Summary of risk management plan for ENHERTU (trastuzumab deruxtecan)

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

Summary of risk management plan for ENHERTU (trastuzumab deruxtecan)

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

The SmPC and package leaflet for trastuzumab deruxtecan give essential information to HCPs and patients on how trastuzumab deruxtecan should be used.

Important new concerns or changes to the current ones will be included in updates of trastuzumab deruxtecan's RMP.

I. The Medicine and What It Is Used For

Trastuzumab deruxtecan is indicated:

- As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least one anti-HER2-based regimen.
- As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer must additionally have received or must be ineligible for endocrine therapy.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of trastuzumab deruxtecan, together with measures to minimise such risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be the following:

• Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and Product Information for human medicinal products 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of trastuzumab deruxtecan, 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 continuously collected and regularly analysed, 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 is not yet available for trastuzumab deruxtecan, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of trastuzumab deruxtecan 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 trastuzumab deruxtecan. 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 (eg, on the long-term use of the medicine).

Table Part VI Module II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Interstitial Lung Disease/Pneumonitis Left Ventricular Dysfunction
Important potential risks	Embryo-foetal Toxicity Product confusion-related medication errors
Missing information	Use in Patients with Moderate or Severe Hepatic Impairment Long-term safety

II.B Summary of Important Risks

Important identified risks with trastuzumab deruxtecan include ILD/pneumonitis and left ventricular dysfunction, as outlined below.

Important Identified Risk 1: Interstitial Lung Disease/Pneumonitis	
Evidence for linking the risk to the medicine	Dose-dependent changes in the lung were seen in nonclinical data (Section Part II: Module SII). ILD/pneumonitis was reported in clinical studies with trastuzumab deruxtecan, including fatal outcomes. An independent Adjudication Committee adjudicated all potential events of ILD.
Risk factors and risk groups	Seven baseline factors of interest were identified: age <65 vs ≥65 years; patients treated in Japan vs non-Japan; dose of >6.4 vs ≤6.4 mg/kg; baseline oxygen saturation <95% vs ≥95%; moderate/severe renal impairment at baseline vs no impairment; presence of lung comorbidities (yes vs no; asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, or radiation pneumonitis); and time since initial diagnosis of >4 vs ≤4 years..
Risk minimisation measures	<u>Routine risk communication:</u> Dosage/Administration section of the Product information for human medicinal products. Warnings and precautions section of the Product information for human medicinal products. Undesirable effects section of the Product information for human medicinal products. <u>Routine risk minimisation measures:</u>

	Recommendation for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in the warnings and precautions section of the Product information for human medicinal products. The use of corticosteroid treatment in ILD/pneumonitis is included in the dosage/administration section of the Product information for human medicinal products. Dose modification guidance for managing the risk of ILD/pneumonitis is included in the dosage/administration section of the Product information for human medicinal products. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in the warnings and precautions section of the Product information for human medicinal products. Additional risk minimisation measures: Healthcare Professional Guide and Patient Card.
Additional pharmacovigilance activities	Prescriber survey

ILD = interstitial lung disease

Important Identified Risk 2: Left Ventricular Dysfunction	
Evidence for linking the risk to the medicine	Cardiotoxicity has been observed with anti-HER2 drugs, including single-agent trastuzumab, which has a warning for cardiomyopathy. LVEF decreases have been observed infrequently in clinical studies with trastuzumab deruxtecan.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk communication: Dosage/Administration section of the Product information for human medicinal products Warnings and precautions section of the Product information for human medicinal products Undesirable effects section of the Product information for human medicinal products Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring of LVEF decrease are included in the warnings and precautions section of the Product information for human medicinal products. Dose modification guidance for managing the risk of LVEF decrease is the dosage/administration section of the Product information for human medicinal products. Additional risk minimisation measures: None

LVEF = left ventricular ejection fraction

Important potential risks considered important for inclusion in the list of safety concerns include embryo-foetal toxicity and product confusion-related medication errors, as outlined below.

Important Potential Risk 1: Embryo-foetal Toxicity	
Evidence for linking the risk to the medicine	Findings from nonclinical data, the potential mechanism of the released drug of trastuzumab deruxtecan and known effects of anti-HER2 agents on embryo-foetal toxicity suggest that trastuzumab deruxtecan may potentially cause foetal harm
Risk factors and risk groups	None
Risk minimisation measures	Routine risk communication: Warnings and precautions section of the Product information for human medicinal products Pregnancy, lactation section of the Product information for human medicinal products Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for pregnancy monitoring and contraception usage are included in the warnings and precautions section and pregnancy, lactation section of the Product information for human medicinal products. Additional risk minimisation measures: None

HER2 = human epidermal growth factor receptor 2

Important Potential Risk 2: Product confusion-related medication errors	
Evidence for linking the risk to the medicine	Medication errors between trastuzumab (ie, Herceptin) and trastuzumab emtansine (ie, KADCYLA) have been reported. Potential for medication errors due to product confusion of trastuzumab deruxtecan with trastuzumab and trastuzumab emtansine indicated for breast cancer treatment is considered.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk communication: Dosage/administration section of the Product information for human medicinal products Other information section of the Product information for human medicinal products Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation measures: Healthcare Professional Guide

Missing information with trastuzumab deruxtecan includes use in patients with moderate or severe hepatic impairment and long-term safety, as outlined below.

Missing Information 1: Use in Patients with Moderate or Severe Hepatic Impairment	
Evidence for linking the risk to the medicine	T-DXd has not been studied in subjects with severe hepatic impairment. A maximum of 10 subjects with moderate hepatic impairment were eligible for inclusion in Study U201; however, only 2 subjects in the All Tumour Types ≥5.4 mg/kg Pool had moderate hepatic impairment at baseline. Based on a population PK analysis, the clearance of the released drug of T-DXd decreases with increasing AST and increasing total bilirubin.
Risk minimisation measures	<u>Routine risk communication:</u> Dosage/Administration section of the Product information for human medicinal products Pharmacokinetics section of the Product information for human medicinal products <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Additional risk minimisation activities:</u> None
Additional pharmacovigilance activities	Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies.

AST = aspartate aminotransaminase; BC = breast cancer; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic; T-DXd = trastuzumab deruxtecan

Missing Information 2: Long-term safety	
Evidence for linking the risk to the medicine	The median treatment duration (defined as: date of last dose − date of first dose + 21) in the HER2-positive BC 5.4 mg/kg Pool (N = 234) was 9.82 months (range: 0.7 to 37.1). A total of 164/234 (70.1%) subjects had been treated for >6 months, 127/234 (54.3%) for >9 months, 69/234 (29.5%) for >12 months, and 5/234 (2.1%) for >24 months.
Risk minimisation measures	<u>Routine risk minimisation communication:</u> None <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Additional risk minimisation activities:</u> None

II.C. Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

Not applicable.

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

Prescriber survey	
Short title	EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis
Purpose of the study	The primary objective is to evaluate the effectiveness of proposed educational material as risk minimization measures by: Evaluating the level of knowledge of educational materials by HCPs of risks, early recognition, diagnosis, and management of ILD/pneumonitis. Evaluating the extent to which HCPs receive the HCP guide and distribute the PC to patients. Safety concern addressed: risk minimization for ILD/pneumonitis.

PK and safety data analysis in patients with moderate hepatic impairment	
Short title	Collection and analysis of PK and safety data in subjects with moderate hepatic impairment from ongoing clinical studies
Purpose of the study	Overall assessment of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies. Safety concern addressed: Missing information: Use in patients with moderate or severe hepatic impairment.

PK = pharmacokinetic