swissmedic

Date: 18 November 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Enhertu

International non-proprietary name: trastuzumab deruxtecan
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strength(s): 100 mg
Route(s) of administration: intravenous
Marketing authorisation holder: Daiichi Sankyo (Schweiz) AG
Marketing authorisation no.: 67967
Decision and decision date: approved on 6 March 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

AE	Adverse event
BC	Breast cancer
BICR	Blinded independent central review
CDK 4/6	Cyclin-dependent kinase 4 and 6
CI	Confidence interval
DCO	Data cut-off
DoR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
ERA	Environmental risk assessment
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
HER2	Human epidermal growth factor receptor 2
HR+	Hormone receptor-positive
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
INN	International non-proprietary name
ISH	*In situ* hybridisation
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PopPK	Population pharmacokinetics
Q3W	Once every 3 weeks
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPC	Treatment of physician's choice
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

HER2-low Breast Cancer
Enhertu as monotherapy is indicated 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 systemic therapy 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 be ineligible for endocrine therapy.

2.2.2 Approved indication

HER2-low breast cancer
Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received 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 be ineligible for endocrine therapy (see section "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:
Dosing regimen in HER2-low breast cancer indication: 5.4 mg/kg as an IV infusion once every 3 weeks (Q3W).

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	17 June 2022
Formal control completed	23 June 2022
Preliminary decision	25 October 2022
Response to preliminary decision	6 December 2022
Labelling corrections	19 January 2023
Response to labelling corrections	10 February 2023
Final decision	6 March 2023
Decision	approval

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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 the metastatic setting, the disease is incurable with a 5-year survival of only about 25%.

The human epidermal growth factor receptor-2 (HER2) is a transmembrane protein overexpressed by around 20% of BC (HER2-positive BC; immunohistochemistry (IHC) 3+ or IHC 2+/ *in situ* hybridisation (ISH) +). Since the advent of anti-HER2-targeted agents, the prognosis of patients with HER2-positive tumours has improved significantly.
Overall, around 55% of all patients with BC cancer have tumours where HER2 protein is detectable, at a lower level of expression (HER2-low BC: IHC 1+ or IHC 2+/ISH-) than in the HER2-positive population.
So far, guidelines for the treatment of patients with HER2-low BC that have progressed after treatment with chemotherapy have recommended the same treatments as those for patients without any expression of HER2, and do not include HER2-targeted agents.
In particular, the treatment options for patients with HER2-low BC with expression of hormone receptor (HR) include endocrine therapy, further chemotherapy, and cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors if not used before. The preferred treatment for patients with BC without expression of HR is treatment with antibody-drug conjugate. Further options are available for patients whose BC has a phosphatidylinositol 3-kinase (PIK3CA) or BReast CAncer gene 1/2 (BRCA 1/2) mutation.

Trastuzumab deruxtecan is an antibody-drug conjugate (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 Nonclinical aspects

The present application is a marketing authorisation application for an extension of the indication for Enhertu (active substance: trastuzumab deruxtecan). The company has not submitted any preclinical documentation other than an environmental risk report showing that trastuzumab deruxtecan does not pose a significant risk to the environment. As the dose strength, route of administration, and dosing recommendation remain unchanged, the lack of preclinical documentation is acceptable.

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5 Clinical and clinical pharmacology aspects

5.1 Clinical pharmacology

The clinical pharmacology profile of trastuzumab deruxtecan (T-DXd) has been characterised previously in a variety of studies. In the current application, this characterisation of the clinical pharmacology of T-DXd was updated to include data from subjects with unresectable and/or metastatic HER2-low BC from Study DS8201-A-U303. No new covariates, including HER2-low status, were identified when compared to the previous PopPK analysis. T-DXd and DXd exposures were similar across subjects with HER2-positive BC or HER2-low BC at the 5.4 mg/kg Q3W dose of T-DXd. The T-DXd and DXd exposures in HER2-low BC subjects were similar across hepatic function, renal function, region, race-country, and country categories.

5.2 Dose finding and dose recommendation

No new dose-finding study was submitted.

5.3 Efficacy

Study DS8201-A-U303 (DESTINY-Breast04) is a multicentre, randomised, open-label trial to compare the efficacy and safety of trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) for HER2-low, unresectable, and/or metastatic BC subjects previously treated with chemotherapy.
Allowed chemotherapies in the TPC arm were capecitabine, eribulin, paclitaxel, nab-paclitaxel, and gemcitabine. HER2-low expression was defined as IHC 2+/ISH- or IHC 1+.

The primary endpoint of the study was progression-free survival (PFS) as determined by a blinded independent central review (BICR) in the HR-positive cohort; no formal interim analysis was planned for PFS. The key secondary endpoints were PFS based on BICR in all randomised subjects (full analysis set, FAS), overall survival (OS) in the HR-positive cohort, and OS in FAS. Up to two interim analyses of OS were planned, of which the first one was to be conducted at the time of the PFS final analysis.
Other secondary endpoints were overall response rate (ORR), duration of response (DoR), and PFS based on investigator assessment.

Trastuzumab deruxtecan was administered at 5.4 mg/kg Q3W as an intravenous infusion on day 1 of each 21-day cycle. Treatment was to be continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Treatment response was assessed every 6 weeks.

Eligible subjects must have been treated with at least one line of chemotherapy in the recurrent or metastatic setting and, if BC was HR-positive, it was to be documented as refractory to endocrine therapy.
In addition, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and adequate organ and bone marrow function. Patients with a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis or unstable brain metastases were excluded from the trial. HER2 status was assessed by central laboratory. Please refer to the attached Information for Healthcare Professionals for additional details on the inclusion and exclusion criteria.

Subjects were randomised in a 2:1 ratio to T-DXd or TPC, respectively, and stratified by HER2 IHC status, number of prior lines of chemotherapy in the recurrent or metastatic setting, and HR/CDK 4/6 status.

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At the data cut-off (DCO) of 11 January 2022, 557 subjects had been randomised into the study (FAS); 15.6% of subjects were still on treatment in the T-DXd arm and 1.7% in the TPC arm. Demographic and baseline disease characteristics were overall balanced in the two arms. Approximately 55% of the subjects had an ECOG PS 0; around 57% were IHC 1+, about 57% had received one prior line of chemotherapy, and more than 90% had received at least one prior line of endocrine therapy. Only two male subjects were enrolled. In total, 62.5% of the subjects were HR-positive with prior CDK4/6 treatment and 26.2% of the subjects were HR-positive without prior CDK4/6 treatment; 11.3% were HR-negative. Around 5% of subjects had baseline CNS metastases.

Overall, 63.7% in the T-DXd arm and 67.5% in the TPC arm in the HR-positive cohort had a PFS event based on BICR; the median duration of PFS follow-up was 16.1 months. The treatment with T-DXd resulted in a statistically significant and clinically meaningful improvement in BICR-assessed PFS compared with TPC (HR 0.51 (95% CI: 0.40, 0.64), p-value <0.0001). Median PFS based on BICR was 10.1 months in the T-DXd arm vs 5.4 months in the TPC arm. There was an early separation of the PFS curves in favour of T-DXd that was maintained throughout the study. The benefit in PFS was observed consistently across all prespecified subgroups.

Given the statistical significance of the primary endpoint, key secondary endpoints were tested in the planned order at the same DCO.

In the FAS, 65.1% of subjects had a PFS event in the T-DXd arm and 69% in the TPC arm. Results in the FAS are consistent with the results observed in the HR-positive cohort (HR: 0.50 [95% CI: 0.40, 0.63]; p-value <0.0001). Median PFS by BICR was 9.9 months in the T-DXd arm vs 5.1 months in the TPC arm.

In the HR-positive cohort, 38.1% of subjects in the T-DXd arm and 44.8% in the TPC arm had died; the median duration of survival follow-up was 18.4 months. Results show a statistically significant and clinically meaningful improvement in OS in the T-DXd arm compared with the TPC arm (HR 0.64 (95% CI: 0.48, 0.86), p-value 0.0028). Median OS was 23.9 months in the T-DXd arm vs 17.5 months in the TPC arm. Starting at approximately 4 months, a separation of the Kaplan-Meier OS curve in favour of the T-DXd arm was observed.

In the FAS, 39.9% of subjects in the T-DXd arm and 48.9% of subjects in the TPC arm had died. Results in the FAS are consistent with the results observed in the HR-positive cohort (HR: 0.64 (95% CI: 0.49, 0.84); p-value = 0.0010). Median OS was 23.4 months in the T-DXd arm vs 16.8 months in the TPC arm.

5.4 Safety

In the pivotal DESTINY- Breast 04 trial treatment-emergent adverse events (TEAE) were reported in nearly all subjects who were treated (99.5% in T-DXd arm and 98.3% in TPC arm). TEAE ≥ Grade 3 were reported in 52.6% of subjects in the T-DXd arm and in 67.4% of subjects in the TPC arm. Serious TEAEs (SAE) were observed in 27.8% in the T-DXd arm and in 25.0% in the TPC arm. TEAEs associated with an outcome of death were reported in 3.8% subjects in the T-DXd arm and 2.9% in the TPC arm.
TEAEs associated with study drug discontinuation were double in the T-DXd arm compared to the TPC arm (16.2 vs 8.1%). TEAEs associated with study drug interruption were similar in the two arms (38.5% vs 41.9%). Dose reductions due to TEAEs were less frequent in the T-DXd arm than in the TPC arm (22.6 vs 38.4%). A higher fraction of patients were hospitalised in the T-DXd arm than in the TPC arm (28.2% vs 20.7%).

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The most common TEAEs in the T-DXd arm were nausea (76%), fatigue (53.6%), vomiting (40.4%), alopecia (39.6%), anaemia (38.5%), neutropenia (34.0%), constipation (34.0%), transaminases increased (32.3%), and decreased appetite (31.8%).

The most frequent SAEs in the T-DXd arm were drug-related adjudicated interstitial lung disease (ILD) (4.3%), pneumonia (1.9%), dyspnoea (1.3%), musculoskeletal pain (1.3%), and sepsis (1.3%). Among the 14 TEAEs associated with an outcome of death in the T-DXd arm, 5 were classified as pneumonitis, dyspnoea, pleural effusion, or respiratory failure.

ILD is a known TEAE of special interest of T-DXd. A total of 15.1% of subjects in the T-DXd arm and 1.2% of subjects in the TPC arm had events of potential ILD/pneumonitis. Among these, 12.1% subjects in the T-DXd arm had events adjudicated as drug-related ILD. Drug-related adjudicated ILD was the most frequent cause of discontinuation in the T-DXd arm (8.4%) and the most frequent cause of SAEs (4.3%). Three subjects in the T-DXd arm had fatal (Grade 5) adjudicated drug-related ILD. A notably higher incidence of adjudicated drug-related ILD has been observed in subjects with moderate renal impairment (22.0%) than in subjects with normal renal function (10.0%). The higher risk of developing an ILD in patients with moderate renal impairment, including fatal cases, has been described in the boxed warning of the product information.

A total of 5.7% of subjects in the T-DXd arm and 1.7% of subjects in the TPC arm had a change from baseline of >60 ms of the QTcF interval. Moreover, 1.9% of subjects in the T-DXd arm had a QTcF of >500 ms, compared to 0.6% subject in the TPC arm. These results have been added to the “Pharmacodynamics” section of the product information.

5.5 Final clinical and clinical pharmacology benefit risk assessment

Breast cancer is the most frequent cancer in women and the leading cause of death from cancer in women. Around 55% of all patients with BC cancer have tumours where HER2 protein is detectableat a lower level of expression (HER2-low BC) than in the HER2-positive population. T-DXd is an antibody-drug conjugate composed of the humanised monoclonal antibody trastuzumab attached to the topoisomerase I inhibitor MAAA-1181a.

The results of the PFS analysis showed a statistically significant and clinically meaningful benefit of T-DXd compared to TPC in the HR-positive cohort and in the FAS.
The OS data at the first interim analysis showed a statistically significant and clinically meaningful benefit of T-DXd compared to TPC in the HR-positive cohort and in the FAS, and an early and constant separation of Kaplan-Meier curves.
The toxicity reported in the study was manageable by an expert physician and was in line with the known toxicity profile of the drug.
In conclusion, the risk-benefit analysis is positive for T-DXd in the second-line setting of metastatic HER2-low BC cancer patients, after progression to chemotherapy. Patients with HR-positive BC must also have received or been ineligible for previous endocrine treatment.

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6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for 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 valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

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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. Patients with moderate renal impairment are at increased risk of developing ILD including fatal cases (see sections “Warnings and precautions” and “Undesirable Effects”).

▼ 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® 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

HER2-positive breast cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens, including trastuzumab and a taxane, and had a progression either in the metastatic setting

or within 6 months after finalization of an adjuvant or neoadjuvant therapy (see section "Properties/Effects").

HER2-low breast cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received 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 be ineligible for endocrine therapy (see section "Properties/Effects").

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.

Patient selection for HER2-low metastatic breast cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer based on IHC 1+ or IHC 2+/ISH- tumor status, as assessed by a validated test (see section "Properties/Effects").

Premedication

Enhertu is moderately emetogenic (see section "Undesirable Effects"), which includes delayed nausea and/or vomiting. Prior to each dose of Enhertu, patients can take antiemetic drugs in accordance with consensus-based and/or local guidelines as per tolerance for prophylaxis or management.

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.

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**
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”).

Adverse reaction	Severity		Treatment modification
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 is less than 10%	• Continue treatment with Enhertu. • Repeat LVEF assessment within 3 weeks.
		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

Adverse reaction	Severity	Treatment modification
		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 5.0 (NCI-CTCAE v.5.0).

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”). Limited data are available in patients with severe renal impairment. A higher incidence of ILD/pneumonitis has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully (see section “Warnings and precautions”).

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 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 with a history of ILD/pneumonitis requiring steroid treatment or present or suspected ILD/pneumonitis at the time of screening and patients with clinically severe pulmonary impairment were not included in clinical studies with Enhertu.
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 further evaluation of the lung using imaging techniques. 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 or moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis and, therefore, should be monitored carefully (see section “Properties/Effects”).

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. LVEF decrease should be managed through treatment interruption. Enhertu should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment. 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 pooled safety population has been evaluated for patients who received at least one dose of Enhertu 5.4 mg/kg and above (n =1590) across multiple tumour types in clinical studies. The median duration of treatment in this pool was 7.8 months (range: 0.2 to 41.0 months).

- The most common adverse reactions were nausea (74.3%), fatigue (57.4%), vomiting (42.2%), decreased appetite (41.1%), anaemia (38.5%), neutropenia (37.9%), alopecia (37.7%), constipation (33.5%), diarrhoea (31.8%), thrombocytopenia (27.0%), leukopenia (26.3%), transaminases increased (26.3%), and musculoskeletal pain (23.6%).
- The most common serious adverse reactions were ILD/pneumonitis (4.8%), pneumonia (2.5%), decreased appetite (1.8%),vomiting (1.6%), nausea (1.3%), and anaemia (1.3%)
- The most common National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5.0) Grade 3 or 4 adverse reactions were neutropenia (21.1%), anaemia (14.8%), leukopenia (9.0%), fatigue (8.1%), thrombocytopenia (7.4%), lymphopenia (5.9%), nausea (5.7%), transaminases increased (4.3%), decreased appetite (4.2%), hypokalaemia (3.8%), vomiting (2.3%), pneumonia (2.3%), febrile neutropenia (1.9%), diarrhoea (1.9%), ILD/pneumonitis (1.3%), dyspnoea (1.3%), weight decreased (1.1%), blood alkaline phosphatase increased (1.1%), and ejection fraction decreased (1.1%).
  Grade 5 adverse reactions occurred in 2.0% of patients, including ILD (1.6%)
- Dose interruptions due to adverse reactions occurred in 35.2% of patients treated with Enhertu. The most frequent adverse reactions associated with dose interruption were neutropenia (13.8%), anaemia (5.6%), fatigue (5.0%), leukopenia (3.8%), upper respiratory tract infection (3.0%), ILD (3.1%), pneumonia (2.7%), thrombocytopenia (2.7%), and decreased appetite (2.0%). Dose reductions occurred in 24.7% of patients treated with Enhertu. The most frequent adverse reactions associated with dose reduction were nausea (5.5%), fatigue (6.8%), neutropenia (4.2%), decreased appetite (2.9%), and thrombocytopenia (2.5%). Discontinuation of therapy due to an adverse reaction occurred in 14.6% of patients treated with Enhertu. The

most frequent adverse reaction associated with permanent discontinuation was ILD/pneumonitis (10.4%).

Tabulated list of adverse reactions

The adverse reactions in patients who received at least one dose of Enhertu in clinical studies 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 in multiple tumour types

System organ class/preferred term or grouped term	**Any Grade (%)**		**Grade 3-4 (%)**
Infections and infestations			
Upper respiratory tract infection[a]	Very common	18.5	0.3
Pneumonia	Common	7.5	2.3
Blood and lymphatic system disorders			
Anaemia[b]	Very common	38.5	14.8
Neutropenia[c]	Very common	37.9	21.1
Thrombocytopenia[d]	Very common	27.0	7.4
Leukopenia[e]	Very common	26.3	9.0
Lymphopenia[f]	Very common	11.3	5.9
Febrile neutropenia	Common	2.0	1.9
Metabolism and nutrition disorders			
Decreased appetite	Very common	41.1	4.2
Hypokalaemia[g]	Very common	12.6	3.8
Dehydration	Common	3.5	0.5
Nervous system disorders			
Headache[h]	Very common	14.7	0.3

System organ class/preferred term or grouped term	Any Grade (%)		Grade 3-4 (%)
Peripheral neuropathy[i]	Very common	10.7	0.2
Dizziness	Common	9.6	0.4
Dysgeusia	Common	8.8	0
Eye disorders			
Vision blurred[j]	Common	3.8	0
Dry eye	Common	5.2	0.1
Cardiac disorders			
Ejection fraction decreased[k]	Very common	15.6	1.1
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease[l]	Very common	14.3	1.3
Cough	Very common	13.5	0.2
Dyspnoea	Very common	10.7	1.3
Epistaxis	Common	9.8	0.1
Gastrointestinal disorders			
Nausea	Very common	74.3	5.7
Vomiting	Very common	42.2	2.3
Constipation	Very common	33.5	0.3
Diarrhoea	Very common	31.8	1.9
Abdominal pain[m]	Very common	16.9	0.8
Stomatitis[n]	Very common	15.2	0.6
Dyspepsia	Common	8.7	0
Abdominal distension	Common	4.1	0.1
Flatulence	Common	1.9	0
Gastritis	Common	1.6	0.1
Hepatobiliary disorders			
Transaminases increased[o]	Very common	26.3	4.3

System organ class/preferred term or grouped term	Any Grade (%)		Grade 3-4 (%)
Blood alkaline phosphatase increased	Common	9.7	1.1
Blood bilirubin increased[p]	Common	7.4	1.0
Skin and subcutaneous tissue disorders			
Alopecia	Very common	37.7	0.1
Rash[q]	Common	9.4	0.1
Pruritus	Common	5.4	0.1
Skin hyperpigmentation[r]	Common	4.2	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[s]	Very Common	23.6	0.9
Renal and urinary disorders			
Blood creatinine increased	Common	3.9	0.2
General disorders and administration site conditions			
Fatigue[t]	Very common	57.4	8.1
Weight decreased	Very common	16.8	1.1
Pyrexia	Very common	15.1	0.4
Oedema peripheral	Common	9.6	0.2
Injury, poisoning and procedural complications			
Infusion-related reactions[u]	Common	1.8	0

[a] Includes influenza, infuenza like illness, nasopharyngitis, pharyngitis, sinusitis, rhinitis and upper respiratory tract infection.

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

[c] Includes neutropenia and neutrophil count decreased.

[d] Includes thrombocytopenia and platelet count decreased.

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

[f] Includes lymphopenia and lymphocyte count decreased.

[g] Includes hypokalaemia and blood potassium decreased.

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

[i] Includes peripheral neuropathy, peripheral sensory neuropathy, and paraesthesia.

[j] Vision blurred (grouped term) includes PTs of vision blurred and visual impairment.

[k] Includes laboratory parameters of LVEF decrease (n=241) and/or preferred terms of ejection fraction decreased (n=42), cardiac failure (n=3) cardiac failure congestive (n=1), and left ventricular dysfunction (n=2).

[l] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis (n=125), interstitial lung disease (n=83), organising pneumonia (n=9), pneumonia (n=4), pulmonary mass (n=1), acute respiratory failure (n=1), lung infiltration (n=1), lymphangitis (n=1), pulmonary fibrosis (n=1), radiation pneumonitis (n=2), respiratory failure (n=9), lung opacity (n=1), and alveolitis (n=2).

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

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

[o] Includes transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal and hepatic function abnormal.

[p] Includes blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased and blood bilirubin unconjugated increased.

[q] Includes rash, rash pustular, rash maculopapular, rash papular, rash macular, and rash pruritic.

[r] Includes skin hyperpigmentation, skin discolouration and pigmentation disorder.

[s] Includes back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain and limb discomfort.

[t] Includes asthenia, fatigue, malaise, and lethargy.

[u] Cases of infusion-related reactions include infusion related reaction (n=17), hypersensitivity (n=3), infusion site extravasation (n=1), rash (n=1), wheezing (n=1), hypotension (n=1), injection site reaction (n=1), chills (n=1) and flushing (n=3).

Description of selected undesirable effects

Interstitial lung disease/pneumonitis

In clinical studies across multiple tumour types (n = 1590), ILD occurred in 14.3% of patients treated with Enhertu 5.4 mg/kg and above. Most ILD cases were Grade 1 (3.7%) and Grade 2 (7.7%). Grade 3 cases occurred in 1.2% and Grade 4 cases in 0.1% of patients. Grade 5 events occurred in 1.6% of patients. One patient had pre-existing ILD that worsened post treatment leading to Grade 5 ILD. Median time to first onset was 5.4 months (range: -0.5 to 23.3).

In clinical studies with patients treated with Enhertu 5.4 mg/kg for breast cancer, the incidence of ILD with moderate renal impairment (27.7%) was higher compared to patients with normal renal function (10.5%).

Neutropenia

In clinical studies (n = 1590) across multiple tumour types in patients treated with Enhertu 5.4 mg/kg and above, neutropenia was reported in 37.9% of patients and 21.1% had Grade 3 or 4 events. Median time of to first onset was 22 days (range: 1 day to 24.8 months), and median duration of the

first event was 15 days (range: 1 day to 17.2 months). Febrile neutropenia was reported in 2.0% of patients (see section “Warnings and precautions”).

Left ventricular ejection fraction decrease

In the 1590 patients, across multiple tumour types in clinical studies who received Enhertu 5.4 mg/kg and above, LVEF decrease was reported in 47 patients (3.0%), of which, 34 (2.1%) were Grade 2, and 8 (0.5%) were Grade 3. The observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 227/1590 (15.6%) for Grade 2, and 14/1590 (1.0%) for Grade 3. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment.

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. Across all doses evaluated in clinical studies, 2.0% (34/1668) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with Enhertu. The incidence of treatment-emergent neutralising antibodies against trastuzumab deruxtecan was 0.1% (1/1668). Due to the limited number of patients who tested positive for ADA, the effect of ADA on safety and efficacy of Enhertu is unknown.

Children and adolescents

Safety has not been established in this population.

Elderly patients

Of the 1590 patients across multiple tumour types in clinical studies treated with Enhertu 5.4 mg/kg and above, 30.3% were 65 years or older and 5.3% were 75 years or older. The incidence of Grade 3-4 adverse reactions observed in patients 65 years or older (55.1%) and in younger patients (48.9%) was similar.

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

L01FD04

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.
In the DESTINY-Breast04 study, it was observed that 21.6% of patients had a QTcF prolongation > 30 ms from baseline, 5.7% of patients had a QTcF prolongation > 60 ms from baseline and 1.9% of patients had a QTcF measurement of > 500 ms.

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.

<u>DESTINY-Breast03</u>
The efficacy and safety of Enhertu were studied in DESTINY-Breast03, a multicentre, open-label, active controlled, randomised, two-arm phase 3 study that enrolled patients with HER2-positive, unresectable or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

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 (non-infectious) ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with untreated or symptomatic brain metastases, patients with a history of clinically significant cardiac disease, patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 and patients with prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting. Patients were randomized 1:1 to receive either Enhertu 5.4 mg/kg (n=261) or trastuzumab emtansine 3.6 mg/kg (n=263) administered by intravenous infusion once every three weeks. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was progression-free survival (PFS) as evaluated by blinded independent central review (BICR) according to RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure.

Patient demographics were balanced between treatment arms. Of the 524 patients randomised, the baseline demographic and disease characteristics were: median age 54 years (range: 20 to 83); 65 years or older (20.2%); 75 years or older (3.1%), female (99.6%); Asian (59.9%), White (27.3%), Black or African-American (3.6%); ECOG performance status 0 (62.8%) or 1 (36.8%); hormone receptor status (positive: 51.9%); presence of visceral disease (73.3%); history of brain metastases (21.8%); and (48.3%) patients received one line of prior systemic therapy in the metastatic setting. The percentage of patients who were previously treated with pertuzumab was 61.1%. The percentage of patients who had not received prior treatment for metastatic disease was 9.5% and 6.7% of patients had received exactly one prior anti-HER2 therapy that was intended for the neoadjuvant or adjuvant therapy and experienced disease progression during or within 6 months of completing treatment (12 months for pertuzumab).

At the prespecified interim analysis for PFS based on 245 events (73% of total events planned for final analysis), the study demonstrated a statistically significant improvement in PFS per BICR in patients randomized to Enhertu compared to trastuzumab emtansine.

Table 4: Efficacy results in DESTINY Breast03 (intent-to-treat analysis set)

Efficacy Parameter	Enhertu N=261	trastuzumab emtansine N=263
Progression-Free Survival (PFS) Primary end-point (BICR)		
Number of events (%)	87 (33.3)	158 (60.1)
Median, months (95% CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.28 (0.22, 0.37)	
p-value	p< 0.0001	

CI = confidence interval; NE=not estimable; NR = not reached

Similar PFS results were observed across pre-specified subgroups including prior pertuzumab therapy, hormone receptor status, presence of stable brain metastases, and presence of visceral disease.

Data regarding OS are not mature yet. At data cut-off, there were 33 (12.6%) deaths in the Enhertu arm and 53 (20.2%) deaths in the trastuzumab emtansine arm. The median OS was not estimable for either arm.

DESTINY-Breast01

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 5.

Table 5: 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.

DESTINY-Breast04

The efficacy of Enhertu was studied in DESTINY-Breast04, a phase 3, randomised, multicentre, open-label study that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor positive (HR+) patients and 63 hormone receptor negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-, as determined by the PATHWAY/VENTANA anti-HER-2/neu (4B5) and when applicable, the INFORM HER2 Dual ISH assay, evaluated at a central laboratory. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Patients were randomised 2:1 to receive either Enhertu 5.4 mg/kg (N = 373) by intravenous infusion every three weeks or physician's choice of chemotherapy (N = 184, eribulin 51.1%, capecitabine 20.1%, gemcitabine 10.3%, nab paclitaxel 10.3%, or paclitaxel 8.2%). Randomisation was stratified by HER2 IHC status of tumour samples (IHC 1+ or IHC 2+/ISH-), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and HR status/prior CDK4/6i treatment (HR+ with prior CDK4/6 inhibitor treatment, HR+ without prior CDK4/6 inhibitor treatment, or HR-). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The study included patients with LVEF ≥50%. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or current

or suspected ILD/pneumonitis at screening and patients with clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses. Patients were also excluded for clinically significant cardiac disease including corrected QT interval (QTc) prolongation >470 ms for female patients or >450 ms in male patients, untreated or symptomatic brain metastases or ECOG performance status > 1.

The primary efficacy outcome measure was progression-free survival (PFS) in patients with HR+ breast cancer assessed by BICR based on RECIST v1.1. Key secondary efficacy outcome measures were PFS assessed by BICR based on RECIST v1.1 in the overall population (all randomised HR+ and HR- patients), overall survival (OS) in HR+ patients, and OS in the overall population.

Demographics and baseline tumour characteristics were similar between treatment arms. Of the 557 patients randomised, the median age was 57 years (range: 28 to 81); 23.5% were age 65 or older; 4.1% were age 75 or older; 99.6% were female and 0.4% were male; 47.9% were White, 40.0% were Asian, and 1.8% were Black or African American. Patients had an ECOG performance status of 0 (54.8%) or 1 (45.2%) at baseline; 57.6% were IHC 1+, 42.4% were IHC 2+/ISH-; 69.8% had liver metastases, 32.9% had lung metastases, and 5.7% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 57.6% having 1 and 40.9% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6 inhibitor treatment.

The study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS in patients randomised to Enhertu compared to chemotherapy in both the HR+ cohort and the overall population. Efficacy results are summarized in Table 6.

Table 6: Efficacy results in DESTINY-Breast04

Efficacy parameter	**HR+ cohort**	
	Enhertu (N = 331)	**Chemotherapy (N = 163)**
Overall survival		
Number of events (%)	126 (38.1)	73 (44.8)
Median, months (95% CI)	23.9 (20.8, 24.8)	17.5 (15.2, 22.4)
Hazard ratio (95% CI)	0.64 (0.48, 0.86)	
p-value	0.0028	
Progression-free survival per BICR		
Number of events (%)	211 (63.7)	110 (67.5)
Median, months (95% CI)	10.1 (9.5, 11.5)	5.4 (4.4, 7.1)
Hazard ratio (95% CI)	0.51 (0.40, 0.64)	
p-value	< 0.0001	

CI = confidence interval

The results in the HR-negative cohort are consistent with the results in the HR+ cohort. In the full analysis set (FAS), median OS was 23.4 months (95% CI: 20.0, 24.8) in patients randomised to Enhertu compared to 16.8 months (95% CI: 14.5, 20.0) in patients randomised to chemotherapy with a hazard ratio of 0.64 (95% CI: 0.49, 0.84). Median PFS was 9.9 months (95% CI: 9.0, 11.3) in patients randomised to Enhertu and 5.1 months (95% CI: 4.2, 6.8) in patients randomised to chemotherapy with a hazard ratio of 0.50 (95% CI: 0.40, 0.63).

Pharmacokinetics

At the recommended dosage of trastuzumab deruxtecan for patients with metastatic breast cancer, the geometric mean (coefficient of variation [CV]%) C_{max} of trastuzumab deruxtecan and DXd were 133 µg/mL (19%) and 4.7 ng/mL (43%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 780 µg·day/mL (27%) and 29 ng·day/mL (42%), 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 2.68 L and 27.0 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 or HER2 low breast cancer and locally advanced or metastatic gastric or GEJ adenocarcinoma, the clearance of trastuzumab deruxtecan was estimated to be 0.41 L/day and the clearance of DXd was 19.6 L/h. The apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan was 5.7-5.8 days and of released DXd was approximately 5.5-5.8 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 (27.3-125.4 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 20-96 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.
- Cover the infusion bag to protect from light.
- 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

February 2023