Drug Policy:

Trastuzumab Products, Pertuzumab™ (pertuzumab), and Phesgo™ (pertuzumab, trastuzumab, and hyaluronidase-zzxf)

POLICY NUMBER UM ONC_1134	**SUBJECT** Trastuzumab Products, Pertuzumab™ (pertuzumab), and Phesgo™ (pertuzumab, trastuzumab, and hyaluronidase-zzxf)		**DEPT/PROGRAM** UM Dept	**PAGE 1 OF 5**
DATES COMMITTEE REVIEWED 07/22/11, 06/12/13, 07/23/14, 04/13/16, 07/26/16, 11/08/16, 09/13/17, 12/13/17, 11/14/18, 01/09/19, 03/13/19, 07/10/19, 09/11/19, 12/11/19, 01/08/20, 02/12/20, 03/11/20, 04/08/20, 06/10/20, 07/08/20, 08/27/20, 01/13/21, 03/10/21, 04/14/21, 11/15/21, 12/08/21, 01/12/22, 04/13/22	**APPROVAL DATE** April 13, 2022	**EFFECTIVE DATE** April 29, 2022	**COMMITTEE APPROVAL DATES** 07/22/11, 06/12/13, 07/23/14, 04/13/16, 07/26/16, 11/08/16, 09/13/17, 12/13/17, 11/14/18, 01/09/19, 03/13/19, 07/10/19, 09/11/19, 12/11/19, 01/08/20, 02/12/20, 03/11/20, 04/08/20, 06/10/20, 07/08/20, 08/27/20, 01/13/21, 03/10/21, 04/14/21, 11/15/21, 12/08/21, 01/12/22, 04/13/22	
PRIMARY BUSINESS OWNER: UM		**COMMITTEE/BOARD APPROVAL** Utilization Management Committee		
URAC STANDARDS HUM 1	**NCQA STANDARDS** UM 2		**ADDITIONAL AREAS OF IMPACT**	
CMS REQUIREMENTS	**STATE/FEDERAL REQUIREMENTS**		**APPLICABLE LINES OF BUSINESS** Commercial, Exchange, Medicaid	

I. PURPOSE

To define and describe the accepted indications for Trastuzumab products [Herceptin (trastuzumab), Herceptin Hylecta (trastuzumab hyaluronidase), Ogivri (trastuzumab-dkst), Herzuma (trastuzumab-pkrb), Ontruzant (trastuzumab-dttb), Kanjinti (trastuzumab-anns), Trazimera (trastuzumab-qyyp)], Pertuzumab (pertuzumab), and Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

New Century Health (NCH) is responsible for processing all medication requests from network ordering providers. Medications not authorized by NCH may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

II. INDICATIONS FOR USE/INCLUSION CRITERIA

A. PREFERRED MEDICATION GUIDANCE FOR INITIAL REQUEST:

1. When health plan Medicaid coverage provisions—including any applicable PDLs (Preferred Drug Lists)—conflict with the coverage provisions in this drug policy, health plan Medicaid coverage provisions take precedence per the Preferred Drug Guidelines OR
2. When health plan Exchange coverage provisions-including any applicable PDLs (Preferred Drug Lists)-conflict with the coverage provisions in this drug policy, health plan Exchange coverage provisions take precedence per the Preferred Drug Guidelines OR
3. For Health Plans that utilize NCH UM Oncology Clinical Policies as the initial clinical criteria, the Preferred Drug Guidelines shall follow NCH L1 Pathways when applicable, otherwise shall follow NCH drug policies AND
4. Continuation requests of previously approved, non-preferred medication are not subject to this provision AND
5. When applicable, generic alternatives are preferred over brand-name drugs.
6. Kanjinti (trastuzumab-anns) and Ogivri (trastuzumab-dkst) are the PREFERRED medications whenever Herceptin (trastuzumab) or Herceptin Hylecta (trastuzumab hyaluronidase) is requested. Kanjinti + Perjeta, Ogivri + Perjeta, or Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) are the PREFERRED options when a combination of trastuzumab and pertuxzumab is used/indicated.
7. Non-preferred trastuzumab will be approved only if there is a contraindication/intolerance to the PREFERRED medication.

B. HER-2 Positive Breast Cancer

1. NOTE 1: For neoadjuvant therapy, Pertuzumab is only indicated in members with node positive and/or tumor stage T2 or greater
2. NOTE 2: For adjuvant therapy, Trastuzumab + Pertuzumab are indicated in members who did not receive neoadjuvant therapy and are node positive at surgery or who have received neoadjuvant therapy and did NOT have any residual disease in the breast and/or axillary lymph node at surgery. If there is evidence of residual disease in the breast and or axillary nodes at surgery, then the Preferred drug per NCH Policy & NCH Pathway for adjuvant therapy is Kadcyla (ado-trastuzumab).
3. NOTE 3: Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) may be used anywhere Trastuzumab + Pertuzumab containing therapy is indicated.
    a. Trastuzumab +/- Pertuzumab may be used as neoadjuvant treatment OR as adjuvant treatment in members who did not receive neoadjuvant therapy or in members who received neoadjuvant therapy and did not have any residual disease in the breast or axillary lymph nodes at surgery. The following regimens are acceptable for use with Trastuzumab +/- Pertuzumab combination therapy:
        i. Trastuzumab +/- Pertuzumab with Paclitaxel following AC
        ii. Trastuzumab +/- Pertuzumab with Docetaxel following AC
        iii. Trastuzumab +/- Pertuzumab with Docetaxel/Paclitaxel
        iv. TCH (docetaxel, carboplatin, and trastuzumab) +/- Pertuzumab

v. Trastuzumab with Docetaxel and Cyclophosphamide.

b. Trastuzumab +/- Pertuzumab may be use as continuation adjuvant therapy following adjuvant Trastuzumab +/- Pertuzumab + Chemotherapy.

c. First line or subsequent line therapy for recurrent or metastatic HER-2 positive breast cancer:

i. In combination with Novaldex (tamoxifen), Faslodex (fulvestrant), or an aromatase inhibitor for a member whose disease is also ER/PR positive OR

ii. In combination with Pertuzumab and a Taxane, Taxotere (docetaxel) or Taxol (paclitaxel), regardless of the ER/PR status OR

iii. In combination with other single agent chemotherapy agents e.g., vinorelbine.

C. HER-2 Positive Gastric/Esophageal and Esophagogastric Junction Cancers

1. The member has a diagnosis of recurrent/metastatic gastric or esophageal or esophagogastric junction cancer and the cancer is HER-2 positive (defined as IHC 3+ or FISH positive) AND
2. Herceptin (trastuzumab), Ogivri (trastuzumab-dkst), Herzuma (trastuzumab-pkrb), Ontruzant (trastuzumab-dttb), Kanjinti (trastuzumab-anns), or Trazimera (trastuzumab-qyyp) is being used in combination with cisplatin oroxaliplatin and 5-fluorouracil (or capecitabine) as first line therapy.

III. EXCLUSION CRITERIA

A. Trastuzumab + Pertuzumab containing therapy is being used in members with tumor stage T1 breast cancer either in the adjuvant setting or in the neoadjuvant setting.

B. Trastuzumab + Pertuzumab is being used in the adjuvant setting without any adjuvant chemotherapy (before/after/during Trastuzumab + Pertuzumab).

C. Herceptin (trastuzumab)/Ogivri (trastuzumab-dkst)/Herzuma (trastuzumab-pkrb)/Ontruzant (trastuzumab-dttb)/Kanjinti (trastuzumab-anns)/Trazimera (trastuzumab-qyyp) use in gastric or gastroesophageal junction cancer after disease progression with first line therapy containing trastuzumab.

D. Continuation of trastuzumab after disease progression on trastuzumab-based therapy in HER-2 positive esophageal, gastroesophageal, and gastric adenocarcinomas.

E. Dosing exceeds single dose limit of trastuzumab 8 mg/kg for the loading dose, 6mg/kg for subsequent doses when given every 3 weeks; 4 mg/kg for the loading dose and 2 mg/kg for the subsequent doses, when trastuzumab is being given weekly.

F. Dosing exceeds single dose limit of Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) 1,800 mg (initial dose) and 1200 mg (subsequent dose).

G. Total treatment duration exceeds a maximum 52 weeks or 1 year (the equivalent of 17 three-week cycles) in non-metastatic HER-2 positive breast cancer. The above duration does not include any necessary therapy interruption, e.g., due to breast surgery and post-operative recovery.

H. Investigational use of Trastuzumab products/Pertuzumab/Phesgo with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:

1. Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
2. Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definition of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of < 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
4. Whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
5. That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
6. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
7. That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

IV. MEDICATION MANAGEMENT

A. Please refer to the FDA label/package insert for details regarding these topics.

V. APPROVAL AUTHORITY

A. Review – Utilization Management Department

B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

A. None

VII. REFERENCES

A. Gianni L et. al, 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016 Jun;17(6):791-800.

B. Piccart et al, APHINITY trial 6 year follow up, J Clin Oncol 2021, February 4, 2021. DOI: https://doi.org/10.1200/JCO.20.01204.

C. KATHERINE: Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. AU von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, Jacot W, Conlin AK, Arce-Salinas C, Wapnir IL, Jackisch C, DiGiovanna MP, Fasching PA, Crown JP, Wülfing P, Shao Z, Rota Caremoli E, Wu H, Lam LH, Tesarowski D, Smitt M, Douthwaite H, Singel SM, Geyer CE Jr, KATHERINE Investigators SO N Engl J Med. 2019;380(7):617. Epub 2018 Dec 5.

D. Results of two open-label, multicenter phase II studies of docetaxel, platinum salts, and trastuzumab in HER2-positive advanced breast cancer. Pegram MD, Pienkowski T, Northfelt DW,

Eiermann W, Patel R, Fumoleau P, Quan E, Crown J, Toppmeyer D, Smylie M, Riva A, Blitz S, Press MF, Reese D, Lindsay MA, Slamon DJ SO J Natl Cancer Inst. 2004;96(10):759

E. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. AU Robert N, Leyland-Jones B, Asmar L, Belt R, Ilegbodu D, Loesch D, Raju R, Valentine E, Sayre R, Cobleigh M, Albain K, McCullough C, Fuchs L, Slamon D SO J Clin Oncol. 2006;24(18):2786.

F. Trastuzumab emtansine for HER2-positive advanced breast cancer. AU Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K, EMILIA Study Group SO N Engl J Med. 2012;367(19):1783. Epub 2012 Oct 1.

G. von Minckwitz G, Procter M, de Azambuja E, et al: Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 377:122-131, 2017. (APHINITY Trial).

H. Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) prescribing information. Genentech, Inc. South San Francisco, CA 2020.

I. Herceptin Hylecta , prescribing information. Genentech, Inc. South San Francisco, CA 2019.

J. Herceptin, prescribing information. Genentech, Inc. South San Francisco, CA 2020.

K. Trazimera prescribing information. Pfizer Belgium NV, Belgium 2020.

L. Ogivri prescribing information. Mylan GmbH Zurich, Switzerland 2020.

M. Ontruzant prescribing information. Merck & Co., Inc., Whitehouse Station, NJ 2020

N. Herzuma prescribing information. Teva Pharmaceuticals USA, Inc. North Wales, PA 2020

O. Kanjinti prescribing information. Amgen Inc. Thousand Oaks, CA 2019.

P. Clinical Pharmacology Elsevier Gold Standard 2021.

Q. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, CO 2021

R. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2021.

S. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.

T. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.