Trastuzumab deruxtecan (Enhertu®) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy 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.	C50	00776a	ODMS 01/08/2024
As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.	C50	00776b	N/A

* This is for post 2012 indications only.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Trastuzumab deruxtecan is administered on Day 1 of a 21 day cycle until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Drug	Dose	Route	Diluent & Rate	Cycle
Trastuzumab deruxtecan	5.4mg/kg	IV infusion	100mL glucose 5% over 90 minutes*	Every 21 days
*The initial dose should be administered as a 90-minute intravenous infusion. If the prior infusion was well tolerated, subsequent doses may be administered as 30-minute infusions The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms. Treatment should be permanently discontinued in case of severe infusion reactions.				
Administer treatment as an intravenous infusion only with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter				

Trastuzumab deruxtecan must not be administered as an intravenous push or bolus

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds

ELIGIBILITY:

- Indication as above
- Adult patients aged > 18 years
- ECOG 0-2
- HER2 overexpression or HER 2 gene amplification as determined by an accurate and validated assay
    - Please see *Recommendations on Reporting on HER2 Status in Breast Cancer Patients* available on NCCP website.
    - **HER2-positive breast cancer:** Patients should have documented HER2- positive tumour status, defined as a score of 3 + by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) assessed by a CE-marked in vitro diagnostic (IVD) medical device. If a CE-marked IVD is not available, the HER2 status should be assessed by an alternate validated test.
    - **HER2-low breast cancer:** Patients should have documented HER2-low tumour status, defined as a score of IHC 1+ or IHC 2+/ISH-, as assessed by a CE-marked IVD medical device. If a CE-marked IVD is not available, the HER2 status should be assessed by an alternate validated test
- Left ventricular ejection fraction ≥50%
- Adequate haematological, renal and liver profile

CAUTIONS:

- Spinal cord compression or untreated or symptomatic CNS metastases

EXCLUSIONS:

- Hypersensitivity to trastuzumab deruxtecan or any of the excipients.
- Clinically significant cardiac disease (unstable angina, symptomatic congestive heart failure, serious cardiac arrhythmia, myocardial infarction within previous 6 months)
- History of interstitial lung disease (ILD) or pneumonitis
- Pregnancy
- Breast feeding

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)
- Pregnancy test in females of childbearing potential

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Cardiac function every 12 weeks. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate
- Pregnancy test in females of childbearing potential if clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation
- Dose should not be re-escalated after a dose reduction is made
- 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

Table 1: Dose reduction schedule for trastuzumab deruxtecan

Dose reduction schedule	Dose to be administered
Recommended starting dose	5.4 mg/kg
First reduction	4.4 mg/kg
Second reduction	3.2 mg/kg
Requirement for further reduction	Discontinue

Renal and Hepatic Impairment:

Table 2: Dose modification of trastuzumab deruxtecan in renal and hepatic impairment

Renal impairment		**Hepatic Impairment**	
CrCl (ml/min)	**Dose**	**Mild**	No dose adjustment is needed
≥30	No dose adjustment is needed	**Moderate**	No need for dose adjustment is expected, close monitoring for toxicity is recommended
<30	No need for dose adjustment is expected	**Severe**	Not recommended
Haemodialysis	No need for dose adjustment is expected		
Renal and hepatic dose modifications: Giraud et al 2023			

Management of adverse events:

Table 3: Dose modifications for trastuzumab deruxtecan for adverse reactions

Adverse reaction	Severity*	Modification
ILD/pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt treatment 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
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	• Permanently discontinue treatment • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected
Neutropenia	Grade 3 (less than 1.0 - 0.5 × 10^9 /L)	• Interrupt treatment until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 × 10^9 /L)	• Interrupt treatment until resolved to Grade 2 or less • Reduce by one dose 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 treatment until resolved • Reduce by one dose 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
	And absolute decrease from	• Continue treatment

	LVEF 40% to 45%	baseline is less than 10%	• Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	• Interrupt treatment • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue treatment. • If LVEF recovers to within 10% from baseline, resume treatment at same dose
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		• Interrupt treatment • 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 treatment
	Symptomatic congestive heart failure (CHF)		• Permanently discontinue treatment

*NCI-CTCAE v5.0

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting available on NCCP website

High **(Refer to local policy).**

For information:

Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) available on NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) available on NCCP website

PREMEDICATIONS: No specific recommendations

OTHER SUPPORTIVE CARE:

- Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose of treatment. 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 treatment.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.
- **This medicine is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Healthcare professional guide for ILD/pneumonitis:

https://www.hpra.ie/img/uploaded/swedocuments/5a01f1d7-242e-4fd3-a054-f9337b29d109.pdf

Patient alert card for ILD:

https://www.hpra.ie/img/uploaded/swedocuments/f01a5860-046f-4da6-96e4-e566b11d0d47.pdf

Healthcare professional guide for prevention of medication errors:

https://www.hpra.ie/img/uploaded/swedocuments/17c43424-141e-4f02-b76d-e3a8a4c64387.pdf

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2. Modi S et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med 2022;387:9-20.
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Antiemesis Version 2.2024 — September 27, 2024
6. Trastuzumab deruxtecan (Enhertu®) Summary of Product Characteristics. Accessed October 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	31/07/2024		Prof Maccon Keane
2	12/11/2024	New indication added (00776b)	Prof Michaela Higgins
3	12/02/2025	Regimen reviewed.Emetogenic potential updated from moderate to high.	Prof Michaela Higgins

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.