SAMSUNG BIOEPIS

Swiss Summary of Risk Management Plan (RMP)

for

Ontruzant® (Trastuzumab)

Samsung Bioepis CH GmbH

Document version: 1.0

Date of this document: Feb 23, 2022

Based on EU RMP version 5.1 (Data Lock Point: Aug 06, 2021)

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 Ontruzant® 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 Ontruzant® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Ontruzant® is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ontruzant®.

The RMP Summary will be checked formally by Swissmedic and, provided there is no cause for complaint, published on the Swissmedic website with a link in www.swissmedicinfo.ch. The marketing authorisation holder will not be informed individually. In the event of a complaint, the marketing authorisation holder will be contacted.

SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ONTRUZANT®

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

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

This summary of the RMP for Ontruzant® 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 Ontruzant®'s RMP.

I. The medicine and what it is used for

Ontruzant® is authorised for early breast cancer, metastatic breast cancer, and metastatic gastric cancer (see SmPC for the full indication). It contains trastuzumab as the active substance and it is given by powder for concentrate for solution for infusion.

Further information about the evaluation of Ontruzant®'s benefits can be found in Ontruzant®'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/ontruzant

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ontruzant®, together with measures to minimise such risks and the proposed studies for learning more about Ontruzant®'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 Ontruzant®, 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 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 Ontruzant® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ontruzant® 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 Ontruzant®. 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 Haematotoxicity Oligohydramnios Pulmonary Disorders
Important potential risks	Infections Medication Error
Missing information	Treatment in Male patients (breast cancer indications only)

II.B Summary of important risks

II.B.1 Important identified risk

Cardiac dysfunction	
Evidence for linking the risk to the medicine	Phase III study SB3-G31-BC; SmPC Herceptin® 150 mg powder for concentrate for solution for infusion; Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	In a systematic review and meta-analysis 27 clinical factors were identified to be associated with risk of incident Heart failure (HF) in 15 observational studies in unselected community populations which followed 456,850 participants over 4–29 years. The strongest independent associations for incident HF were coronary artery disease

Cardiac dysfunction	
	(HR=2.94; 95% CI 1.36 to 6.33), diabetes mellitus (HR=2.00; 95% CI 1.68 to 2.38), age (HR (per 10 years)=1.80; 95% CI 1.13 to 2.87) followed by hypertension (HR=1.61; 95% CI 1.33 to 1.96), smoking (HR=1.60; 95% CI 1.45 to 1.77), male gender (HR=1.52; 95% CI 1.24 to 1.87) and body mass index (HR (per 5 kg/m^2)=1.15; 95% CI 1.06 to 1.25). Atrial fibrillation (HR=1.88; 95% CI 1.60 to 2.21), left ventricular hypertrophy (HR=2.46; 95% CI 1.71 to 3.53) and valvular heart disease (HR=1.74; 95% CI 1.07 to 2.84) were also strongly associated with incident HF but were not examined in sufficient papers to provide pooled hazard estimates.
Risk minimisation measures	<Routine risk minimisation measures> Warning in section 4.4 of the SmPC concerning the risk of cardiac dysfunction and the need for caution in patients with increased cardiac risk. Recommendations concerning cardiac assessment and monitoring before, during and after treatment with trastuzumab. Criteria for discontinuing or interrupting treatment with trastuzumab based on LVEF. The need to institute CHF treatment. Cardiac undesirable effects listed in section 4.8 of the SmPC including Ejection fraction decreased, Cardiac failure congestive, Cardiogenic shock, Acute pulmonary oedema, Pulmonary oedema and Orthopnoea. Prescription only medicine.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: SB3-G31-BC-E (Terminated)

Administration-related reactions	
Evidence for linking the risk to the medicine	Phase III study SB3-G31-BC; SmPC Herceptin® 150 mg powder for concentrate for solution for infusion· Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Patients who are experiencing dyspnoea at rest, due to complications of advanced malignancy or co-morbidities, may be at greater risk of developing a fatal infusion reaction.
Risk minimisation measures	<Routine risk minimisation measures> Section 4.2 of the SmPC describes the correct method of administration for the first and subsequent infusions and the recommended observation

Administration-related reactions	
	times following these infusions. The need to be prepared for managing anaphylaxis and possible actions including interrupting or slowing the infusion rate if infusion-related reactions occur are also described. Section 4.4 warns about the risk of infusion-related-reactions and informs that patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. This section also provides information concerning pre-medication and treatment for these reactions and warns about the possibility of delayed reactions. Section 4.8 of the SmPC lists the following undesirable effects: Infusion related reaction, Erythema, Rash, Swelling face, Wheezing, Dyspnoea, Cough and Lip swelling, Hypersensitivity, Maculopapular rash, Pruritus, Asthma and Hypotension, Urticaria, Anaphylactic reaction, Anaphylactic shock, Angioedema, Respiratory distress, Respiratory failure, Bronchospasm and Laryngeal oedema. Prescription only medicine.

Haematotoxicity	
Evidence for linking the risk to the medicine	Phase III study SB3-G31-BC; SmPC Herceptin® 150 mg powder for concentrate for solution for infusion; Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Risk factors for febrile neutropenia include: increasing age (elderly), abnormal baseline laboratory values in particular, aspartate aminotransferase > 35 U/L, alkaline phosphatase > 120 U/L, or total bilirubin > 1 mg/dl, impaired health status, impaired nutritional status, radiation therapy to the bone marrow and low baseline white cell count. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.
Risk minimisation measures	<Routine risk minimisation measures> The following undesirable effects are listed in section 4.8 of the SmPC: Febrile neutropenia, Anaemia, Neutropenia, White blood cell count decreased/leukopenia and Thrombocytopenia. Prescription only medicine.

Oligohydramnios	
Evidence for linking the risk to the medicine	Phase III study SB3-G31-BC; SmPC Herceptin® 150 mg powder for concentrate for solution for infusion; Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Foetal causes of oligohydramnios include: chromosomal factors, congenital factors, intrauterine growth restriction, post-term pregnancy, premature rupture of the membranes and foetal demise. Placental causes of oligohydramnios include: abruption and twin t o twin transfusion syndrome. Maternal causes of oligohydramnios include: Maternal dehydration, uteroplacental insufficiency, hypertension, pre-eclampsia, diabetes and chronic hypoxia. Drug induced causes of oligohydramnios include: indomethacin an d angiotensin-converting enzyme inhibitors.
Risk minimisation measures	<Routine risk minimisation measures> Section 4.6 of the SmPC warns about the risk of oligohydramnios and foetal harm and advises that women of childbearing potential should use effective contraception during treatment and for 7 months after treatment with trastuzumab. It also states that trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. If a pregnant woman is treated with trastuzumab, or if a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable. Section 4.8 of the SmPC lists the following undesirable effects: Oligohydramnios, Pulmonary hypoplasia and Renal hypoplasia. Prescription only medicine.

Pulmonary disorders	
Evidence for linking the risk to the medicine	Phase III study SB3-G31-BC; SmPC Herceptin® 150 mg powder for concentrate for solution for infusion; Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk	Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be

Pulmonary disorders	
groups	associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. In addition, patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Other risk factors include exposure to environmental toxins, family history of interstitial lung disease and history of smoking.
Risk minimisation measures	<Routine risk minimisation measures> Section 4.3 contraindicates use of trastuzumab in patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy. Section 4.4 warns about the risk of severe pulmonary events including interstitial lung disease together with associated risk factors. These events may occur as part of an infusion-related reaction or with a delayed onset. Section 4.8 of the SmPC lists the following undesirable effects: Pulmonary fibrosis, Lung infiltration and Interstitial lung disease. Prescription only medicine.

II.B.2 Important potential risk

Infections	
Evidence for linking the risk to the medicine	Phase III study SB3-G31-BC; SmPC Herceptin® 150 mg powder for concentrate for solution for infusion. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Risk factors: underlying immunodeficiency, medical co-morbidities (e.g. diabetes, obesity), past infections (re-activation), poor nutritional status, and psychological stress, surgery (especially gastrointestinal), radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures. Tumours of the GI tract can invade the mucosa, causing local abscess formation, bacteraemia, or perforation and resulting peritonitis. Neutrophils are the single most important cells for defence against bacterial infection in cancer patients. Solid organ tumours, such as metastatic carcinoma of the breast, prostate, lung, adrenal, thyroid, and kidney, can all infiltrate the bone marrow and result in neutropenia.
Risk minimisation measures	<Routine risk minimisation measures> Section 4.8 of the SmPC lists the following undesirable effects: Infection, Nasopharyngitis, Neutropenic sepsis, Cystitis, Herpes zoster,

Infections	
	Influenza, Sinusitis, Skin infection, Rhinitis, Upper respiratory tract infection, Urinary tract infection, Erysipelas, Cellulitis, Pharyngitis and Sepsis. Prescription only medicine.

Medication error	
Evidence for linking the risk to the medicine	Phase III study SB3-G31-BC; Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Not applicable.
Risk minimisation measures	<Routine risk minimisation measures> Section 4.2 of the SmPC sates that Ontruzant® treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy. It emphasises the importance of checking the product label to avoid medication errors and stresses that Ontruzant® IV formulation is not intended for subcutaneous administration and should be administered via an IV infusion only. Prescription only medicine.

II.B.3 Missing information

Treatment in male patients (breast cancer indications only)	
Risk minimisation measures	<Routine risk minimisation measures> Prescription only medicine.

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 Ontruzant®.

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

Study Status	Summary of objectives	Safety concern addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
SB3-G31-BC-E: A long-term follow up study for cardiac safety in patients with HER2 positive early or locally advanced breast cancer who have completed the SB3-G31-BC (Terminated)	Primary Objective: To observe the incidence of symptomatic CHF NYHA class II, III and IV and asymptomatic significant LVEF decrease in patients who participated in the SB3-G31-BC study and were treated with SB3 or Herceptin® as neoadjuvant and adjuvant treatment. Secondary Objectives: To observe the incidence of cardiac death and other significant cardiac conditions To observe the long term efficacy of SB3 compared to Herceptin® by: - event-free survival - disease-free survival - overall survival	Cardiac dysfunction	Protocol Submission	Aug 16, 2016
			Study Start	Apr 28, 2016
			Study Finish	Jan 21, 2021 (Last Subject Last Follow-Up)
			Final Report Submission	Jun 16, 2021

< SB3-G31-BC-E summary>

Study short name and title: SB3-G31-BC-E – A long-term follow up study for cardiac safety in patients with HER2 positive early or locally advanced breast cancer who have completed the SB3-G31-BC

Rationale and study objectives: To observe the incidence of cardiac event regarding LVEF decrease after discontinuation of treatment in patients who participated in the SB3-G31-BC study and treated with SB3 or Herceptin®

Study design: Observational cohort study

Study population: Patients with HER2 positive early or locally advanced breast cancer who received Ontruzant® or Herceptin® according to clinical trial SB3-G31-BC

Milestones:

- Study Start: Apr 28, 2016
- Study Finish: Jan 21, 2021 (Last Subject Last Follow-Up)

FINAL REPORT SUBMISSION: JUN 16, 2021