HEALTHCARE PROFESSIONAL GUIDE

Important Risk Minimization Information on ILD/Pneumonitis with Treatment of PrENHERTU® (trastuzumab deruxtecan) for HER2-Positive Gastric and Gastroesophageal Junction (GEJ) Cancer

This Healthcare Professional (HCP) Guide is:

- provided for HCPs who are involved in the administration of ENHERTU.
- an important tool to ensure the prompt and appropriate diagnosis and management of ILD/pneumonitis.
- to be read before prescribing and administering ENHERTU. Full details including DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS for use are provided in the Product Monograph.
- a reminder to distribute a Patient Guide to any patient receiving ENHERTU treatment for the first time or if asked for a new copy. The Patient Guide may be used to help patients understand their ENHERTU treatment. The Patient Guide will also help the patients understand what to do if they experience lung problems. Moreover, it includes a Patient Wallet Card, with contact details, for the patients to carry at all times.

Not all possible side effects are listed in this Guide. Please read the ENHERTU Product Monograph for full details, including DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS.

This material was developed by AstraZeneca as part of the risk minimization plan for ENHERTU.

This material is not intended for promotional use.

What is ENHERTU?

ENHERTU (trastuzumab deruxtecan) as monotherapy, indicated for:

- the treatment of adult patients with unresectable, locally advanced or metastatic human epidermal growth factor 2 (HER2)-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen, has been issued marketing authorization ***with conditions***, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ENHERTU, please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

This guide is specific to the above indication for gastric or GEJ adenocarcinoma only.
The below indications in breast cancer are for information only.

ENHERTU (trastuzumab deruxtecan) as monotherapy, also indicated for:

- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1),
- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least one prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy, and
- the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received at least one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy,

have been issued market authorization without conditions.

IHC=immunohistochemistry; ISH=*in situ* hybridization.

CONTRAINDICATIONS for ENHERTU

ENHERTU (trastuzumab deruxtecan) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING of the Product Monograph.

It is recommended that Healthcare Professionals (HCP) submit a report to Health Canada when serious adverse events occur due to ENHERTU use.

You are also encouraged to report any suspected adverse reactions via email or phone to Health Canada.

Summary of Important Information on ILD/Pneumonitis with ENHERTU

ILD was more frequently reported in patients with moderate renal impairment (CrCL ≥30 and <60 mL/min) at baseline.

In clinical studies, of the 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 25 (10.9%) of patients as determined by independent review; 7.3% of patients were aged <65 years (8/109) and 14.2% of patients were aged ≥65 years (17/120). Most ILD cases were Grade 1 (2.6%) and Grade 2 (6.6%). Grade 3 cases occurred in 0.9% and Grade 4 in 0.4% of patients. One (0.4%) Grade 5 event occurred. Median time to first onset was 2.8 months (range: 1.2 to 21.0). In these studies, There were 2 (0.9%) patients with adverse reactions leading to death, one each attributed to ILD and pneumonia. 3.5% of dose interruptions were due to ILD and the most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (6.6%).

In clinical studies, of the 1287 patients with unresectable or metastatic breast cancer treated with ENHERTU 5.4 mg/kg, adjudicated drug-related ILD occurred in 165 (12.8%) patients as determined by independent review. Most ILD cases were Grade 1 (3.3%) or Grade 2 (7.6%). Grade 3 events occurred in 0.9% of patients. Grade 5 events occurred in 1.0% of patients. Median time to first onset was 5.8 months (range: 0.9 to 31.5).

ILD/Pneumonitis Diagnosis and Management for ENHERTU

Early diagnosis and appropriate management of events of ILD/pneumonitis are essential to minimize serious outcomes. Patients should be closely monitored and advised to immediately report signs and symptoms of ILD/pneumonitis including cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Evidence of ILD/pneumonitis should be promptly investigated. Patients with suspected ILD should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered. Promptly hold drug and initiate management at the first suspicion of ILD/pneumonitis (please **Management of Suspected ILD/Pneumonitis with ENHERTU** below).

Patients with a history of ILD/pneumonitis or patients with moderate or severe renal impairment may be at an increased risk of developing ILD/pneumonitis and should be monitored carefully.

At the first visit (before prescribing ENHERTU):

- Check whether the patient has a history of ILD/pneumonitis, of lung comorbidities or of corticosteroids treatment.
- Check whether the patient has moderate or severe renal impairment.
- Check for signs and symptoms of lung problems.
- Provide the patient with the Patient Guide and discuss the therapy with the patient before starting treatment with ENHERTU. Fill in the Patient Wallet Card and inform the patient to carry it at all times.
- Instruct the patient to contact you immediately or to go to the nearest Emergency Department if they experience even mild signs or symptoms (e.g., cough, dyspnea, fever, and/or any new or worsening respiratory symptoms), as some events can worsen rapidly if not treated.
- Keep an updated record of patient weight (in kilograms).
- Instruct the patient not to treat their own symptoms.

At all visits:

- Check for signs and symptoms of lung problems.
- Remind the patient that early diagnosis and appropriate management of lung problems are essential to minimize life-threatening complications.
- Remind the patient of the importance of adhering to scheduled appointments.
- Remind the patient to carry the Patient Wallet Card at all times.

Potential questions to ask your patients to help with early identification of ILD/pneumonitis:

- Have you been coughing recently? Is it a dry cough?
- Have you had any shortness of breath, especially during or after physical activity?
- Have you experienced any new breathing or respiratory problems?
- If you already have respiratory problems, have they become worse?
- Have you had a fever?
- Have you been feeling tired?
- Have you lost weight?
- Do you smoke or use e-cigarettes?

Management Options for Suspected Drug-induced ILD/Pneumonitis

Any evidence of ILD/pneumonitis should be promptly investigated and managed with the goal of suppressing inflammation and preventing irreversible fibrosis with a potentially fatal outcome.

For Suspected ILD/Pneumonitis[2-4]

- Consider further evaluations, which could include:
  - Radiographic imaging (e.g., high-resolution CT)
  - Pulmonologist consultation
  - Pulmonary function tests and pulse oximetry (SpO_2)
  - Clinical laboratory tests
    - Arterial blood gases, if clinically indicated
    - Blood cell count, differential, WBC count, CRP, liver function tests, markers associated with interstitial pneumonia (KL-6, SP-A, SP-D, DLST)
- If ILD/pneumonitis is suspected, follow the ILD/pneumonitis management guidance as outlined below

Instructions for Management of Suspected ILD/Pneumonitis with ENHERTU: In HER2-Positive Gastric and GEJ Cancer

ENHERTU dose should not be re-escalated after a dose reduction is made.

Dose reduction schedule	Gastric/GEJ Cancer Dosage
Recommended starting dose	6.4 mg/kg
First dose reduction	5.4 mg/kg
Second dose reduction	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

ENHERTU is given once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

CTCAE Grade	Description	Gastric/GEJ Cancer Treatment Modification
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Interrupt ENHERTU until the event resolves 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 (e.g., first dose reduction: 5.4 mg/kg). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent).
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental activities of daily living	Permanently discontinue ENHERTU. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days. • Then gradually taper for at least 4 weeks.
Grade 3	Severe symptoms; limiting self-care activities of daily living; oxygen indicated	
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	
Grade 5	Death	

Grading based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[5]

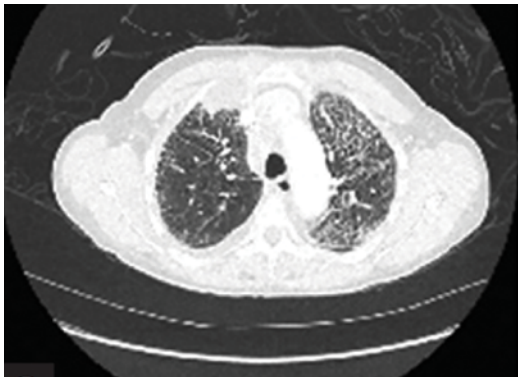
What is Interstitial Lung Disease (ILD)/Pneumonitis?

ILD is a broad term for a group of diffuse, parenchymal lung disorders that present as nonspecific cough, fever, and shortness of breath (dyspnea), including pneumonitis and idiopathic pulmonary fibrosis (unknown cause).

Characteristics of ILD/Pneumonitis

ILD is marked by the presence of inflammation or scarring of the lung interstitium and characterized by the following:[6]

- Respiratory symptoms (e.g., fever, shortness of breath [dyspnea], dry cough, chest pain, wheezing, and bloody sputum)
- Chest radiographic/CT abnormalities
- Changes in pulmonary function tests (PFTs) reflecting decreased lung volume
- Microscopic patterns of inflammation and fibrosis



Example of nonspecific interstitial pneumonitis in a patient receiving precision oncology therapy[7]

Causes of ILD/Pneumonitis

ILD may be the result of several different conditions, including but not limited to the following. It may also be idiopathic in nature (i.e., cause unknown).[8]

- Autoimmune or collagen vascular diseases, infections, genetic abnormalities
- Drug or chemical exposure
  - Several classes of anticancer agents used in metastatic breast cancer increase the risk of ILD, including HER2-targeted therapies such as trastuzumab, T-DM1, ENHERTU, and lapatinib[9-11] as well as agents that inhibit PI3K or mTOR
  - Checkpoint inhibitors and certain chemotherapies, such as irinotecan, bleomycin, and methotrexate have also been linked to a risk of ILD[2,12]
  - Other medications can also cause ILD; please check guidelines or prescribing information

General Risk Factors Linked to Drug-Induced ILD/Pneumonitis

The exact mechanisms via which ENHERTU may cause ILD are not yet known.[13]

General risk factors for the development of drug-induced ILD vary according to the disease, drug, and population being considered and include the following:[1,2,12,14,15]

- Patient history of ILD
- Patient history of lung disease
- Poor overall health: in oncology, poor performance status or metastatic disease
- Moderate or severe renal impairment
- Metastatic disease
- Poor performance status
- Smoking
- >60 years of age
- Japanese or African American race
- Prior treatment (prior chemotherapy, treatment with multiple chemotherapy regimens, thoracic radiotherapy, and combination therapy with multiple molecular targeted agents with or without cytotoxic agents)

References: 1. ENHERTU Product Monograph. AstraZeneca Canada Inc. January 17, 2025. **2.** Kubo K, Azuma A, Kanazawa M, *et al*. Japanese Respiratory Society Committee. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. *Respir Invest*. 2013;51(4):260-277. **3.** Modi S, *et al*. *N Engl J Med*. 2020; 382:610-621. doi:10.1056/NEJMoa1914510. **4.** Modi S, *et al*. *N Engl J Med*. 2022; 387:9-20. doi: 10.1056/NEJMoa2203690. **5.** US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Published November 27, 2017. **6.** Meyer KC. Diagnosis and management of interstitial lung disease. *Transl Respir Med*. 2014; 2(4):1-13. **7.** Jain A, Shannon VR, Sheshadri A. Pneumonitis after precision oncology therapies: a concise review. *J Immunother Precis Oncol*. 2018;1:26-37. **8.** European Respiratory Society: European Lung White Book, Chapter 22 – Interstitial lung disease: https://www.erswhitebook.org/chapters/interstitial-lung-diseases/. **9.** HERCEPTIN, EU SmPC Available from: https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf. **10.** KADCYLA, EU SmPC Available from: https://www.ema.europa.eu/en/documents/product-information/kadcyla-epar-product-information_en.pdf. **11.** TYVERB, EU SmPC Available from: https://www.ema.europa.eu/en/documents/product-information/tyverb-epar-product-information_en.pdf. **12.** Skeoch S, Weatherley N, Swift AJ, *et al*. Drug-induced interstitial lung disease: a systematic review. *J Clin Med*. 2018;7(10). **13.** Ogitani Y, Aida T, Hagihara K, *et al*. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin Cancer Res*. 2016;22(20):5097-108. **14.** Yonemori K, Hirakawa A, Kawachi A, *et al*. Drug induced interstitial lung disease in oncology phase I trials. *Cancer Sci*. 2016;107(12):1830-1836. **15.** Schwaiblmair M, Behr W, Haeckel T, *et al*. Drug induced interstitial lung disease. *Open Respir Med J*. 2012;6:63-74.