Physician/Oncologist communication
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Observational post marketing safety study to monitor VTE See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Arterial thromboembolic events	
Evidence for linking the risk to the medicine	There are no systematic analyses on the background incidence or prevalence of ATEs in cancer patients by tumour type and stage. Because of their disease, patients with cancer (that is, NSCLC) are generally at a higher risk for ATEs, which further increases with stage of disease (Moore et al. 2011; Suter and Ewer 2013). The risk of ATEs is further increased by systemic cytotoxic therapy (that is, cisplatin-based regimens). Two meta-analyses that included NSCLC reported incidences of ATEs for patients undergoing chemotherapy for different tumours: Scappaticci et al. 2007 (N=1745) reported 1.7% and Petrelli et al. 2012 (N=7611) reported 3.4%. The meta-analysis of incidence and relative risk of ATEs associated with 2 EGFR mAbs in combination with chemotherapy (including cisplatin-based regimens) showed an increased incidence versus chemotherapy alone (4.6% vs. 3.4%) (Petrelli et al. 2012).
Risk factors and risk groups	Arterial thromboembolic events, including fatal cases, were observed with necitumumab in combination with gemcitabine and cisplatin (see Section 4.8 of the SmPC). Administration of necitumumab should be carefully considered in those patients with a history of thromboembolic events (such as pulmonary embolism, deep vein thrombosis, myocardial infarction, or stroke) or pre-existing risk factors for thromboembolic events (such as advanced age, patients with prolonged periods of immobilisation, severely hypovolemic patients, or patients with acquired or inherited thrombophilic disorders).The relative risk of ATEs was approximately three-fold higher in patients with a reported history of ATE. Necitumumab should not be administered to patients with multiple risk factors for thromboembolic events unless the benefits outweigh the risks to the patient. In a clinical trial in advanced non-squamous NSCLC, patients experienced an increased rate of serious thromboembolic events (including fatal events) in the necitumumab plus pemetrexed and cisplatin arm as compared to the pemetrexed and cisplatin arm (see also Section 4.8 of the SmPC). The addition of necitumumab did not improve the efficacy outcome over pemetrexed and cisplatin alone in advanced non-squamous NSCLC. EGFR mAbs (for example, cetuximab, panitumumab) in combination with platinum-based chemotherapy across multiple cancer types showed a non-statistically significant increased risk of ATEs (Petrelli et al. 2012).
Risk minimisation measures	**Routine risk minimisation measures:**

	SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 **Additional risk minimisation measures:** Physician/Oncologist communication
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Observational post marketing safety study to monitor ATEs See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Severe skin reactions	
Evidence for linking the risk to the medicine	Treatment with EGFR inhibitors, such as mAbs, frequently results in skin toxicity due to expression of the EGFR in the skin. Rash is an early and frequent phenomenon during treatment with EGFR mAbs. In a study by LaCouture et al. (2010), rash occurred in approximately 90% of patients on cetuximab and panitumumab. Incidence of acne-like rash of any grade that arose at any time was reported for 382 (70%) of 548 patients in the chemotherapy plus cetuximab group of the Phase 3 FLEX study safety population and this reached Grade 3 in 57 (10%) patients (Pirker 2009). A meta-analysis (Petrelli et al. 2013) reviewed studies of skin toxicities of cetuximab and panitumumab in metastatic colorectal cancer patients. One study (Lévi et al. 2011) reported that 34% of patients developed Grade 3 skin rash with cetuximab+circadian treatment. Other studies reported Grade 3 skin reactions ranging from 5.3% to 13.3% with cetuximab treatment (Cunningham et al. 2004; Lenz et al. 2006; Jonker et al. 2007; Gamucci et al. 2008; Racca et al. 2008; Lévi et al. 2011; Park et al. 2011; Jehn et al. 2012). In comparison, only 0.4% of patients treated with supportive care developed Grade 3 skin rash (Jonker et al. 2007). Paez et al. (2010) reported that among patients treated with cetuximab or panitumumab, 65% developed Grade 2-3 skin toxicities. Skin reactions are very commonly observed in EGFR mAb-treated patients; severe cases are reported in up to approximately 30% of patients, Grade 4 reported in <1% of patients treated with panitumumab, single cases of skin necrosis in patients treated with cetuximab (Vectibix® [Panitumumab] SmPC 2014; Erbitux® SmPC 2014 [Cetuximab]).
Risk factors and risk groups	Patients receiving EGFR inhibitors for cancer are at risk. Several manifestations of severe skin toxicity have been reported in patients treated with currently marketed EGFR-inhibiting mAbs such as skin necrosis, infectious complications of skin reactions, and in very rare cases Stevens-Johnson Syndrome/toxic epidermal necrolysis. So far, in the necitumumab clinical trial programme such severe skin reactions have not been reported. Skin reactions are a known class side effect of EGFR inhibitors due to the expression of EGFR in the skin in epidermal cells (Petrelli et al. 2012). The majority of EGFR-related skin reactions, though, are of low severity (Grade 1 and 2). Other than fair skin, there are no specific predisposing factors identified in the target population.
Risk minimisation measures	**Routine risk minimisation measures:**

	SmPC Sections 4.2, 4.4, and 4.8 PL Sections 2 and 4 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Observational post marketing safety study to monitor skin reactions See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Developmental and reproductive toxicity	
Evidence for linking the risk to the medicine	Based on scientific assessment of the target (EGFR) and the effects observed in monkeys exposed to other antibodies that bind EGFR (cetuximab and panitumumab), administration of necitumumab to patients poses a potential risk to establishing and maintaining pregnancy and to embryo-foetal and postnatal development. Inhibition of EGFR by necitumumab is biologically plausible and will likely have an adverse effect on reproductive parameters in animals. Human IgG1 is known to cross the placenta; therefore, necitumumab has the potential to be transmitted from the mother to the developing foetus. No animal studies have been specifically conducted to evaluate the effect of necitumumab on reproduction and foetal development; however, based on its mechanism of action and animal models where EGFR expression is disrupted, necitumumab may cause foetal harm or developmental anomalies. In our clinical trial programme with necitumumab, there was only 1 instance of DART (amenorrhea) that was classified under the narrow SMQ definition of DART. This event was not in the SQUIRE or INSPIRE study, but was in Study I4X-IE-JFCD.
Risk factors and risk groups	Premenopausal women and any foetus are at risk.
Risk minimisation	**Routine risk minimisation measures:** SmPC Sections 4.4, 4.6, and 5.3 PL Section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Life-threatening cardiorespiratory disorders	
Evidence for linking the risk to the medicine	Chronic pulmonary disease and cardiovascular disease are commonly diagnosed co-morbidities amongst NSCLC patients and squamous cell NSCLC patients (Janssen-Heijnen et al. 1998; Wang et al. 2012; Vaslamatzis et al. 2013). Data from the US Veterans Affair Central Cancer Registry between 2003 and 2008 showed that among 20,511 veterans aged ≥65 years who were diagnosed with NSCLC, 52% had chronic pulmonary disease as the most prevalent comorbidity, followed by 25% with diabetes, 21% with non-lung malignancies, 18% with peripheral vascular disease, 13% with congestive heart failure, and 13% with cerebrovascular disease (Wang et al. 2012). In a Dutch registry of diagnosed patients diagnosed with cancer, 1533 patients with squamous NSCLC were identified; 56% were younger than 70 years and 44% were 70 years or older (Janssen Heijnen et al. 1998). The most prevalent comorbidity was chronic pulmonary disease (23% of patients <70 years and 31% of patients ≥70 years), followed by cardiovascular disease (20% of patients <70 years and 30% of patients ≥70 years) and hypertension (11% of patients <70 years and 13% of patients ≥70 years), as well as other malignancies (14% of patients <70 years 19% of patients ≥70 years). More recent data from a Greek hospital showed that among 50 patients with NSCLC (Stage >IIIA) whose median age was 71 years, the most commonly diagnosed comorbidity was hypertension (40%), followed by ischaemic disease (18%), diabetes (18%), and COPD (14%) (Vaslamatzis et al. 2013). Chronic pulmonary disease and cardiovascular disease are commonly diagnosed comorbidities among patients with NSCLC and patients with squamous cell NSCLC (Janssen-Heijnen et al. 1998; Wang et al. 2012; Vaslamatzis et al. 2013). Data from the US Veterans Affair Central Cancer Registry between 2003 and 2008 showed that among 20,511 veterans aged ≥65 years who were diagnosed with NSCLC, 52% had chronic pulmonary disease as the most prevalent comorbidity, followed by 25% with diabetes, 21% with non-lung malignancies, 18% with peripheral vascular disease, 13% with congestive heart failure, and 13% with cerebrovascular disease (Wang et al. 2012). In a Dutch registry of patients diagnosed with cancer, 1533 squamous patients with NSCLC were identified; 56% were younger than 70 years and 44% were 70 years or older (Janssen Heijnen et al. 1998). The most prevalent comorbidity was chronic pulmonary disease (23% of patients <70 years and 31% of patients ≥70 years), followed by cardiovascular disease (20% of patients <70 years and 30% of patients ≥70 years) and hypertension (11% of patients <70 years and 13% of patients ≥70 years), as well as other malignancies (14% of patients <70 years and 19% of patients ≥70 years).

Risk factors and risk groups	Patients with a history for cardiovascular and chronic respiratory disease are at risk. Also, chronic pulmonary disease and cardiovascular disease are commonly diagnosed comorbidities among patients with NSCLC and patients with squamous cell NSCLC (Janssen-Heijnen et al. 1998; Wang et al. 2012; Vaslamatzis et al. 2013). The incremental risk of cardiopulmonary arrest or sudden death in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias as compared to those without these comorbid conditions is not known.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8 PL Section 2 **Additional risk minimisation measures:** Physician/Oncologist communication
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Observational post marketing safety study to monitor cardiorespiratory disorders See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Activity in biomarker-defined tumour subtypes (EGFR and KRAS and other downstream markers)	
Evidence for linking the risk to the medicine	A type II variation to address a post-authorisation Category 3 commitment in relation to exploratory analyses of biomarkers was in the initially approved Risk Management Plan (RMP) (Version 8). Across the 3 Phase 1b/2 clinical studies for which correlative analysis between EGFR protein expression status and efficacy was performed, there was a modest trend toward reduced benefit in the EGFR-negative subpopulations. In Study I4X-MC-JFCU, the primary (3-month PFS) and secondary efficacy endpoints consistently favored patients with EGFR-positive status. Study I4X-MC-JFCP demonstrated greater ORR (primary efficacy endpoint) and PFS in patients with EGFR-positive status but no difference in DCR between the EGFR subpopulations. In Study I4X-MC-JFCQ, only the primary efficacy endpoint of ORR favored EGFR-positive patients while secondary efficacy endpoints were similar in both the EGFR-positive and -negative subpopulations. In Study 16A-MC-CBBE, within the TR population, 13 patients (72.2%) had EGFR-positive status and 5 patients (27.8%) had EGFR-negative status. Due to the limited sample size of the TR population, no correlative analysis with efficacy outcomes was performed. *KRAS* mutation status was only assessed in Study JFCU. The primary endpoint of 3-month PFS was similar in *KRAS* mutation–positive and *KRAS* mutation–negative subpopulations. However, the small sample size for the *KRAS* mutation–positive subpopulation significantly limits the ability to draw meaningful conclusions regarding the role of *KRAS* in response.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 5.1

	Additional risk minimisation measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Exploratory analyses of biomarker status in the necitumumab clinical development programme of 4 Phase 1b/2 clinical trials. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: ATE = arterial thromboembolic event; EGFR = epidermal growth factor receptor 1; DCR = duration of confirmed response; Ig = immunoglobulin; KRAS = Kirsten Rat Sarcoma; NSCLC = non-small cell lung cancer; mAb = monoclonal antibody; ORR = overall response rate; PFS = progression-free survival; SmPC = summary of product characteristics; TR = translational research; VTE = venous thromboembolic event.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Portrazza.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: Observational Prospective PASS to characterise serious life-threatening safety concerns of necitumumab (I4X-MC-B002)

Purpose of the study: The Pharmacovigilance Risk Assessment Committee (PRAC) requested a post-authorisation safety study (PASS) to be conducted to characterise the safety of necitumumab in patients with squamous NSCLC under real-world disease conditions.

The overall study objective is to evaluate the safety of necitumumab administered in combination with gemcitabine and cisplatin in comparison to cisplatin doublets, for treatment of adult patients with locally advanced or metastatic squamous NSCLC who have not received prior chemotherapy for this condition. Patients will be evaluated under real-world conditions in EU countries.

Study short name: Physician/Oncologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Portrazza® (necitumumab) 800 mg concentrate for solution for infusion (I4X-MC-B003)

Purpose of the study: The risk minimisation activities for Portrazza (necitumumab) include a communication that will be distributed prior to launch to Oncologists as agreed to with each National Competent Authority (NCA) and the Summary of Product Characteristics (SmPC).

This study will assess the understanding of the key conditions for the safe use of Portrazza (necitumumab) regarding venous thromboembolic events (VTEs), arterial thromboembolic events (ATEs), cardiorespiratory disorders, hypersensitivity/infusion-related reactions, severe skin reactions and severe hypomagnesaemia as communicated in the Physician/Oncologist Communication and the Portrazza (necitumumab) SmPC.