Date: 18 January 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Enhertu

International non-proprietary name: trastuzumab deruxtecan

Pharmaceutical form: powder for concentrate for solution for infusion

Dosage strength: 100 mg

Route(s) of administration: intravenous

Marketing Authorisation Holder: Daiichi Sankyo (Schweiz) AG

Marketing Authorisation No.: 67967

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 29 November 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BC	Breast cancer
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CR	Complete response
CYP	Cytochrome P450
DCO	Data cut-off
DoR	Duration of response
DP	Drug product
DS-8201a	Drug substance trastuzumab deruxtecan
ERA	Environmental Risk Assessment
FL-DP2	Frozen liquid-drug product 2
GLP	Good Laboratory Practice
HER2	Human epidermal growth factor receptor-2
ICH	International Council for Harmonisation
ICR	Independent central review
Ig	Immunoglobulin
ILD	Interstitial lung disease
INN	International Nonproprietary Name
LoQ	List of Questions
Lyo-DP	lyophilised-drug product
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PR	Partial response
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
T-DM1	Trastuzumab emtansine
TKI	Tyrosine kinase inhibitor
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance trastuzumab deruxtecan of the medicinal product mentioned above.

Temporary authorisation for human medical products
The applicant requested a marketing authorisation in accordance with Art. 9, para. 1 TPA. However, based on the submitted clinical data material and the results of the evaluation, Swissmedic granted a temporary authorisation in accordance with Art. 9a TPA and with regard to the guidance document "Authorisation procedures for COVID-19 medicinal products during a pandemic, HMV4"

2.2 Indication and Dosage

2.2.1 Requested Indication

Trastuzumab deruxtecan is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

2.2.2 Approved Indication

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens, including trastuzumab, and have had disease progression on trastuzumab emtansine (T-DM1).

2.2.3 Requested Dosage

5.4 mg/kg administered intravenously over 90 minutes in the first cycle and over 30 minutes in subsequent cycles if the previous infusion was well tolerated, once every 3 weeks (Q3W).

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	14 August 2020
Formal control completed	10 September 2020
List of Questions (LoQ)	8 January 2021
Answers to LoQ	8 April 2021
Predecision	2 July 2021
Answers to Predecision	5 August 2021
Labelling corrections	23 September 2021
Answers to Labelling corrections:	15 October 2021
Final Decision	29 November 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Breast cancer (BC) is the most frequent cancer in women and the leading cause of death from cancer in women. In Switzerland, there are nearly 6,000 new cases of breast cancer per year, with approximately 1,400 deaths from the disease (www.nicer.org). While localised breast cancer is often curable, once the disease has metastasised beyond loco-regional lymph nodes, it remains incurable, with a median overall survival of approximately 3 years and a 5-year survival of about 25%.

The human epidermal growth factor receptor-2 (HER2), is a transmembrane protein overexpressed by approximately 15-20% of invasive breast carcinomas. Since the advent of anti-HER2 targeted agents, the prognosis of patients with HER2-positive tumours has improved significantly. Anti-HER2 targeted agents comprise antibodies such as trastuzumab and pertuzumab, as well as trastuzumab emtansine (T-DM1).

Established first-line treatment of HER2 positive metastatic breast cancer is the combination of the anti-HER2 antibodies trastuzumab and pertuzumab with a taxane, resulting in a median progression-free survival (PFS) of 18.5 months. T-DM1, an antibody-drug conjugate (ADC), is recommended in the second-line setting. Lapatinib can be used in combination with trastuzumab or chemotherapy but has less activity.
Most recently, progress had been made regarding the therapy options for patients pre-treated with standard 1L and 2L treatments. Tucatinib, a tyrosine kinase inhibitor (TKI) of HER2, has been authorised by FDA and Swissmedic earlier this year. Tucatinib combined with capecitabine and trastuzumab improved median PFS from 5.6 months to 7.8 months and median overall survival (OS) from 17.4 months to 21.9 months in patients with metastatic HER2-positive BC pretreated with trastuzumab, pertuzumab and T-DM1 (HER2CLIMB study). Neratinib, another TKI, combined with capecitabine was authorised by the FDA in patients with metastatic HER2-positive BC pretreated with two or more prior anti-HER2 regimens based on the results of the NALA study in February 2021. Median PFS was 5.6 months and median OS 21.0 months compared to 5.5 months and 18.7 months in the control arm lapatinib + trastuzumab, respectively.

Trastuzumab deruxtecan is an ADC consisting of the humanised monoclonal antibody trastuzumab attached to the topoisomerase I inhibitor MAAA-1181a via a cleavable peptide-linker. After cell internalisation, the released drug leads to apoptosis of the target tumour cells via the inhibition of topoisomerase I.

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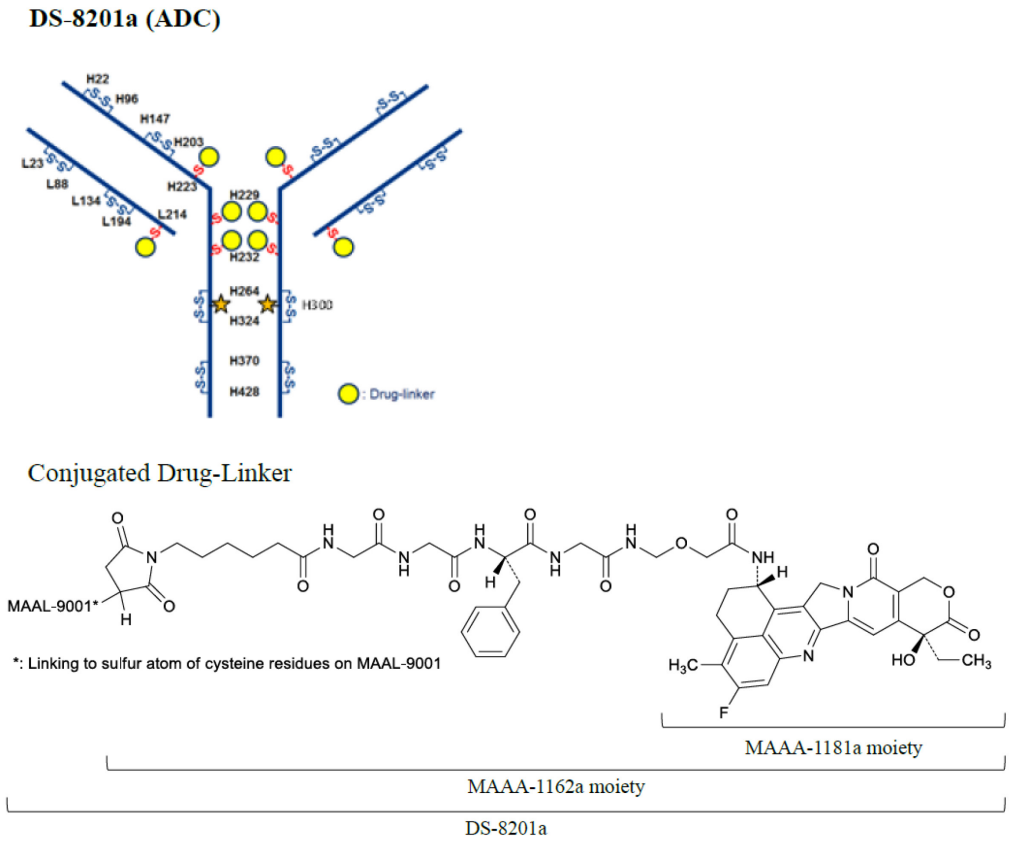
4 Quality Aspects

4.1 Drug Substance

Trastuzumab deruxtecan (DS-8201a drug substance) is an antibody-drug conjugate composed of a monoclonal antibody, MAAL-9001, and a drug-linker, MAAA-1162a. MAAA-1162a is conjugated to reduced cysteine residues at the sites of the inter-chain disulfide bonds between light chain and heavy chain or between heavy chains. The target number of drug-linkers conjugated to each antibody molecule (drug-to-antibody ratio) is 8. The schematic structure of trastuzumab deruxtecan drug substance is shown in Figure 1.1 below.



The intermediate drug substance, the antibody MAAL-9001, is produced from a mammalian cell line (Chinese Hamster Ovary) using a fed-batch production process in a production bioreactor. The other drug substance intermediate MAAA-1162a is manufactured by a multi-step chemical synthesis. The DS-8201a drug substance manufacturing process itself consists of reduction of MAAL-9001, followed by introduction of MAAA-1162a for conjugation, and removal of impurities by diafiltration. Finally, DS-8201a drug substance is concentrated by ultrafiltration, and the pH is adjusted.

Several changes were implemented during the development of the drug substance intermediates and drug substance process, including changes to the manufacturing site or the addition of manufacturing line, production scale, composition of the DS-8201a drug substance, and changes in the cell line for the production of the monoclonal antibody. However, the analytical comparability studies, which included batch release data, extended characterisation, forced degradation studies, and stability data, demonstrated comparability between the different process changes.

The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity tests (e.g. SE-HPLC, rCE-SDS, CEX), protein concentration, and a cell-based potency assay.

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Specifications are based on clinical experience, batch analysis data (release and stability data), and are in conformance with current compendial or regulatory guidelines.

Batch analysis data of non-clinical batches, clinical batches, process performance qualification batches and commercial batches were provided. All specific analytical methods are described and were fully validated.

During storage, no changes were observed under the proposed storage conditions. A shelf-life of 24 months has been accepted.

4.2 Drug Product

Trastuzumab deruxtecan (DS-8201a) drug product (DP) is a 100 mg single-use sterile, lyophilised powder for concentrate for solution for infusion in a type I amber glass vial sealed with a rubber stopper and a flip-off crimp cap. Prior to use, the DP is reconstituted with 5 mL of water for injection to provide a solution with a concentration of DS-8201a of 20 mg/mL, in 25mM histidine buffer that includes 90 mg/mL sucrose and 0.03% (w/v) of polysorbate 80 at pH 5.5. The reconstituted solution is then diluted in an infusion bag containing 5% glucose for dosing via intravenous infusion. All excipients used comply with the European Pharmacopoeia.

During process development of drug product, a few changes were implemented, e.g. the frozen liquid formulation was replaced by a lyophilised powder. Furthermore, a site change was implemented. However, comprehensive characterisation studies, release data, and forced degradation studies, demonstrated comparability with respect to quantitative and qualitative critical quality attributes.

The finished product manufacturing process consists of thawing of formulated drug substance, compounding, sterile filtration, filling, lyophilisation, capping, visual inspection, labelling and secondary packaging.

The process was validated using two filling lines each with three consecutive process performance qualification batches.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, water content, purity tests (e.g. SE-HPLC, rCE-SDS, CEX), protein concentration, visible and subvisible particles, sterility, and bacterial endotoxins, and a cell-based potency assay. All specific methods were validated.

Batch analysis data for several batches, including development batches, clinical batches, process performance qualification batches of both filling lines, and commercial batches were provided. All batch release data comply with the drug product specifications that were valid at the time of batch release.

The drug product is stored at 2 – 8°C. Due to its pharmaceutical form (lyophilisate), the product is quite stable. A shelf-life of 24 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed.

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5 Nonclinical Aspects

Regarding the marketing authorisation application of Enhertu (trastuzumab deruxtecan), the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the FDA assessment report (BLA 761139, dated June 11, 2019).

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Enhertu in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Several safety issues that are of concern for human use were identified in the nonclinical studies. The Nonclinical Safety Specifications in the RMP adequately address these nonclinical findings and their relevance for clinical use. All nonclinical data that are relevant for safety are also adequately mentioned in the information for healthcare professionals.

There is no safety concern regarding impurities and excipients.

According to the ERA provided, the risk of trastuzumab deruxtecan to the environment is assumed to be low.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data in this application has been carried out in reliance on previous regulatory decisions by FDA. The available assessment reports and respective product information were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, see Chapter 8.1 of this report.

6.2 Dose Finding and Dose Recommendation

Study DS8201-A-J101 was a non-randomised, open-label, multiple-dose, first-in-human study of DS-8201a in patients with advanced solid malignant tumours and included a dose escalation part evaluating a dose range of 0.8 mg/kg to 8.0 mg/kg Q3W (once every 3 weeks) to identify the maximum tolerated dose and the recommended phase 2 dose (RP2D). Doses up to 8 mg/kg were tolerable, and no drug limiting toxicity was reported. No maximum tolerated dose was reached. Based on the exposure-response analyses and the balance between efficacy and safety across the dose range evaluated in Part 1 of study DS8201-A-J101, doses of 5.4 mg/kg and 6.4 mg/kg administered Q3W were selected for the dose expansion part (Part 2) of the pivotal study DS8201-A-U201. The 6.4 mg/kg dose regimen did not show a relevant dose effect in terms of efficacy, supporting the choice of 5.4 mg/kg from an efficacy point of view.

6.3 Efficacy

The applicant submits one pivotal phase 2 study (DS8201-A-U201) in patients with HER2-positive unresectable or metastatic breast cancer (BC) with a PK/dose finding part and a confirmation part and one supportive phase 1 study (DS8201-A-J101) with dose escalation and dose expansion parts in patients with HER2-expressing solid tumours including breast cancer.

Study U201 (DS8201-A-U201) is an ongoing, open-label, multicentre, two-part study designed to justify the recommended dose of DS-8201a and to investigate further its safety and efficacy in patients with unresectable and/or metastatic HER2-positive BC previously treated with T-DM1.

The study consisted of two parts: The first randomised part was composed of a PK stage and a dose finding stage after selection of two dose levels of the PK stage. The dose finding stage was randomised 1:1 to the two doses selected based on the PK stage (5.4 mg/kg and 6.4 mg/kg), and a dose-justification exposure-response (exposure-efficacy and exposure-safety) analysis was performed in order to determine the recommended phase 2 dose (RP2D) of trastuzumab deruxtecan. In the second non-randomised part all patients received trastuzumab deruxtecan at the RP2D of 5.4 mg/kg.

The primary objective of the study was to establish the objective response rate (ORR), assessed by an independent central review (ICR) based on response evaluation criteria in solid tumours (RECIST 1.1). Key secondary endpoints were duration of response (DoR), progression-free survival (PFS), and overall survival (OS).

Trastuzumab deruxtecan was administered at 5.4 mg/kg (6.4 mg or 7.4 mg/kg in part 1 only) as an intravenous (IV) infusion once every 3 weeks, on day 1 of each 21-day cycle. Treatment was to be continued until progressive disease (PD), unacceptable toxicity or withdrawal of consent. Two drug product dosage forms were used: frozen liquid-drug product 2 (FL-DP2) and its lyophilised form, and lyophilised-drug product (Lyo-DP). Drug formulation FL-DP2 was applied in 76/184 (41.3%) patients and Lyo-DP in 108/184 (58.7%) patients as it became available. The two drug dosage forms were equivalent with regard to efficacy and safety.

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Treatment response was assessed every 6 weeks by a CT or MRI scan of the chest, abdomen and pelvis. A blinded ICR of patient radiographic studies with assessment of response using modified RECIST 1.1 was conducted on an ongoing basis by two independent radiologists.

Patients were eligible if they had centrally confirmed HER2-positive (according to American Society of Clinical Oncology - College of American Pathologists guidelines), unresectable or metastatic BC that was resistant or refractory to T-DM1 and with documented clinical or radiographic progression of disease during or after treatment with T-DM1. In addition, patients needed to have measurable disease, Eastern Co-operative of Oncology Group (ECOG) performance status of 0-1 and adequate organ and bone marrow function. Patients with a history of interstitial lung disease (ILD)/pneumonitis or unstable brain metastases were excluded from the trial.

A sample size of 150 patients (50 patients from part 1 who received the optimal dose level and 100 patients from Part 2a) provided an ORR with 95% CI within plus or minus 10% of the ORR. The probabilities of observing the lower bound of the 95% CI > 20% and an ORR of ≥ 30% were 98.2% and 91.6% under the expected ORR=35%, respectively. No formal interim analysis of efficacy was performed. Efficacy endpoints were summarised by descriptive statistics.

Overall n=253 patients were enrolled (n=119 in part 1, n=134 in part 2). This assessment report will focus on the n=184 patients with HER2-positive BC of part 1 and part 2 (n=50 part 1 [n=22 PK stage and n=28 dose finding stage] and n=134 part 2), who were treated with the proposed dose and are representing the target population.

Results were presented with the most recent data cut-off (DCO) of 08 Jun 2020, with a median duration of survival follow-up of 20.5 months.

At DCO, treatment was ongoing in 20.1% (n=37) of patients. The most common reasons for discontinuation were progression of disease (81/147, 55.1%), adverse events (33/147, 22.4%), and withdrawal of consent (10/147, 6.8%).

The median age was 55.0 years (range 28.0 – 96.0 years). All patients were female (100%) and mostly White (54.9%) or Asian (38.0%).
The majority of patients presented with metastatic disease at baseline (93.5%), most commonly with visceral (91.8%), pulmonary (57.1%), and liver metastases (30.4%). Brain metastases were present in 13% (24/184) of patients. HER2 status was centrally assessed in all patients with the exception of n=2.

The study population was heavily pre-treated, and the majority of patients (90.8%) had received three or more prior regimens for locally advanced/metastatic disease (excluding hormone therapy). Prior therapy with trastuzumab, T-DM1 and pertuzumab was reported in 100%, 100% and 65.8% of patients, respectively.
Almost all patients had a prior anti-HER2 regimen in the locally advanced/metastatic setting (94.6%) with a median number of three prior regimens. The remainder had received it in the adjuvant setting. Almost all patients had progressive disease as a reason for discontinuation of prior T-DM1 (97.8%).

The primary endpoint, confirmed ORR based on ICR, was 61.4% (95% CI: 54.0, 68.5) in the intention-to-treat (ITT) population: 12/184 (6.5%) of patients had a complete response (CR) and 101/184 (54.9%) had a partial response (PR). Only n=2 patients were non-evaluable. ORR results across subgroups were overall consistent although regarded as exploratory. ORR according to drug formulation (frozen-liquid vs lyophilised) was comparable.

The secondary endpoint, median DoR in 112 responders, was 20.8 months (95% CI: 15.0, NE). Data were immature at DCO (event rate 35%), and a high number of patients was censored due to reasons other than ongoing without progressive disease (46/73). Reasons were defined as “discontinuation

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before PD/death", "initiation of new anti-cancer therapy", and "PD/death observed after missing two or more assessments". A sensitivity analysis of DoR considering these three situations as events resulted in a median DoR of 10.0 months (95% CI: 7.9, 12.7).

Median PFS was 19.4 months (95% CI: 14.1, NE). Data were immature with an event rate of 38%. The applicant provided a sensitivity analysis with conservative censoring rules considering "discontinuation before PD/death", "initiation of new anti-cancer therapy", and "PD/death observed after missing two or more assessments" as events. The recalculated median PFS was 9.5 months (95% CI: 7.0, 11.3).

Both the median DoR and the median PFS appear to be overestimated by the initial analyses.

Updated OS data with DCO of 15 Jan 2021 showed an increase from 24.6 months (95% CI: 23.1, NE) to 28.4 months (95% CI: 24.6, 37.2) compared to the DCO of Jun 2020. The event rate was 49.5%.

6.4 Safety

The pooled safety data are based on the data for n=234 patients with HER2-positive BC treated at 5.4 mg/kg of study J101 and study U201 at DCO of 01 Aug 2019. In parts, updated safety data with DCO of 08 Jun 2020 were available.
Median exposure to trastuzumab deruxtecan was 9.8 months in the 234 BC patients. A total of 69/234 (29.5%) of patients were treated for at least 12 months. Uncertainty remains regarding long-term toxicity due to the limited duration of exposure and the proposed "long-term" use.

Almost all patients experienced a treatment-emergent adverse event (TEAE) of any grade (99.6%). Nausea was the most frequently observed TEAE of any grade (79.9%), followed by fatigue (49.1%), vomiting (48.7%), alopecia (46.2%), constipation (35.9%), decreased appetite (34.6%), red blood cell count decrease/anaemia (33.8%), neutrophil count decrease/neutropenia (32.5%), diarrhoea (30.8%), platelet count decrease/thrombopenia (23.1%), cough (21.4%), and white blood cell count decrease/leukopenia (20.5%). Haematological toxicity was reported frequently. Neutrophil count decreased/neutropenia was ≥G3 in 44/234 (18.8%) of patients. However, no treatment discontinuation due to neutrophil count decreased/neutropenia was reported and rate of febrile neutropenia was rather low (4/234 [1.7%]).
Also very common was gastrointestinal toxicity: nausea was ≥ G3 in 16/234 (6.8%), however no treatment discontinuation was required. Diarrhoea was ≥G3 in 6/234 (2.6%) leading to treatment discontinuation in n=1 patient.

The rate of ILD adjudicated as study drug-related in the pooled HER2-positive BC population treated at a dose level of 5.4 mg/kg in study J101 and U201 was 15.0% (35/234) at DCO 08 Jun 2020. Most of these events were G1-2 (27/35). N=7 grade 5 events were reported, which means 20% of all ILD/pneumonitis events reported. Approximately one third of the ILD events recovered and another third did not recover. Median time to onset of ILD event was 168 days (5.5 months) with a range of 1.2 months up to 20.8 months. Of note, the rates of ILD in patients receiving higher doses of trastuzumab deruxtecan (≥ 6.4 mg/kg) were significantly higher both in the BC and all-cancer cohorts, at 25.5% and 21.3%, respectively.
Uncertainty remains regarding the use of trastuzumab deruxtecan in patients with a history of ILD, which is described as a risk of prior treatments as T-DM1 and trastuzumab. Study data for patients with a history of ILD are very limited.

With DCO of 01 Aug 2019, overall n=39 (17.8%) events of left ventricular ejection fraction decrease (broader definition combined with laboratory data) were reported in the pooled BC population with available post-baseline data (n=219). Most of these events were G1-2 (38/39), a single event of G3 was reported.

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Hypokalaemia (12.8%, G3-4: 3.4%) was common, although no event of cardiac arrhythmia was reported. Mild, transient, and reversible increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed (10.7% [G3-4: 1.3%] and 15.0% [G3-4: 0.9%], respectively). Infusion-related reactions were reported in 2.6% of patients, all events were G1-2. The event of QTc prolongation was reported in 6.0% of patients, and 3.4% of patients had a maximum change from baseline >60 ms. No symptomatic QT prolongation, torsade de pointes, or severe arrhythmic events were reported.

More than half of the patients had a ≥G3 TEAE (54.7%). The most frequently reported ≥G3 TEAEs (in at least 5% of patients) were neutrophil count decrease/neutropenia (18.8%), red blood cell count decrease/anaemia (9.0%), nausea (6.8%), fatigue (5.6%), white blood cell count decrease/leukopenia (5.6%) and lymphocyte count decrease (5.1%).

TEAEs leading to death were reported in n=13 patients (5.6%); n=10 from study U201 and n=3 from study J101 (at DCO Jun 2020). TEAEs leading to death by preferred term were respiratory failure (n=3), disease progression, pneumonitis (n=2 each), acute hepatic failure and acute kidney injury (in n=1 patient), acute respiratory failure, general physical health deterioration, lymphangitis (pulmonary), pneumonia, and shock haemorrhagic (n=1 patient each). There is a significant risk of respiratory/pulmonary mortality associated with the treatment of trastuzumab deruxtecan.

Treatment-emergent serious adverse events were reported in 54 (23.1%) patients in the HER2-positive BC 5.4 mg/kg pool, with events reported in ≥1% of patients in the following preferred terms: pneumonia (n=5), respiratory failure (n=5), cellulitis (n=4), vomiting (n=4), pleural effusion (n=3), nausea (n=3), intestinal obstruction (n=3), and hypokalaemia (n=3), and adjudicated drug-related ILD in 12 (5.1%) patients.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Breast cancer (BC) is the most frequent cancer in women and the leading cause of death from cancer in women. In Switzerland, there are nearly 6,000 new cases of breast cancer per year with approximately 1,400 deaths from the disease. In the metastatic setting, the disease is incurable with a median overall survival (OS) of approximately 3 years and a 5-year survival of only about 25%. While considerable progress has been made in the treatment of metastatic HER2-positive breast cancer, there remains an important medical need for safe and efficacious treatment options, particularly in this late line setting.

Trastuzumab deruxtecan is an ADC composed of the humanised monoclonal antibody trastuzumab attached to the topoisomerase I inhibitor MAAA-1181a. The drug has been approved in the US (accelerated approval in Dec 2019) and in the EU (conditional approval in Jan 2021). The applicant requested regular approval in Switzerland and provided efficacy data from the pivotal phase 2 study U201 supported by efficacy results from the dose finding study J101 for the 3L indication of locally advanced or metastatic HER2-positive BC after at least two prior anti-HER2 regimens. Patients were to have documented progression on previous T-DM1 therapy.
To date, three phase 3 studies evaluating the efficacy and safety of trastuzumab deruxtecan are ongoing, of which study U301 could serve as confirmatory trial. The target population consists of HER2-positive, unresectable and or metastatic BC patients who progressed after prior standard of care HER2 therapies, including T-DM1.
The requested dose of 5.4 mg/kg Q3W was chosen as RP2D, based on the comparison of safety and efficacy data at 5.4 mg/kg and 6.4 mg/kg Q3W evaluated in Study J101 (Part 1 and Part 2) and Part 1 of Study U201, and is acceptable. Two different drug formulations were used: FL-DP1 in study J101 (with the exception of cohort 2e, which received FL-DP2) and FL-DP2 in study U201 (in about 40% of patients). The commercially available product Lyo-DP was used in the remaining 60% of patients in study U201, no change to the formulation was made. Efficacy and safety were not significantly different in both drug dosage forms.

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Beneficial effects
Trastuzumab deruxtecan showed clinically meaningful efficacy in this heavily pre-treated population. ORR was high, at 61.4%, and durable, with more than half of the patients having an ongoing response at 18 months (57.1%). The observed response rate exceeds the results reported in similar patient populations with the caveat of known limitations of cross-study comparisons.
With its response to the list of questions, the applicant provided updated OS data with the lower bound of the 95% confidence interval exceeding median OS of historic control data. So far, 49.5% of OS events have occurred in study U201.

Uncertainty in the knowledge about the beneficial effects
The design of study U201 as a single-arm, open-label, phase 2 study does not meet the regulatory requirements of a confirmatory trial according to the ICH E9 guidelines. Due to the missing comparator arm, selection bias cannot be excluded.
The primary endpoint of ORR is not established as a valid surrogate parameter in the setting of metastatic breast cancer. Without a comparator arm, no valid assessment of time to event endpoints such as duration of response (DoR), progression-free survival (PFS) and overall survival (OS) is possible. In addition, the data are immature to borderline mature. The secondary endpoints, DoR and PFS, did not show robust results when applying conservative censoring.

Unfavourable effects (risks)
The safety assessment is based primarily on n=234 patients with HER2-positive BC treated at the proposed dose level of 5.4 mg/kg in study J101 and study U201, with a median exposure to trastuzumab deruxtecan of 10 months. Toxicity observed was a combination of the known toxicity profile of trastuzumab and the topoisomerase inhibitor I component MAAA-1181a, with high rates of haematological and gastrointestinal toxicity. Approximately half of all TEAEs leading to death (overall rate 5%) were due to pneumonitis/ILD, which is an important identified risk of trastuzumab deruxtecan.

Uncertainty in the knowledge about the unfavourable effects
There are no safety data available in humans regarding the tolerability and safety of free MAAA-1181a. In addition, there are no data directly comparing trastuzumab-deruxtecan with free trastuzumab.
Uncertainty exists regarding long-term toxicity due to the limited duration of exposure and the proposed “long-term” use. In addition, the safety population is of limited size.
Patients with a history of ILD/pneumonitis were excluded from the later phase of the studies, and only n=2 patients with known prior ILD/pneumonitis were investigated. Although these data are very limited, exclusion of patients with a history of ILD by adding a contraindication appears inappropriate from a clinical perspective, given that these patients are heavily pre-treated and have very limited treatment options. However, careful instructions for the prescribers are mandatory regarding the fatal cases of ILD/pneumonitis. The proposed mitigating strategies for ILD, including guidance for health care professionals and patients, are considered appropriate, and includes a boxed warning in the product information.

Updated benefit-risk assessment
There is a high unmet medical need in this target population after a minimum of two anti-HER2 based regimens and a lack of standard of care. The ORR and DoR reported in study U201 are considered clinically meaningful compared to historic controls in this setting and supported by favourable OS results. Nevertheless, multiple uncertainties persist due to the missing comparator arm leading to potential selection bias, the lack of robustness of secondary endpoints, and relevant toxicity.
Therefore, the currently available data are considered insufficient to support regular approval of trastuzumab deruxtecan. Therefore, a temporary approval has been granted. The ongoing phase 3 study U301 is supposed to provide randomised confirmatory data for the requested indication within the next two years.

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6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Enhertu was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Enhertu is temporarily authorised – see "Properties/Effects" section.

Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with Enhertu. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue Enhertu in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.

Enhertu 100 mg powder for concentrate for solution for infusion

Composition

Active substances

Trastuzumabum deruxtecanum is composed of an antibody (produced in Chinese hamster ovary cells by recombinant DNA technology) conjugated via a linker to the topoisomerase I inhibitor, DXd.

Excipients

L-histidinum, L-histidini hydrochloridum monohydricum, saccharum, polysorbatum 80.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion.
White to yellowish white lyophilised powder.
One vial of lyophilised powder for concentrate for solution for infusion contains 100 mg of trastuzumab deruxtecan.

Indications/Uses

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based

regimens, including trastuzumab and have had disease progression on trastuzumab emtansine (T-DM1).

Dosage/Administration

Enhertu should be prescribed by a physician and administered under the supervision of a healthcare professional experienced in the use of anticancer medicinal products. In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.
Do not substitute Enhertu for or with trastuzumab or trastuzumab emtansine.

Posology

The recommended dose of Enhertu is 5.4 mg/kg given as an intravenous infusion once every three weeks (21-day cycle) until disease progression or unacceptable toxicity.
The initial dose should be administered as a 90-minute intravenous infusion. If the prior infusion was well tolerated, subsequent doses of Enhertu may be administered as 30-minute infusions.
The infusion rate of Enhertu should be slowed or interrupted if the patient develops infusion-related symptoms. Enhertu should be permanently discontinued in case of severe infusion reactions.
Antiemetics may be administered in accordance with local medical practice as per patient tolerance for prophylaxis or management.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Dose modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of Enhertu per guidelines provided in Tables 1 and 2.
Enhertu dose should not be re-escalated after a dose reduction is made.

Table 1: Dose reduction schedule

Dose reduction schedule (Starting dose is 5.4 mg/kg.)	**Dose to be administered**
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment.

Table 2: Dose modifications for adverse reactions

Adverse reaction	**Severity**	**Treatment modification**

Adverse reaction	Severity		Treatment modification
Interstitial lung disease (ILD)/pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)		Interrupt Enhertu until resolved to Grade 0, then: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section “Warnings and precautions”).
	Symptomatic ILD/pneumonitis (Grade 2 or greater)		• Permanently discontinue Enhertu. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section “Warnings and precautions”).
Neutropenia	Grade 3 (less than 1.0-0.5 × 10^9/L)		• Interrupt Enhertu until subsided to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 × 10^9/L)		• Interrupt Enhertu until subsided to Grade 2 or less. • Reduce dose by one level (see Table 1).
Febrile neutropenia	Absolute neutrophil count of less than 1.0 × 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour.		• Interrupt Enhertu until resolved. • Reduce dose by one level (see Table 1).
Left ventricular ejection fraction (LVEF) decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with Enhertu.
	LVEF 40% to 45%	And absolute decrease from baseline	• Continue treatment with Enhertu. • Repeat LVEF assessment within 3 weeks.

Adverse reaction	Severity		Treatment modification
		is less than 10%	
		And absolute decrease from baseline is 10% to 20%	• Interrupt Enhertu. • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue Enhertu. • If LVEF recovers to within 10% from baseline, resume treatment with Enhertu at the same dose.
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		• Interrupt Enhertu. • Repeat LVEF assessment within 3 weeks. • If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue Enhertu.
	Symptomatic congestive heart failure (CHF)		• Permanently discontinue Enhertu.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

Delayed or missed dose

If a planned dose is delayed or missed, it should be administered as soon as possible without waiting until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion should be administered at the dose and rate the patient tolerated in the most recent infusion.

Special populations

Elderly patients

No dose adjustment of Enhertu is required in patients aged 65 years or older. Limited data are available in patients ≥75 years of age.

Patients with renal impairment

No dose adjustment is required in patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment (see section “Pharmacokinetics”). No data are available in patients with severe renal impairment.

Patients with hepatic impairment

No dose adjustment is required in patients with mild (total bilirubin ≤ upper limit of normal [ULN] and any aspartate transaminase [AST] >ULN or total bilirubin >1 to 1.5 times ULN and any AST) hepatic impairment. There are insufficient data to make a recommendation on dose adjustment in patients with moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment (see section “Pharmacokinetics”). No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment.

Children and adolescents

The safety and efficacy in children and adolescents below 18 years of age have not been established as there is no relevant use in the paediatric population for the indication of metastatic breast cancer.

Mode of administration

Enhertu is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. Enhertu must not be administered as an intravenous push or bolus.
For instructions on reconstitution and dilution of the medicinal product before administration (see section “Other information”, “Instructions and special precautions for handling and disposal”).

Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section “Composition”.

Warnings and precautions

Interstitial lung disease/pneumonitis

Cases of interstitial lung disease (ILD), and/or pneumonitis, have been reported with Enhertu (see section “Undesirable effects”). Fatal outcomes have been observed. Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. Patients should be monitored for signs and symptoms of ILD/pneumonitis. Evidence of ILD/pneumonitis should be promptly investigated. Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g. ≥0.5 mg/kg/day

prednisolone or equivalent). Enhertu should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see section “Dosage/Administration”). For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g. ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Enhertu should be permanently discontinued in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD/pneumonitis (see section “Dosage/Administration”). Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis.

Neutropenia

Cases of neutropenia, including febrile neutropenia, were reported in clinical studies of Enhertu. Complete blood counts should be monitored prior to initiation of Enhertu and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, Enhertu may require dose interruption or reduction (see section “Dosage/Administration”).

Left ventricular ejection fraction decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. LVEF should be assessed prior to initiation of Enhertu and at regular intervals during treatment as clinically indicated. Enhertu should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Enhertu should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (see section “Dosage/Administration”).

Embryo-foetal toxicity

Enhertu can cause foetal harm when administered to a pregnant woman. In postmarketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu, DXd, can also cause embryo-foetal harm when administered to a pregnant woman (see section “Pregnancy, lactation”).
The pregnancy status of females of reproductive potential should be verified prior to the initiation of Enhertu. The patient should be informed of the potential risks to the foetus. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose of Enhertu. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Enhertu and for at least 4 months after the last dose of Enhertu (see section “Pregnancy, lactation”).

Interactions

Effects of other medicinal products on the pharmacokinetics of Enhertu

In vitro, DXd was a substrate of P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP.
Co-administration with ritonavir, a dual inhibitor of OATP1B/CYP3A, or with itraconazole, a strong CYP3A inhibitor, resulted in no clinically meaningful increase in exposures of Enhertu or the released topoisomerase I inhibitor, DXd. No dose adjustment is required during co-administration of Enhertu with medicinal products that are inhibitors of OATP1B or CYP3A.
No clinically meaningful interaction is expected with medicinal products that are inhibitors of P-glycoprotein (P-gp), MATE2-K, MRP1, or BCRP transporters.

Effects of Enhertu on the pharmacokinetics of other medicinal products

In vitro studies indicate DXd does not inhibit or induce major CYP450 enzymes including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A. *In vitro* studies indicate that DXd does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters. No clinically meaningful drug-drug interaction is expected with medicinal products that are substrates of OAT1 or OATP1B1 transporters.

Pregnancy, lactation

Women of childbearing potential/contraception in males and females

Pregnancy status of women of childbearing potential should be verified prior to initiation of Enhertu.
Women of childbearing potential should use effective contraception during treatment with Enhertu and for at least 7 months following the last dose.
Men with female partners of childbearing potential should use effective contraception during treatment with Enhertu and for at least 4 months following the last dose.

Pregnancy

There are no available data on the use of Enhertu in pregnant women. However, in postmarketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu, DXd, can also cause embryo-foetal harm when administered to a pregnant woman (see section “Preclinical data”).
Enhertu must not be used during pregnancy unless clearly necessary. If Enhertu is administered during pregnancy, or if a woman becomes pregnant during treatment or within 7 months following the last dose of Enhertu, it is necessary to point out the possibility of harm to the foetus.

Lactation

It is not known if trastuzumab deruxtecan is excreted in human milk. Due to the potential for serious adverse reactions in breast-feeding infants, women should discontinue breast-feeding prior to initiating treatment with Enhertu and breast-feeding must not take place during treatment. Women may begin breast-feeding 7 months after concluding treatment.

Fertility

No dedicated fertility studies have been conducted with Enhertu. Based on results from animal toxicity studies, Enhertu may impair male reproductive function and fertility (see section “Preclinical data”).

It is not known whether trastuzumab deruxtecan or its metabolites are found in seminal fluid. Before starting treatment, male patients should be advised to seek counselling on sperm storage. Male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of Enhertu.

Effects on ability to drive and use machines

Enhertu is not expected to affect patients’ ability to drive or use machines. Because of potential adverse reactions such as fatigue, headache and dizziness (see section “Undesirable effects”), patients should be advised to use caution when driving or operating machinery.

Undesirable effects

Summary of the safety profile

The safety of Enhertu has been evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of Enhertu 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101.

- The most common adverse reactions (frequency ≥20%) were nausea (79.9%), fatigue (60.3%), vomiting (48.7%), alopecia (46.2%), constipation (35.9%), decreased appetite (34.6%), anaemia (33.8%), neutropenia (32.5%), diarrhoea (30.8%), thrombocytopenia (23.1%), cough (21.4%), leukopenia (20.5%), and headache (20.1%).
- The most common serious adverse reactions (frequency ≥1%) were ILD (5.1%), vomiting (1.7%), nausea (1.3%), and hypokalaemia (1.3%).
- The most common National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE v.4.03) Grade ≥3 adverse reactions (frequency >1%) were neutropenia (18.8%), anaemia (9.0%), nausea (6.8%), fatigue (6.4%), leukopenia (5.6%), lymphopenia (5.1%), vomiting (4.3%), thrombocytopenia (4.3%), hypokalaemia (3.4%), interstitial lung disease (ILD, 3.0%), diarrhoea (2.6%), febrile neutropenia (1.7%), dyspnoea (1.7%), abdominal

pain (1.3%), decreased appetite (1.3%), and alanine aminotransferase increased (1.3%). In 2.6% patients ILD led to death.

- Dose interruptions due to adverse reactions occurred in 25% of patients treated with Enhertu. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (14.5%), anaemia (3.4%), upper respiratory tract infection (3.0%), leukopenia (3.0%), ILD (2.6%), thrombocytopenia (2.6%), and fatigue (2.1%). Dose reductions occurred in 15% of patients treated with Enhertu. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue (3.8%), nausea (3.4%), and neutropenia (3.4%). Discontinuation of therapy due to an adverse reaction occurred in 11% of patients treated with Enhertu. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (9.4%).

Tabulated list of adverse reactions

The adverse reactions in 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of Enhertu 5.4 mg/kg are presented in Table 3. The adverse reactions are listed by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions in patients treated with trastuzumab deruxtecan

System organ class/preferred term or grouped term	Frequency
Infections and infestations	
Upper respiratory tract infection[a]	Very common (18.4%)
Blood and lymphatic system disorders	
Neutropenia[b]	Very common (32.5%)
Anaemia[c]	Very common (33.8%)
Leukopenia[d]	Very common (20.5%)
Lymphopenia[e]	Very common (11.1%)
Thrombocytopenia[f]	Very common (23.1%)
Febrile neutropenia	Common (1.7%)
Metabolism and nutrition disorders	

Hypokalaemia	Very common (12.8%)
Decreased appetite	Very common (34.6%)
Nervous system disorders	
Headache[g]	Very common (20.1%)
Dizziness	Very common (10.7%)
Eye disorders	
Dry eye	Very common (11.5%)
Respiratory, thoracic and mediastinal disorders	
Interstitial lung disease[h]	Very common (13.7%)
Dyspnoea	Very common (14.5%)
Cough	Very common (21.4%)
Epistaxis	Very common (14.1%)
Gastrointestinal disorders	
Nausea	Very common (79.9%)
Vomiting	Very common (48.7%)
Diarrhoea	Very common (30.8%)
Abdominal pain[i]	Very common (19.7%)
Constipation	Very common (35.9%)
Stomatitis[j]	Very common (15.0%)
Dyspepsia	Very common (14.1%)
Skin and subcutaneous tissue disorders	
Alopecia	Very common (46.2%)
Rash[k]	Very common (12.8%)
General disorders and administration site conditions	
Fatigue[l]	Very common (60.3%)
Investigations	
Alanine aminotransferase increased	Very common (10.7%)
Aspartate aminotransferase increased	Very common (15.0%)

Ejection fraction decreased[m]	Very common (16.7%)
Injury, poisoning and procedural complications	
Infusion-related reactions[n]	Common (2.6%)

[a] Includes influenza, influenza-like illness, and upper respiratory tract infection.

[b] Includes neutropenia and neutrophil count decreased.

[c] Includes anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased.

[d] Includes leukopenia and white blood cell count decreased.

[e] Includes lymphopenia and lymphocyte count decreased.

[f] Includes thrombocytopenia and platelet count decreased.

[g] Includes headache, sinus headache, and migraine.

[h] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organising pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

[i] Includes abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.

[j] Includes stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

[k] Includes rash, rash pustular, and rash maculopapular.

[l] Includes fatigue and asthenia.

[m] Includes laboratory parameters of LVEF decrease (n = 37) and/or preferred terms of ejection fraction decreased (n = 3), cardiac failure (n = 1) and cardiac failure congestive (n = 1).

[n] Cases of infusion-related reactions include infusion-related reaction (n = 4), hypersensitivity (n = 1), and flushing (n = 1).

Description of selected undesirable effects

Interstitial lung disease

In clinical studies (n = 234), ILD occurred in 13.7% of patients. Most ILD cases were Grade 1 (2.6%), Grade 2 (8.1%) or Grade 3 (0.4%). Grade 5 events occurred in 2.6% of patients. Median time to first onset was 4.4 months (range: 1.2 to 11.1) (see section “Warnings and precautions”).

Neutropenia

In clinical studies (n = 234), a decrease in neutrophil count was reported in 32.5% of patients and 18.8% had Grade 3 or 4 events. Febrile neutropenia was reported in 1.7% of patients (see section “Warnings and precautions”).

Left ventricular ejection fraction decrease

In clinical studies (n = 234), three cases (1.3%) of asymptomatic LVEF decrease, of which 2 (0.9%) were Grade 2 and 1 (0.4%) was Grade 3, were reported. Observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 37 (16.9%); all were Grade 2. No decreases of LVEF to less than 40% or absolute decrease from baseline of greater than 20% were observed. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment (see section “Warnings and precautions”).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The measurement of antibodies is dependent on assay sensitivity and specificity. The rate of antibody positivity found is dependent on numerous factors; therefore, comparison of the rates with other therapies may be misleading. A neutralising effect of antibodies to Enhertu was not investigated. Across all doses evaluated in clinical studies, 0.6% (4/640) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with Enhertu. There was no association between development of antibodies and allergic-type reactions.

Children and adolescents

Safety has not been established in this population.

Elderly patients

Of the 234 patients with HER2-positive breast cancer treated with Enhertu 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (49%) as compared to younger patients (37%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no information on overdose with trastuzumab deruxtecan. In the event of overdose, patients should be monitored and appropriate supportive care should be given.

Properties/Effects

ATC code

L01XC41 (proposed)

Mechanism of action

Enhertu, trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate (ADC). The antibody is a humanised anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd), bound by a tetrapeptide-based cleavable linker. The ADC is stable in plasma. Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. DXd, an exatecan derivative, is approximately 10 times more potent than SN-38, the active metabolite of irinotecan.

Pharmacodynamics

The administration of multiple doses of trastuzumab deruxtecan (6.4 mg/kg every 3 weeks) did not show any clinically meaningful effect on the QTc interval (i.e., >20 ms) in an open-label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer.

Clinical efficacy

Temporary authorisation

The medicinal product Enhertu has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

The efficacy and safety of Enhertu were demonstrated in DESTINY-Breast01, a multicentre, open-label, single-arm Phase 2 study that enrolled patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2-based regimens, including trastuzumab emtansine (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumour samples were required to show HER2-positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of treated ILD or ILD at screening, patients with a history of clinically significant cardiac disease as well as patients with clinically unstable brain metastases. Enhertu was administered by intravenous infusion at 5.4 mg/kg once every three weeks until disease progression or unacceptable toxicity. The primary efficacy outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) in the intent-to-treat (ITT) population as evaluated by independent central review. Secondary efficacy outcome measures were duration of response (DOR) and progression-free survival (PFS).
Of the 184 patients enrolled in DESTINY-Breast01, baseline demographic and disease characteristics were: median age 55 years (range 28 to 96); female (100%); White (54.9%), Asian (38.0%), Black or African-American (2.2%); Eastern Cooperative Oncology Group (ECOG) performance status 0

(55.4%) or 1 (44.0%); hormone receptor status (positive: 52.7%); presence of visceral disease (91.8%); median number of prior therapies in the metastatic setting: 5 (range: 2 to 17); prior pertuzumab therapy (65.8%); sum of diameters of target lesions (<5 cm: 42.4%, ≥5 cm: 50.0%). Efficacy results are summarised in Table 4.

Table 4: Efficacy results in DESTINY-Breast01 (intent-to-treat analysis set)

	DESTINY-Breast01 **N = 184**
Confirmed objective response rate (95% CI)	61.4% (54.0, 68.5)
Complete response (CR)	6.5%
Partial response (PR)	54.9%
Duration of response‡	
Median, months (95% CI)	20.8 (15.0, NR)
% with duration of response ≥6 months (95% CI)§	81.5% (72.2, 88.0)

ORR 95% CI calculated using Clopper-Pearson method

CI = confidence interval

95% CIs calculated using Brookmeyer-Crowley method

‡Includes 73 patients with censored data

§Based on Kaplan-Meier estimation

NR = not reached

Consistent anti-tumour activity was observed across pre-specified subgroups based on prior pertuzumab therapy and hormone receptor status.

Safety and efficacy in paediatric patients

Swissmedic has acknowledged the waiver to submit the results of studies with Enhertu in all subsets of the paediatric population in breast cancer (see section “Dosage/Administration” for information on children and adolescents).

Pharmacokinetics

At the recommended dosage of trastuzumab deruxtecan, the geometric mean (coefficient of variation [CV]%) C_{max} of trastuzumab deruxtecan and DXd were 122 µg/mL (20%) and 4.4 ng/mL (40%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 735 µg·day/mL (31%) and 28 ng·day/mL (37%), respectively, based on population pharmacokinetic analysis.

Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.

Absorption

Trastuzumab deruxtecan is administered intravenously. There have been no studies performed with other routes of administration.

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan and topoisomerase I inhibitor, DXd, was estimated to be 2.77 L and 27.4 L, respectively.
In vitro, the mean human plasma protein binding of the topoisomerase I inhibitor, DXd, was approximately 97%.
In vitro, the blood to plasma concentration ratio of DXd was approximately 0.6.

Metabolism

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the DXd. The humanised HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
In vitro metabolism studies in human liver microsomes indicate that DXd is metabolised mainly by CYP3A4 via oxidative pathways.

Elimination

Based on population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2-positive breast cancer, the clearance of trastuzumab deruxtecan was estimated to be 0.42 L/day and the clearance of DXd was 19.2 L/h. The apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan and released DXd was approximately 5.7 days.
Excretion pathways were studied in rats and monkeys.

Linearity/non-linearity

The exposure of trastuzumab deruxtecan and released DXd when administered intravenously increased in proportion to dose in the 3.2 mg/kg to 8.0 mg/kg dose range (approximately 0.6 to 1.5 times the recommended dose) with low to moderate interindividual variability.

Special populations

Based on population pharmacokinetic analysis, race, ethnicity, sex and body weight (35-125 kg) did not have a clinically meaningful effect on exposure of trastuzumab deruxtecan or released DXd.

Elderly patients

The population pharmacokinetic analysis showed that age (range 23-96 years) did not affect the pharmacokinetics of trastuzumab deruxtecan.

Patients with renal impairment

No dedicated renal impairment study was conducted. Based on population pharmacokinetic analysis including patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment (estimated by Cockcroft-Gault), the pharmacokinetics of the released DXd was not affected by mild or moderate renal impairment as compared to normal renal function (CLcr ≥90 mL/min).

Patients with hepatic impairment

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, the impact of changes on pharmacokinetics of trastuzumab deruxtecan in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment is not clinically meaningful.

Children and adolescents

No studies have been conducted to investigate the pharmacokinetics of trastuzumab deruxtecan in children or adolescents.

Preclinical data

Safety Pharmacology

In telemetered male cynomolgus monkeys treated with a single intravenous dose of trastuzumab deruxtecan, no effects on the cardiovascular, respiratory, or central nervous systems were observed at dose levels up to 78.8 mg/kg.

Repeated Dose Toxicity

In a six-week repeat-dose toxicity study, up to 197 mg/kg of trastuzumab deruxtecan was administered to rats once every three weeks. Toxicities were observed in intestines, lymphatic/haematopoietic organs (thymus, lymph nodes, bone marrow), kidneys, skin, testes, and incisor teeth. All changes observed, except for kidney, testicular and incisor teeth changes, were reversible following a nine-week recovery period. The severely toxic dose in 10% of the rats (STD_{10}) was determined to be >197 mg/kg (approximately 31 times the clinical dose of 5.4 mg/kg based on AUC).

In a three-month repeat-dose toxicity study, trastuzumab deruxtecan was administered to monkeys once every three weeks at 3, 10, and 30 mg/kg. Toxicities were observed in intestines, testes, skin, bone marrow, kidneys, and lungs. Pulmonary toxicity was observed at the highest dose (30 mg/kg) and was histopathologically characterised by aggregation of foamy alveolar macrophages and focal alveolus and/or interstitial inflammation, which showed reversibility after a three-month recovery period. The highest non-severely toxic dose was determined to be 30 mg/kg (approximately 7 times the clinical dose of 5.4 mg/kg based on AUC).
Changes observed in other organs, except for those in the skin and kidney, also showed reversibility or a trend toward reversibility by the end of a three-month recovery period.

Genotoxicity

The topoisomerase I inhibitor component of trastuzumab deruxtecan, DXd, was clastogenic in both an *in vivo* rat bone marrow micronucleus assay and an *in vitro* Chinese hamster lung chromosome aberration assay and was not mutagenic in an *in vitro* bacterial reverse mutation assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

Reproductive toxicity

Dedicated fertility studies have not been conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan may impair male reproductive function and fertility.
There were no animal reproductive or developmental toxicity studies conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan and DXd were toxic to rapidly dividing cells (lymphatic/haematopoietic organs, intestine, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Sodium chloride solution for infusion must not be used for reconstitution or dilution since it may cause particulate formation.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

Reconstituted solution
The reconstituted preparation is not preserved. It is recommended that the reconstituted solution be used immediately. If not used immediately, the reconstituted solution may be stored in a refrigerator at 2-8ºC for up to 24 hours from the time of reconstitution, protected from light.
Diluted solution
It is recommended that the diluted solution be used immediately. If not used immediately, the diluted solution may be stored at room temperature for up to 4 hours or in a refrigerator at 2-8ºC for up to 24 hours, protected from light. These storage times start from the time of reconstitution.

Special precautions for storage

Store in the refrigerator (2-8°C) until time of reconstitution.
Do not freeze.
Keep out of the reach of children.
For storage conditions after reconstitution and dilution of the medicinal product, see section “Other information”, “Shelf life after opening”.

Instructions and special precautions for handling and disposal

In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.
Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used.
Appropriate aseptic technique should be used for the following reconstitution and dilution procedures.

Reconstitution

- Reconstitute immediately before dilution.

- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted Enhertu solution required, and the number of vial(s) of Enhertu needed (see section “Dosage/Administration”).
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of sterile water for injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- Inspect the reconstituted solution for particulates and discolouration. The solution should be clear and colourless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discoloured.
- If not used immediately, store the reconstituted Enhertu vials in a refrigerator at 2-8ºC for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused Enhertu after 24 hours refrigerated.

Dilution

- Dilute the calculated volume of reconstituted Enhertu in an infusion bag containing 100 mL of 5% glucose solution. Do not use sodium chloride solution (see section “Other information”, “Incompatibilities”). An infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene) is recommended.
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion or in a refrigerator at 2-8ºC for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2-8ºC), it is recommended that the solution be allowed to equilibrate to room temperature prior to administration, protected from light.
- Administer Enhertu as an intravenous infusion only with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus.
- Do not mix Enhertu with other medicinal products or administer other medicinal products through the same intravenous line.

Disposal

The reconstituted product contains no preservative and is intended for single use only. Discard any unused portion left in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67967 (Swissmedic)

Packs

Enhertu is provided in 10 mL Type 1 amber borosilicate glass vial sealed with a fluoro-resin laminated butyl rubber stopper, and a polypropylene/aluminium yellow flip-off crimp cap.

Pack containing 1 vial with 100 mg of trastuzumab deruxtecan (A)

Marketing authorisation holder

DAIICHI SANKYO (Schweiz) AG, Zürich

Date of revision of the text

September 2021