Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM108	**Last Approval:**	09/19/2018
Title:	Pertuzumab (Perjeta®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW.

Documentation required to determine medical necessity for Pertuzumab (Perjeta): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Prescribed by or in consultation with an oncologist -Labs/diagnostics -Medication list (current and past) to include all chemotherapy agents.

BACKGROUND

Perjeta, a human epidermal growth factor receptor 2 (HER2) antagonist, is indicated for use in combination with Herceptin® (trastuzumab intravenous infusion) and docetaxel intravenous injection (Docefrez™, Taxotere®) for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.[1-2] Perjeta is also indicated in combination with Herceptin and chemotherapy as 1) neoadjuvant treatment of patients with HER2- positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer, OR 2) adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.
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Perjeta is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the HER2 protein and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including epidermal growth factor receptor (EGFR), HER3, and HER4.[1] As a result, Perjeta inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein kinase and phosphoinositide 3-kinase. Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, Perjeta mediates antibody-dependent cell-mediated cytotoxicity. Perjeta and Herceptin bind to different epitopes of the HER2 receptor and have complementary mechanisms of action.[2]

Perjeta is available as 420 mg/14 mL (30 mg/mL) single-use vials containing preservative-free solution.[1] Dilute Perjeta solution using 250 mL of 0.9% Sodium Chloride Injection (do not use Dextrose 5% solution). The diluted solution is infused intravenously over 30 to 60 minutes. Perjeta should not be administered as an intravenous push or bolus.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

Coverage of Perjeta is recommended in those who meet one of the following criteria:

FDA-Approved Indications

i. Breast Cancer.

Criteria. *The patient must meet the following criteria (A, B, C, AND D):*

A) Perjeta is prescribed by or in consultation with an oncologist; AND
B) The patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
C) The patient meets ONE of the following criteria (i, ii, or iii):
- **i.** Perjeta is being used for neoadjuvant (preoperative) therapy for locally advanced, inflammatory, or early stage disease AND will be used in combination with a taxane (e.g., docetaxel, paclitaxel); OR
- **ii.** Perjeta is being used for adjuvant therapy for early breast cancer at high risk of recurrence (e.g., node positive), according to the prescribing physician AND will be used in combination with a taxane (e.g., docetaxel, paclitaxel); OR
- **iii.** Perjeta is being used for recurrent or metastatic disease; AND

D) Perjeta is being used in combination with Herceptin (trastuzumab intravenous infusion).

Perjeta is indicated for use in combination with Herceptin and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.[1] Perjeta is also indicated in combination with Herceptin and docetaxel as neoadjuvant therapy in patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either > 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.[1,3] Perjeta should be withheld or discontinued if Herceptin is withheld or discontinued.[1]

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 1.2018) recommended uses for Perjeta are as follows:[3]

- Preoperative therapy for patients with HER2-positive clinical Stage TO-1, N1, MO or T2-3, NO-1, MO disease who desire breast preservation and fulfill criteria for breast-conserving surgery except for tumor size, or for those who have node positive disease likely to become node-negative with preoperative systemic therapy, or for locally advanced clinical Stage TO-3, N2, MO; T4,NO-2, MO or any T, N3, MO disease as follows: 1) in combination with Herceptin and paclitaxel following therapy with AC (doxorubicin and cyclophosphamide) regimen (preferred regimen); 2) in combination with Herceptin and docetaxel following therapy with AC regimen; or

3) in combination with TCH (docetaxel, carboplatin, and Herceptin) regimen (preferred regimen) [all of these regimens are category 2A]; OR

- Adjuvant therapy for patients with node positive HER2-positive tumors in combination with 1) Herceptin and paclitaxel (preferred regimen) following therapy with AC regimen; 2) Herceptin and docetaxel following therapy with AC regimen; or 3) TCH regimen (preferred regimen) [all of these regimens are category 2A]; OR
- For recurrent or Stage IV (M1) HER2-positive disease that is either hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory, for symptomatic visceral disease or visceral crisis for one of the following: 1) as preferred first-line therapy in combination with Herceptin with either docetaxel or paclitaxel (category 1); or 2) may be considered in combination with Herceptin with or without cytotoxic therapy (e.g., vinorelbine or a taxane) for one line of therapy beyond first-line therapy in patients previously treated with chemotherapy and Herceptin but without Perjeta) [category 2A].

Recently updated American Society of Clinical Oncology (ASCO) clinical practice guidelines on Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy[4] state that 1 year of adjuvant Perjeta may be added to Herceptin-based combination chemotherapy in patients with high-risk, early-stage, HER2-positive breast cancer. The Expert Panel preferentially supports Perjeta in patients with node positive, HER2-positive disease because there is a clinically insignificant absolute benefit among node-negative patients. In the Phase III APHINITY trial, after a median follow-up of 3.8 years, Perjeta showed a modest disease-free survival (DFS) benefit. The first planned interim analysis did not show an overall survival benefit. There are no data to guide the duration of Perjeta in patient who receive neoadjuvant Perjeta and achieve a pathologic complete response (pCR).

In one Phase III trial (CLEOPATRA), patients with HER2-positive *metastatic breast cancer* (n = 808) were randomized to receive first-line therapy with either Perjeta or placebo plus Herceptin and docetaxel.[1-2] Median overall survival was 56.5 months (95% confidence interval [CI]: 49.3, not reached) in the patients receiving Perjeta vs. 40.8 months (95% CI: 35.8, 48.3) in the group receiving placebo (hazard ratio [HR] 0.68; 95% CI: 0.56, 0.84; P < 0.001). Median progression-free survival (PFS) improved by 6.3 months in the Perjeta group (HR 0.68; 95% CI: 0.58, 0.80).[2]

In one multicenter, open-label, Phase II, proof of concept trial (NeoSphere), treatment naïve women (n = 417) with locally advanced, inflammatory, or early HER2-positive breast cancer who were scheduled for *neoadjuvant therapy* were randomized to 1 of 4 neoadjuvant regimens before surgery.[1,5] Patients received four cycles of one of the following regimens every 3 weeks: Herceptin and docetaxel (n = 107); Perjeta, Herceptin, and docetaxel (n = 107); Herceptin and Perjeta (n = 107); or Perjeta and docetaxel (n = 96). After surgery, all of the patients received FEC (5-FU, epirubicin, and cyclophosphamide) every 3 weeks for three cycles and Herceptin every 3 weeks to complete 1 year of therapy. After surgery, patients who initially received Perjeta plus Herceptin received docetaxel every 3 weeks for four cycles prior to FEC. The primary endpoint in the intent-to-treat population was the pCR rate in the breast at the time of surgery.[5] This measure is defined as pathological evidence of eradication of invasive cancer in the breast and lymph nodes after pre-surgery drug administration and is used as a surrogate for long-term efficacy. ***Results.*** Patients who received Perjeta, Herceptin, and docetaxel had a significantly improved pCR rate in 45.8% of

patients (n = 49/107; 95% CI: 36.1%, 55.7%) compared with Herceptin and docetaxel in 29.0% (n = 31/107; 95% CI: 20.6%, 38.5%); P = 0.0141) of patients. The pCR response rates were greater in patients with hormone receptor-negative tumors than in patients with hormone receptor-positive tumors. In the group that received Perjeta, Herceptin, and docetaxel, 63.2% (n = 36/57; 95% CI: 49.3%, 75.6%) of women who were hormone receptor-negative had a pCR vs. 26% (n = 13/50; 95% CI: 14.6%, 40.3%) of women who were hormone receptor-positive. An objective response rate (complete or partial response) in the primary lesion was reported in 88.1% (n = 89/101; 95% CI: 80.2%, 93.7%) of patients on Perjeta, Herceptin, and docetaxel and in 79.8% (n = 79/99; 95% CI: 70.5%, 87.2%) of patients on Herceptin plus docetaxel. Secondary endpoints of 5-year PFS in the ITT population and DFS have been reported.[6] At clinical cutoff 87 patients had disease progression or died. In patients on Perjeta, Herceptin, and docetaxel, the 5-year PFS rate was 86% (95% CI: 77%, 91%) and the DFS rate was 84% (95% CI: 72%, 91%).

In a second *neoadjuvant* Phase II trial (TRYPHAENA), patients with HER2-positive early breast cancer were randomized to one of three neoadjuvant regimens of Perjeta and Herceptin with anthracycline-containing or anthracycline-free chemotherapy.[1] After surgery all patients received Herceptin to complete 1 year of therapy. The pCR rates were 56.2%, 54.7%, and 63.6% for patients in the three regimens.

In another non-randomized, open-label, phase 2 study (BERENICE), patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer received Perjeta and Herceptin with anthracycline-based chemotherapy as *neoadjuvant therapy*.[1] After surgery, patients received Perjeta and Herceptin every 3 weeks to complete 1 year of therapy. In the two cohorts of patients, the pCR rates were 61.8% and 60.7%.

The Phase III trial pivotal trial (APHINITY) assessed the safety and efficacy of Perjeta in addition to chemotherapy plus Herceptin as adjuvant therapy in patients with operable HER2-positive primary breast cancer.[1,7] After surgery, patients were randomized to receive either Perjeta or placebo intravenously every 3 weeks for 1 year, plus six to eight cycles of chemotherapy and Herceptin every 3 weeks for 1 year. Perjeta significantly improved the rates of invasive DFS in patients with HER2-positive, operable breast cancer when given with Herceptin and chemotherapy. In the cohort of patients with node-positive disease, the 3-year rate of invasive DFS was 92.0% in the Perjeta group and 90.2% in the placebo group (HR for an invasive disease event 0.77; 95% CI: 0.62, 0.96; P = 0.02).

Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for Perjeta therapy because these were the only patients studied and for whom benefit has been shown.[1] Details on testing are reviewed in guidelines.[3,8] Treatment guidelines indicate that HER2-tumor status should be determined for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible if previously unknown or negative.

Dosing in Breast Cancer: *Dosing must meet ONE of the following (A,B, C, or D):*[1]

A) Recurrent or metastatic disease: 840 mg intravenous infusion followed by 420 mg intravenous infusion every 3 weeks;[1,3] OR

B) Neoadjuvant (Preoperative) therapy: 840 mg intravenous infusion followed by 420 mg intravenous infusion every 3 weeks for 3 to 6 cycles.[1] Then, followed after surgery by 420 mg every 3 weeks; OR

C) C) Adjuvant therapy: 840 mg intravenous infusion followed by 420 mg intravenous infusion every 3 weeks; OR

D) Dose modification for delayed or missed doses: If the time between two sequential infusions is 6 weeks or greater, the initial dose of 840 mg is re-administered and followed every 3 weeks by a dose of 420 mg.

The approved initial dose of Perjeta is 840 mg administered as a 60-minute intravenous infusion and followed every 3 weeks thereafter by 420 mg given as a 30- to 60-minute infusion.[1] For *recurrent or metastatic breast cancer*, Perjeta, Herceptin, and docetaxel are given every 3 weeks. For *neoadjuvant therapy*, Perjeta, Herceptin, and chemotherapy are given preoperatively every 3 weeks for three to six cycles as part of one of the following treatment regimens for early breast cancer: 1) four preoperative cycles of Perjeta plus Herceptin and docetaxel followed by three postoperative cycles of FEC (5-FU, epirubicin, and cyclophosphamide) as given in the NeoSphere trial; 2) three or four preoperative cycles of FEC alone followed by three or four preoperative cycles of Perjeta plus Herceptin and docetaxel as given in the TRYPHAENA and BERENICE trials, respectively; 3) six preoperative cycles of Perjeta in combination with the TCH (docetaxel, carboplatin, and Herceptin) regimen as given in the TRYPHAENA trial; or 4) four preoperative cycles of ddAC (dose-dense doxorubicin and cyclophosphamide) alone followed by four preoperative cycles of Perjeta in combination with paclitaxel and Herceptin as given in the BERENICE trial. Following surgery, Herceptin should be continued to complete 1 year of treatment (up to 18 cycles). For *adjuvant treatment of breast cancer*, Perjeta is administered in combination with Herceptin and chemotherapy postoperatively every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy as given in the APHINITY trial. Perjeta and Herceptin should start on Day 1 of the first taxane-containing cycle. For delayed or missed doses, if the time between two sequential infusions is < 6 weeks, the 420 mg dose should be administered. Do not wait until the next planned dose. If the time between two sequential infusions is ≥ 6 weeks, the initial dose of 840 mg should be re-administered, followed every 3 weeks thereafter by 420 mg. The infusion rate may be slowed or interrupted if the patient develops an infusion-related reaction. The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction. Perjeta should be discontinued if Herceptin treatment is discontinued.

Note: Dose reductions are not recommended for Perjeta. Dose modifications are recommended for the management of left ventricular ejection fraction (LVEF),[1] and are determined by the prescribing physician. **Initial Approval/Extended Approval.**

A) Recurrent or metastatic disease:

- **i.** *Initial Approval:* Initial approval is for 6 months of therapy.
- **ii.** *Extended Approval:* Approve at additional 6-month intervals if the patient does not have disease progression, as determined by the prescribing physician.

B) **Neoadjuvant** (Preoperative) therapy:

i. *Initial Approval*: Initial approval is for up to 6 cycles.
ii. *Extended Approval*: Complete 1 year of therapy (up to 18 cycles).

C) Adjuvant therapy:
i. *Initial Approval:* Initial approval is for 6 months of therapy.
ii. *Extended Approval:* Complete 1 year of therapy (up to 18 cycles).

Duration of Therapy in Breast Cancer.

A) Recurrent or Metastatic disease: Indefinite if the patient does not have disease progression. Neoadjuvant (Preoperative) or Adjuvant therapy: up to 1 year (up to 18 cycles).

Labs/Diagnostics. Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for Perjeta therapy. See criteria above.

Other Uses with Supportive Evidence

ii. Patient has been Started on Perjeta.

Criteria. *The patient must meet the following criteria (A, B, AND C):*

A) Patient has HER2-positive breast cancer; AND
B) Perjeta is being used in combination with Herceptin (trastuzumab intravenous injection); AND
C) The patient meets the conditions for coverage required for **Dosing**, **Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** for an approved use in this *Perjeta Utilization Review* policy.

iii. Other Cancer Indications. Forward to the Medical Director for review on a case-by-case basis.

Waste Management for All Indications.

The dose is 840 mg (28 mL) initially, followed by 420 mg (14 mL) every 3 weeks by intravenous infusion. Perjeta is available in single-use vials.

Conditions Not Recommended for Approval.

Perjeta has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References

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2. Swain SM, Baselga J, Kim SB, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med.* 2015;372:724-734.
3. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 1.2018 – March 20, 2018). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 25, 2018.
4. Denduluri N, Chavez-MacGregor M, Telli ML, et al. Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2018 May 22. [Epub ahead of print].
5. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13:25-32.
6. Gianni L, Pienkowski T, Im YH, 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;17(6):791-800.

7. von Minckwitz G, Procter M, de Azambuja E, et al; APHINITY steering committee and investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122-131.
8. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2018 May 30. [Epub ahead of print]

OTHER REFERENCES UTILIZED

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- Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018 Jun 25. [Epub ahead of print].

CFR		
WAC	WAC 284-43-2050	
RCW		
Contract Citation	☐ WAH	
	☐ IMC	
	☐ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
11/22/2017	No revisions	Sonya Ou, PharmD
12/21/2017	Approval	MMLT
05/04/2018	Transferred to new template	Cindy Bush
05/25/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee
08/09/2018	Revised	Jennifer Farley, PharmD
09/19/2018	Approval	UM Committee