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Date of request: February 28, 2019
NCCN Guidelines Panel: Breast Cancer

Dear NCCN Breast Panel,

Please find enclosed information for your review regarding Herceptin Hylecta™ (trastuzumab and hyaluronidase-oysk) subcutaneous (SC) injection. This submission also references Herceptin® (trastuzumab) intravenous (IV) injection.

Request:

Consider the recent Food and Drug Administration (FDA) approval of Herceptin Hylecta in HER2-positive adjuvant and metastatic breast cancer on February 28, 2019 and the supporting pivotal trial publications for inclusion into the guidelines.¹⁻⁵

Rationale:

The FDA approval is based on data from the HannaH, SafeHer, and PrefHer studies, which are enclosed for your reference and summarized below:

HannaH was a Phase III, randomized, open-label trial conducted to compare the pharmacokinetic (PK) profile, efficacy, and safety of Herceptin Hylecta and Herceptin IV in patients with HER2-positive conducted (neo) adjuvant breast cancer.³ HannaH demonstrated non-inferiority of Herceptin Hylecta to Herceptin based on co-primary PK (trastuzumab C_{trough} at pre-dose Cycle 8) and efficacy (pathological complete response (pCR) rate at definitive surgery) endpoints. For safety, although the incidence of Grade 3-5 AE's was similar between IV and SC groups, more patients in the SC group had serious AE's than in the IV group, mainly due to infections and infestations.

SafeHer was a prospective, two-cohort, non-randomized, multinational, open-label study designed to assess the overall safety and tolerability of Herceptin Hylecta with chemotherapy in patients with early HER2-positive breast cancer.⁴ In the primary safety analysis (median follow-up 23.7 months), no new safety signals were identified for Herceptin Hylecta. Overall, Grade ≥3 AE were experienced in 23.2% of patients, with the highest classified as "Blood/lymphatic system disorders" (7.3%).

PrefHer was a randomized, multi-center, two-arm, cross-over trial conducted in patients with HER2-positive breast cancer undergoing neoadjuvant or adjuvant treatment.⁵ The primary endpoint of this study was the proportion of patients reporting preference for either the Herceptin Hylecta SC or Herceptin IV route, which was assessed by 2 patient interviews. After the 2nd interview, 91.5% of patients preferred Herceptin Hylecta, 6.8% preferred Herceptin IV, and 1.7% had no preference. Grade 3 AE were reported in 4.5% of patients and no patient experienced a Grade 4 or 5 AE.

FDA Clearance:

- Herceptin Hylecta is FDA-approved for adjuvant and metastatic breast cancer. Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/herceptin_hylecta_prescribing.pdf
 - The recommended dose of Herceptin Hylecta is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over

approximately 2-5 minutes once every three weeks. No loading dose is required. No dose adjustments for patient body weight or for different concomitant chemotherapy regimens are required.

- Herceptin is FDA-approved for adjuvant and metastatic breast cancer and metastatic gastric cancer. Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at:
https://www.gene.com/download/pdf/herceptin_prescribing.pdf

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Thank you for your consideration and I hope this information is helpful to you. If you have any questions, please contact us at the phone number and email provided above.

Respectfully submitted,
Ellen Yang, PharmD

References

1. Herceptin Hylecta® [package insert]. Genentech; South San Francisco, CA. 2019.
2. FDA Approves Herceptin Hylecta for Subcutaneous Injection in Certain HER2-Positive Breast Cancers [Press Release]. South San Francisco, CA; Genentech, Inc. February 28, 2018. Accessed from: <https://www.gene.com/media/press-releases/14779/2019-02-28/fda-approves-herceptin-hylecta-for-subcu>
3. Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. *Lancet Oncol*. 2012 Sep; 13(9): 869-78. <https://www.ncbi.nlm.nih.gov/pubmed/22884505>
4. Gligorov J, Ataseven B, Verrill M, et al. Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients. *Eur J Cancer*. 2017 Sep; 82:237-246. <https://www.ncbi.nlm.nih.gov/pubmed/28625777>
5. Pivot X, Gligorov J, Muller V, et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. *Lancet Oncol*. 2013 Sep;14(10):962-70. <https://www.ncbi.nlm.nih.gov/pubmed/23965225>