KADCYLA®
Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
Zul.-Nr. 62’892

Public Risk Management Plan (RMP) Summary

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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 “Kadcyla” 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 “Kadcyla” in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. “Roche Pharma (Schweiz) AG” is fully responsible for the accuracy and correctness of the content of the published summary RMP of Kadcyla.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR KADCYLA (TRASTUZUMAB EMTANSINE)

This is a summary of the risk management plan (RMP) for Kadcyla. The RMP details important risks of Kadcyla, how these risks can be minimized, and how more information will be obtained about Kadcyla's risks and uncertainties (missing information).
Kadcyla's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kadcyla should be used.
This summary of the RMP for Kadcyla 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 Kadcyla's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Kadcyla is authorized for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. It contains Trastuzumab Emtansine as the active substance and it is given by intravenous infusion.
Kadcyla is also authorized for treatment in patients with HER2-positive early breast cancer with residual disease in the breast and/or lymph nodes, after pre-operative treatment.
Further information about the evaluation of Kadcyla benefits can be found in Kadcyla's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Kadcyla, together with measures to minimize such risks and the proposed studies for learning more about Kadcyla's 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 package leaflet 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.
In the case of Kadcyla, these measures are supplemented with a*dditional risk minimization* measures mentioned under relevant risks, below.
In addition to these measures, information about adverse events 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 Kadcyla is not yet available, it is listed under 'missing information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Kadcyla 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 Kadcyla.
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 longterm use of the medicine).

List of important risks and missing information	
Important identified risks	• Interstitial lung disease/Acute Respiratory Distress Syndrome • Hepatic Toxicity • Nodular regenerative hyperplasia • Infusion-related reaction • Hypersensitivity • Left ventricular dysfunction • Thrombocytopenia • Peripheral neuropathy
Important potential risks	• Fetal harm • Medication error
Missing information	• Use in patients with hepatic impairment • Use in patients with LVEF <50% • Use in pregnant women • Use in lactating women

II.B Summary of Important Risks

Important identified risk	
Interstitial lung disease/Acute Respiratory Distress Syndrome	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	General risk factors 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. Based on the results from the primary analysis of study BO27938 (KATHERINE), there is a small increase in risk of pneumonitis/radiation pneumonitis associated with concurrent pulmonary radiotherapy and trastuzumab emtansine in EBC patients. However, the majority of pneumonitis/radiation pneumonitis events reported in the study were Grade 1-2, were manageable and had recovered by the clinical cut-off date of the primary analysis. 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.
Risk minimization measures	**Routine risk communication:** Summary of Product Characteristic (SmPC): Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with Interstitial lung disease (ILD) or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥Grade 3 or for Grade 2 not responding to standard treatment. This has been adequately captured in Section 4.4 of European

Important identified risk	
	Union Summary of Product Characteristic (EU SmPC). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Hepatic Toxicity	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Risk factors (in the general population) include age and genetic factors affecting hepatic metabolism of drugs (Bleibel et al. 2007). There are currently no reliable predictors of patients who may or may not be susceptible to hepatotoxicity to trastuzumab emtansine.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.2 (Pharmacokinetic properties) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × upper limit of normal (ULN) and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of European

Important identified risk	
	Union Summary of Product Characteristic (EU SmPC). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Nodular regenerative hyperplasia (NRH)	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	The risk of development of NRH and its potential complications increases with age. Sex and ethnicity do not seem to play a role in the development of NRH (Hartleb et al. 2011). NRH may develop as a result of underlying autoimmune, inflammatory, neoplastic, or idiopathic disease (Hartleb et al. 2011). In an ante-mortem case series, 74% of patients had a coexistent malignant, prothrombotic or rheumatological disease (Morris et al. 2010). It is hypothesized that immunosuppressive medications may induce NRH by damaging endothelial cells of small hepatic veins (Hartleb et al. 2011). There are currently no reliable predictors of patients receiving trastuzumab emtansine who may or may not be susceptible to NRH.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects: Other side effects include: Uncommon

Important identified risk	
	Routine risk minimization activities recommending specific clinical measures to address the risk: Diagnosis of NRH can be confirmed only by histopathology. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued. This has been adequately captured in European Union Summary of Product Characteristics (EU SmPC) Section 4.4 **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Infusion-related reaction	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to infusion-related reactions to trastuzumab emtansine. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnoea at rest, may be at greater risk of severe reactions on the day of or the day after a trastuzumab emtansine infusion. Additionally, patients with a history of infusion reaction to trastuzumab may be at greater risk of a severe reaction due to the trastuzumab component of trastuzumab emtansine. However, patients with severe infusion-related reactions to trastuzumab were excluded from the trastuzumab emtansine clinical studies and therefore data regarding this risk are not available.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.7 Effects on ability to drive and use machines Section 4.8 (Undesirable effects)

Important identified risk	
	Patient Information Leaflet: Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions, driving and using machinery Section 3 How you are given Kadcyla Section 4 Possible side effects: Common (infusion-related reactions) **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Left ventricular dysfunction	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Previous anthracycline therapy, prior or concurrent exposure to taxanes, patients over the age of 50 years, prior or concurrent anti-hypertensive medication use and low LVEF levels prior to or following the use of paclitaxel.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions

Important identified risk	
	Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristics (EU SmPC). The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see Section 4.2). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Hypersensitivity	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	General factors that increase the likelihood of experiencing type I hypersensitivity reactions include repeated exposure to agent, a history of drug hypersensitivity, and use of the IV route (Kang and Saif. 2007). Epidemiological data on the risk factors associated with hypersensitivity to trastuzumab emtansine are discussed under infusion-related reactions.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions

Important identified risk	
	Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8 of European Union Summary of Product Characteristics (EU SmPC). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Thrombocytopenia	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Radiation therapy and certain chemotherapy medications can damage the bone marrow, lowering its production of platelets, and lead to thrombocytopenia. Patients receiving a combination of radiation therapy and chemotherapy are at greater risk for thrombocytopenia. It was noted in study TDM4370g/BO21977 (EMILIA) that Asian patients had a lower baseline platelet count than non-Asian patients. Asian patients had a higher incidence of Grade 3 or Grade 4 thrombocytopenia, as well as a slightly higher incidence of hemorrhagic AEs. However, the frequency of severe hemorrhage was similar among Asian and non-Asian patients. A higher incidence of Grade ⧃3 AEs of platelet count decreased was also reported among Asian patients compared with white patients in EBC Study BO27938 (KATHERINE). The significance of these data is not known.

Important identified risk	
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. See Section 4.4 European Union Summary of Product Characteristics (EU SmPC) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Peripheral neuropathy	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Chemotherapeutic agents that target microtubules (e.g., taxanes, vinca alkaloids) are recognized to cause peripheral neuropathy; the degree and type of peripheral neuropathy depends on the chemotherapy regimen, cumulative dose, administrative schedule, route of administration and presence of pre-existing risk factors (e.g. diabetes mellitus and concurrent or prior use of neurotoxic drugs) (Nurgalieva et al. 2010). In a large population-based study of chemotherapy-induced peripheral neuropathy in the US, a total of 65,316 breast

Important identified risk	
	cancer, 9242 ovarian cancer and 86,278 non-small cell lung cancer patients from 1991-2002 were identified in the Surveillance, Epidemiology and End Results (SEER) cancer registry. Patients treated with taxanes were 2 times more likely to develop peripheral neuropathy compared to those not receiving chemotherapy (adjusted HR=2.22; 95% CI: 1.85-2.66), while patients treated with a platinum-taxane combination were 3 times more likely to develop peripheral neuropathy (adjusted HR=3.33; 95% CI: 2.05-5.05). (Nurgalieva et al. 2010).
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristics (EU SmPC). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Fetal harm	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Oligohydramnios:

Important identified risk	
	Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the antiproliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with metastatic breast cancer (MBC) make pregnancies less likely to occur. Teratogenicity: Treatment with chemotherapy in the first trimester, during organogenesis, substantially increases the risk of fetal malformation compared to exposure to chemotherapy in the second and third trimesters of pregnancy (Gwyn et al. 2005).
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.6 (Fertility, pregnancy and lactation) Section 5.3 (Preclinical safety data) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should use effective contraception while receiving trastuzumab emtansine and for 7 months following the last dose of trastuzumab emtansine. Male patients or their female partners should also use effective contraception. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription.

Important identified risk	
	Additional risk minimization measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Medication error	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Not applicable
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 6.6 (Special precautions for disposal and other handling) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 5 How to store Kadcyla Section 6 Contents of the pack and other information **Routine risk minimization activities recommending specific clinical measures to address the risk:** In order to prevent medication errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not another trastuzumab-containing medicine, like trastuzumab or trastuzumab deruxtecan. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** Educational materials for health care providers.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information	
Use in patients with hepatic impairment	
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × upper limit of normal (ULN) and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristics (EU SmPC). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Use in patients with LVEF <50%	
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla:

Missing information	
	Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. This has been adequately captured in Section 4.4 of EU SmPC. The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see Section 4.2). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Use in pregnant women	
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.6 (Fertility, pregnancy and lactation) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should use effective contraception while receiving trastuzumab emtansine. Male patients or their female partners should also use effective contraception. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical

Missing information	
	prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Use in lactating women	
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.6 (Fertility, pregnancy and lactation) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women should discontinue breast feeding prior to initiating treatment with trastuzumab emtansine. Women may begin breast feeding 7 months following the last dose of trastuzumab emtansine. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 STUDIES WHICH ARE CONDITIONS OF THE MARKETING AUTHORIZATION

None

II.C.2 OTHER STUDIES IN POST-AUTHORIZATION DEVELOPMENT PLAN

None.