Important Safety Information

on ILD/Pneumonitis with Treatment of ENHERTU® (Trastuzumab deruxtecan)

Health Care Professional Guide

ENHERTU® ▼
(trastuzumab deruxtecan)

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This Health Care Professional (HCP) Guide is

- provided for HCPs to read before prescribing and administering ENHERTU®.
- an important tool to ensure the early recognition and diagnosis of ILD/pneumonitis, to allow prompt and appropriate treatment and minimise serious outcomes.
- a reminder to distribute a Patient Card to any patient receiving ENHERTU® treatment for the first time or if asked for a new copy.

Not all possible side effects are listed in this Guide. Please read the ENHERTU® product label for full details including Posology and Warnings and Special Precautions for use.

The summary of product characteristics (EU SmPC) can be found www.hpra.ie.

What is ENHERTU®?

ENHERTU® is a HER2-directed antibody and topoisomerase inhibitor conjugate (for information on approved indications and posology, see approved EU SmPC).

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 (dyspnoea), including pneumonitis and idiopathic pulmonary fibrosis (unknown cause).

Risk of ILD/Pneumonitis with ENHERTU®

Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU®. More details are available in the EU SmPC.[1]

Identification and minimisation of ILD/Pneumonitis

Early diagnosis and appropriate management of events of ILD/pneumonitis are essential to minimise serious outcomes. Patients should be monitored closely and advised to immediately report signs or symptoms of ILD/pneumonitis (eg, cough, dyspnoea at rest or exertion, fever, not otherwise explained fatigue, decrease in oxygen saturation, and/or any other new or worsening respiratory symptoms). Promptly initiate management at the first suspicion of ILD/pneumonitis. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully.

Investigating suspected ILD/Pneumonitis

Any evidence of ILD/pneumonitis should be promptly investigated.

For Suspected ILD/Pneumonitis[2,3]

- Consider further evaluations, which could include:
  - High-resolution computed tomography (HRCT)[4]
  - Respiratory physician consultation (infectious disease consultation as clinically indicated)
  - Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
  - Pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO_2)
  - Clinical laboratory tests
    - Arterial blood gases, if clinically indicated
    - Blood culture, blood cell count, differential WBC count, CRP, markers associated with interstitial pneumonia (KL-6, SP-A, SP-D)[5]
    - Covid-19 (SARS-CoV-2) test

General Risk Factors Linked to ILD/Pneumonitis related to other drugs

The exact mechanisms via which ENHERTU® may cause ILD are not yet known.[6]

General risk factors for the development of drug-induced ILD vary according to the disease, drug, and population being considered and include the following.[7,8,9]

- **Patient history of ILD or lung disease:** preexisting lung disease and reduced lung function are important risk factors for drug-induced ILD[7,9,10,11]
- **Poor overall health:** in oncology, poor performance status or metastatic disease may increase the risk for drug-induced ILD[8]
- **Smoking status:** smokers are at an increased risk for drug-induced ILD[7]
- **Advanced age:** the older age, especially those over 60 years old, may have a significantly higher risk for drug-induced ILD[7,9,11]
- **Ethnicity:** Japanese or African American patients may be at an increased risk for drug-induced ILD[9,12]
- **Male sex:** men may be at an increased risk for drug-induced ILD[7,11]
- **Prior treatment:** prior chemotherapy, treatment with multiple chemotherapy regimens, thoracic radiotherapy, and combination therapy with multiple molecular targeted agents with or without cytotoxic agents may increase a patient's risk for drug-induced ILD[7,8,9]

Instructions for Management of Suspected ENHERTU® related ILD/Pneumonitis:

The goal of ILD management is to suppress inflammation and prevent irreversible fibrosis with potential fatal outcome.[9] Corticosteroid treatment is considered to be most effective during the inflammatory phase of ILD.[7] On occasions, ILD can present acutely and progress rapidly. Appropriate management for ILD should be instituted promptly as per management guideline below when ILD is suspected and adjusted if an alternative etiology is identified.

<table>
<tr><th>CTCAE Grade</th><th>Treatment Modification</th></tr>
<tr><td>Grade 1</td><td>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.
<table><tr><th colspan="3">ENHERTU® Schedule for dose reduction</th></tr><tr><th></th><th>Breast Cancer</th><th>Gastric Cancer</th></tr><tr><td>Initial dose</td><td>5.4 mg/kg</td><td>6.4 mg/kg</td></tr><tr><td>First dose reduction</td><td>4.4 mg/kg</td><td>5.4 mg/kg</td></tr><tr><td>Second dose reduction</td><td>3.2 mg/kg</td><td>4.4 mg/kg</td></tr><tr><td>Further dose reductions if necessary</td><td>Stop treatment</td><td>Stop treatment</td></tr></table>
Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g. ≥0.5 mg/kg/day prednisolone or equivalent).</td></tr>
<tr><td>Grade 2</td><td rowspan="3">Permanently discontinue ENHERTU®
Promptly initiate corticosteroid treatment (e.g. ≥1 mg/kg/day prednisolone or equivalent) as soon as ILD/ pneumonitis is suspected for at least 14 days.
Then gradually taper for at least 4 weeks.</td></tr>
<tr><td>Grade 3</td></tr>
<tr><td>Grade 4</td></tr>
<tr><td>Grade 5</td><td></td></tr>
</table>

Grading based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[13]

Talking points for Patient's Visit (First or Following)

At the first visit (before prescribing ENHERTU®):

- Inform the patient there is a potential risk of serious side effects affecting the lungs. In a few patients these have the potential to be fatal.
- Check whether the patient has a history of ILD/pneumonitis, a history of lung comorbidities or history of corticosteroids treatment.
- Check for signs and symptoms of lung problems.
- Inform the patient that the early diagnosis and appropriate management of lung related problems is essential to prevent a worsening of the condition.
- Instruct the patient to contact you immediately if they experience even mild signs or symptoms of ILD/pneumonitis, as some events can worsen rapidly if not treated. Patient should seek immediate medical assistance and should show the Patient Alert Card to doctor(s) at other health facility(ies) if the treating oncologist is not available.
- Instruct the patient not to treat their own symptoms.
- Provide the patient with the Patient Card and discuss the therapy with the patient before starting treatment with ENHERTU®.
- Fill in the Patient Card and remind the patient to carry it at all times.

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 minimise life-threatening complications.
- Remind the patient of the importance of adhering to scheduled appointments.
- Check if patient carries the Patient Alert Card.

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?
- Do you smoke or use e-cigarettes?

For comprehensive product information please see the accompanying Summary of Product Characteristics (EU SmPC). Over time, the product information is likely to change.

These updates to the product information will be available at www.hpra.ie.

Reporting suspected adverse drug reactions (ADRs)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance Website: www.hpra.ie.

References

1. EU SmPC: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf. **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, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610-621. **4.** Conte P, Ascierto PA, Patelli G, et al. Drug-induced interstitial lung disease during cancer therapies: expert opinion on diagnosis and treatment. ESMO Open. 2022; 7 (2): 100404. **5.** A brief introduction to identifying and managing drug-induced interstitial lung disease. Daiichi Sankyo/AstraZeneca. PP-US-8201a-0397. Nov 2019. **6.** 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):5097-5108. **7.** Skeoch S, Weatherley N, Swift AJ, et al. Drug-induced interstitial lung disease: a systematic review. J Clin Med. 2018;7(10):356. **8.** 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. **9.** Schwaiblmair M, Behr W, Haeckel T, et al. Drug induced interstitial lung disease. Open Respir Med J. 2012; 6:63-74. **10.** Sakurada T, Kakiuchi S, Tajima S, et al. Characteristics of and risk factors for interstitial lung disease induced by chemotherapy for lung cancer. Ann Pharmacother. 2015;49(4):398-404. **11.** Osawa M, Kudoh S, Sakai F, et al. Clinical features and risk factors of panitumumab-induced interstitial lung disease: a postmarketing all-case surveillance study. Int J Clin Oncol. 2015;20(6):1063-1071. **12.** Vansteenkiste J. Nivolumab for NSCLC in Japanese patients: similar benefits, but beware of pneumonitis. ESMO Open. 2017;2(suppl 1):e000119. **13.** US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Published November 27, 2017.

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