Summary of Risk Management Plan for Herzuma®

Active substance:	Trastuzumab
Pharmaceutical form:	Powder for concentrate for solution for infusion
Version number of RMP summary:	3.0
Name of Marketing Authorisation Holder:	iQone Healthcare Switzerland SA
Date:	24 February 2023
Reference RMP:	EU RMP version 5.0

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 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.

Further information about the evaluation of Herzuma's benefits can be found in Herzuma's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002575/human_med_002230.jsp&mid=WC0b01ac058001d124

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) - Oligohydramnios
Important potential risks	- Medication errors (e.g. reduced efficacy due to SC administration of IV formulation, incorrect dosing leading to adverse events)
Missing information	- 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 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 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: - SmPC section 4.8 - 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: - SmPC section 4.8 - SmPC sections 4.2 and 4.3 - SmPC section 4.4 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: - SmPC section 4.6 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 intravenous (IV) and subcutaneous (SC) formulation, Herzuma is only available IV formulation. Therefore, an accidental or an intentional SC administration of IV formulation for Herzuma can be predictable. In addition, since Herzuma is available as two different presentations - 150 mg/vial and 420 mg/vial, and both presentations are for single-dose, accidental dosing error can be caused by confusion between the two presentations. In

	case the smaller vial (150 mg/vial) is used instead of the larger vial (420 mg/vial), the dose of trastuzumab per kilogram body weight would be lower than originally intended. Such underdosing may lead to reduced efficacy which can possibly harm patients by causing adverse events such as progressive disease.
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.2 - SmPC section 6.6 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: - 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.