Summary of Risk Management Plan for Herzuma®

Active substance:	Trastuzumab
Dosage strength of reconstituted solution :	21 mg/ml
Pharmaceutical form:	Powder for concentrate for solution for infusion
Version number of current RMP	2.0
Name of Marketing Authorisation Holder:	iQone Healthcare Switzerland SA
Date:	31 August 2021
Reference RMP	RMP for Herzuma® Switzerland version 2.0

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Herzuma® is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of Herzuma® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. iQone Healthcare Switzerland SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Herzuma®.

SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Herzuma (Trastuzumab)

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

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

This summary of the RMP for Herzuma 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 Herzuma's RMP.

I. The Medicine and What It Is Used for

Herzuma is authorised for the treatment of adult patients with HER2-positive cancer as following (see SmPC for the full indication):

- Breast cancer (Cancer develops in the lining of a duct or lobule in one of the breasts): Herzuma is used for Metastatic Breast Cancer (MBC) and Early Breast Cancer (EBC).
- Gastric Cancer (Cancer starts in any part of the stomach or the stomach wall, mostly in the gland cells in the inner stomach lining): Herzuma is used for Metastatic Gastric Cancer (MGC)

It contains trastuzumab as the active substance and it is given by intravenous infusion.

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

Important risks of Herzuma, together with measures to minimise such risks and the proposed studies for learning more about Herzuma'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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR 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 Herzuma is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Herzuma 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 Herzuma. 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	- Cardiac dysfunction - Administration-Related Reactions (ARRs) - Haematotoxicity - Oligohydramnios - Pulmonary disorders
Important potential risks	- Infections - Medication errors (e.g. reduced efficacy due to subcutaneous (SC) administration of intravenous (IV) formulation, incorrect dosing leading to adverse events (AEs))
Missing information	- Treatment in male patients (breast cancer only) - Safety of 75 mg/m^2 v 100 mg/m^2 docetaxel dose

II.B Summary of Important Risks

Important Identified Risk – Cardiac Dysfunction	
Evidence for linking the risk to the medicine	**MBC, First-line HER2-positive** The incidence of symptomatic CHF (National Cancer Institute-Common Toxicity Criteria [NCI-CTC] Grades 3 or 4) for non-trastuzumab containing regimens: • Without anthracyclines: 0.3 % to 1 % • With anthracyclines: 3 % to 4.7 % **MBC, Second-line HER2-positive** Based on three lapatinib studies, the incidence of symptomatic Congestive Heart Failure (CHF) (Grades 3 or 4) was < 1 % for non-trastuzumab containing regimens. In a pooled analysis of 3,689 lapatinib patients enrolled in clinical trials, the incidence of symptomatic cardiac toxicity by prior treatment was:

	• Anthracyclines: 0.5 %. • Trastuzumab: 0.1 %. • Neither anthracyclines nor trastuzumab: 0.1 %. **EBC, HER2-positive** Based on data from three randomised controlled trials conducted in the US, US/Canada, and Europe, the incidence of NCI-CTC Grade 3 - 4 CHF was 0 % - 0.49 % among HER2-positive patients with EBC not treated with trastuzumab. The incidence of Left Ventricular Ejection Fraction (LVEF) decrease (of > 10 %) ranged from 2.2 % to 17 % of the study population. **Advanced Gastric Cancer** A recent randomised trial reported a 1.1 % incidence of decreased LVEF (unspecified criteria) among HER2-positive patients with advanced gastric cancer not treated with Herceptin.
Risk factors and risk groups	The risks of both symptomatic and asymptomatic LVEF events following initiation of treatment were increased with lower on-study LVEF values. Older patients (> 50 years old) had an increased risk of both symptomatic cardiac and asymptomatic LVEF events regardless of treatment received.
Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 4.8 - EU SmPC section 4.4 Additional risk minimisation measures: - No additional risk minimisation measures proposed.

Important Identified Risk – Administration-Related Reactions (ARRs)	
Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to Administration-Related Reactions (ARRs) to trastuzumab. However, the SmPC indicates that patients, who are experiencing dyspnoea at rest due to complications of advanced malignancy or co-morbidities, may be at greater risk of severe reactions including fatal outcomes.
Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 4.8 - EU SmPC sections 4.2 and 4.3 - EU SmPC section 4.4

	Additional risk minimisation measures: - No additional risk minimisation measures proposed.

Important Identified Risk – Haematotoxicity	
Evidence for linking the risk to the medicine	**MBC** The incidence of neutropenia ranged from 2 % (Grades 3 - 4) to 64 % (Grade 4) depending on which non-trastuzumab, doxorubicin-containing regimen was provided. The incidence of neutropenia was 26 % among HER2-positive patients in the control arm of a US trial. **EBC** Based on data from two randomised controlled trials conducted in the US, US/Canada, and Europe, the incidence of neutropenia ranged from 0.7 % (Grade 4 - 5) to 4.5 % (Grades 2 - 5) among HER2-positive patients with EBC not treated with trastuzumab. **Advanced Gastric Cancer** A trial examining three different MGC regimens yielded an incidence for Grade 3 - 4 neutropenia of 59 % - 80 % depending on the (non trastuzumab) regimen.
Risk factors and risk groups	In general, all cancer patients undergoing chemotherapeutic/radio-therapeutic regimens, are at risk of developing some degree of haematotoxicity, including neutropenia, anaemia, and thrombocytopenia.
Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 4.8 Additional risk minimisation measures: - No additional risk minimisation measures proposed.

Important Identified Risk – Oligohydramnios	
Evidence for linking the risk to the medicine	Stoll *et al* reviewed 225,669 consecutive pregnancies births and that 0.99/1000 pregnancies were complicated by oligohydramnios. However, since there is no accepted standard definition of oligohydramnios, incidence has been estimated as being between 0.4 % and 1 % of pregnancies.
Risk factors and risk groups	There are no reliable indicators of patients who may or may not be at risk.
Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 4.6

	Additional risk minimisation measures: - No additional risk minimisation measures proposed.

Important Identified Risk – Pulmonary Disorders	
Evidence for linking the risk to the medicine	Estimation of the incidence and prevalence of Interstitial Lung Disease (ILD) is complicated by the fact that there are more than 200 sub-types of ILD and the use of confusing and evolving diagnostic criteria and classification schema that may vary by country. Limited epidemiological evidence from observational studies exists on the incidence of ILD by common breast cancer chemotherapies. An incidence rate of 1.2/100,000 Person-Years (PY) (95 % Cl: 0.25 - 3.9/100,000 PY) among 35,823 breast cancer patients in a Danish registry has been reported. Drug-induced interstitial pneumonitis appears to account for only a small proportion of interstitial pneumonitis cases. The incidence of trastuzumab induced pneumonitis has been between 0.4 % - 0.6 %, with a mortality of 0.1 %.
Risk factors and risk groups	General risk factors may include prior lung disease, pneumonectomy, or abnormal baseline pulmonary physiology. Concomitant or sequential pneumotoxic drugs, or the addition of radiation therapy to the chest may significantly enhance the likelihood of developing adverse pulmonary effects. Administration of chemotherapeutic agents to patients who have received radiation therapy in the past may also "recall" a severe skin and/or lung reaction within the previously irradiated area. Analysis of post marketing surveillance data for trastuzumab and ILD found that risk factors appear to be associated with prior or concomitant chemotherapy: Cases with a fatal outcome were associated with prior or concomitant use of taxanes. Other associated therapies included radiation, gemcitabine, vinorelbine, and cyclophosphamide.
Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 4.8 - EU SmPC section 4.3 - EU SmPC section 4.4 Additional risk minimisation measures: - No additional risk minimisation measures proposed.

Important Potential Risk – Infections	
Evidence for linking the risk to the medicine	**Infections in Breast Cancer patients following surgery**

	Surgical Site Infections (SSI) are a direct result of the surgical procedure and occur at or near the incision within 30 days of the procedure or up to a year later if the surgical procedure requires placement of prosthesis such as breast implant. In a retrospective review of 949 patients in the US undergoing breast surgery at a tertiary care hospital from 1999 – 2002, 5.2 % of patients developed a SSI within 1 year of surgery. The incidence of SSI was 12.4 % following mastectomy with immediate implant reconstruction, 6.2 % following mastectomy with immediate reconstruction using a transverse rectus abdominis myocutaneous flap, 4.4 % following mastectomy only and 1.1 % following breast reduction surgery. **EBC** In a Finnish study evaluating adjuvant docetaxel or vinorelbine with or without Herceptin in node-positive or high-risk node-negative EBC patient population, in the subset of patients (includes HER2-positive and HER-negative patients) not receiving Herceptin, the incidence of non-neutropenic infections were as follows in the docetaxel and vinorelbine arms, respectively: (all Grades: 44 % and 32 %) and (Grade 3 or 4: 5 % and 2 %). Incidence of infections in patients treated with high dose chemotherapy followed by autologous Bone Marrow Transplantation (BMT) or Peripheral Stem Cell Transplantation (PSCT) has also been reported. This treatment has been evaluated in high risk primary breast cancer patients with multiple lymph node involvement, advanced inflammatory breast cancer and MBC. Damon *et al* 2000 examined a mitoxantrone based high-dose chemotherapy regimen followed by BMT in 199 stage II – IV breast cancer patients and observed occurrence of Cytomegalovirus (CMV) infections (3.7 %) and CMV pneumonia (2.1 %). Another retrospective medical chart review of 127 breast patients (61 % MBC, 34% high risk EBC) who underwent BMT or PSCT following various chemotherapy regimens at a US university medical centre between 1991 – 1995 reported on infectious complications occurring in the immediate post-transplant period and during the first year after autologous transplantation. Initial infectious complications included catheter-site cellulitis (16 %), bacteraemia (13 %), clostridium difficile colitis (10 %), urinary tract infections (8 %), and pneumonia (4 %). During the year after transplantation, upper respiratory tract infections were most common (10 %), followed by dermatomal zoster (8 %) and urinary tract infection (5 %). In a single institution prospective study of adjuvant high-dose chemotherapy in Denmark, of 52 primary high-risk breast cancer patients, the rate of non-haematological toxicity during high dose

	chemotherapy was 23 % (any grade) and 3.8 % (Grade ≥ 3). No treatment-related deaths were reported. In a multicenter, randomised trial across Europe, Australia, and Asia comparing adjuvant dose-intensive chemotherapy followed by PSCT with standard-dose anthracycline based therapy, the rates of Grade 3 – 4 sepsis were 18 % and 4 %, respectively. **Gastric Cancer** Post-operative infections in gastric cancer were reported in 2 studies. Of 529 patients undergoing elective gastric resections between 2001 and 2005 from 10 Japanese hospitals, 3.6 % (n = 20) developed hospital-acquired pneumonia. Male gender and intra-and/or post-operative blood transfusion were independently associated with increased risk of post-operative hospital-acquired pneumonia. In a study of 40 locally advanced gastric adenocarcinoma patients, diagnosed from 2005 – 2008 in a single centre in Spain and received adjuvant chemo radiotherapy prior to surgery, the most frequent complications were pneumonia (12.9 %) and catheter-related sepsis (9.7 %). **MBC** Most trials of chemotherapeutic options reported haematological toxicities such as neutropenia and febrile neutropenia; however not all reported on infections in general. Among 11 (phase II or randomised phase III) trials of advanced gastric cancer or oesophagogastric cancer, six specifically reported on the frequency of infections. Based on these 6 trials, the incidence of infections ranged from 12 % - 38 % (all Grades) and 5 % -13 % (Grade 3 or 4). In a pooled analysis of 8 consecutive multicenter cooperative group trials, 367 patients with metastatic adenocarcinoma of the oesophageal, gastroesophageal, and stomach receiving first-line therapy were evaluated. First line chemotherapy regimens included various agents: 5-FU, etoposide, capecitabine, irinotecan, cisplatin levamisole, docetaxel, oxaliplatin, bortezomib, paclitaxel, and carboplatin. In this pooled analysis, the incidence of infection (Grade 3 – 5) was higher in older patients (≥ 65 years old) compared with younger patients (< 65 years old): 9 % versus 4 %, respectively. Van Cutsem *et al* 2006 also observed higher proportion of infections in patents aged 65 years and older (20 % in docetaxel, cisplatin and fluorouracil arm and 9 % in cisplatin and fluorouracil arm).
Risk factors and risk groups	Occurrence of infections in patients treated with trastuzumab tends to be seen in patients who receive concomitant taxane therapy, predominantly docetaxel, in association with other immune-suppressing agents, e.g., steroids, predominantly dexamethasone.

Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 4.8 Additional risk minimisation measures: - No additional risk minimisation measures proposed.

Important Potential Risk – Medication Errors (e.g. reduced efficacy due to SC administration of IV formulation, incorrect dosing leading to adverse events)	
Evidence for linking the risk to the medicine	At one outpatient cancer center in the US utilising a computerised medication ordering system, the rate of outpatient medication errors was 3 % (249/2454). A similar rate (3%) was reported among chemotherapy orders. Of 92 chemotherapy errors, 80 were potential adverse drug events. At three adult clinics and one paediatric oncology clinic in the Southwest, Southeast, Northeast, and Northwest US, the medication error rate was 7.1 % (95 % CI, 5.7 to 8.6). Among the 90 medication errors, 61 % had the potential to injure the patient, including 11 errors that resulted in injury. At a French university hospital, 5.2 % of antineoplastic prescriptions contained at least one error. However, most of the errors were intercepted before medication was administered to patients. Data by age, sex, and race/ethnicity are not available.
Risk factors and risk groups	Not known. While the reference product Herceptin is available both IV and SC formulation, Herzuma is only available IV formulation. Therefore, an accidental or an intentional SC administration of IV formulation for Herzuma can be predictable.
Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 4.2 Additional risk minimisation measures: - No additional risk minimisation measures proposed.

Missing Information - Treatment in male patients (breast cancer only)	
Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 5.3 Additional risk minimisation measures: - No additional risk minimisation measures proposed.

Missing Information - Safety of 75 mg/m^2 v 100 mg/m^2 docetaxel dose

Risk minimisation measures	Routine risk minimisation measures: - EU SmPC section 4.2 Additional risk minimisation measures: - No additional risk minimisation measures proposed.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Herzuma.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Herzuma.