UnitedHealthcare

DRUG POLICY

Human Epidermal Growth Factor Receptor 2 (HER2) Targeting Drugs

Policy Number: 2014D0001K
Effective Date: 1/1/2014

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Related Medical or Drug Policies:
Maximum Dosage Policy

Oncology Medication Clinical Coverage Policy

Related Coverage Determination Guidelines:
None

INSTRUCTIONS FOR USE
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

Please refer to the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium for updated information on oncology indications for ado-trastuzumab emtansine, pertuzumab and trastuzumab. This policy will continue to be updated for HER2 testing requirements. For related information please refer to the Oncology Medication Clinical Coverage Policy.

Breast Cancer

Ado-trastuzumab emtansine (Kadcyla™), pertuzumab (Perjeta®) and trastuzumab (Herceptin®) are proven only in patients whose tumors have HER2 protein overexpression as confirmed by a

positive HER2 test.[1,6,7] HER2 overexpression must be confirmed by a positive HER2 test - immunohistochemistry (IHC) staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of > 6 HER2 gene copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals (CEP17) of 2.0 or greater. A negative HER2 test is defined as either an IHC result of 0 or 1+ for cellular membrane protein expression (no staining or weak, incomplete membrane staining in any proportion of tumor cells), or a FISH result showing HER2/CEP17 ratio of less than 1.8 or an average of < 4 copies of HER2 gene per nucleus. Equivocal HER2 results for both the IHC and FISH assays require additional testing for final determination.

Gastric Cancer

Trastuzumab is proven only in patients with HER2 over-expressing metastatic gastric or gastroesophageal junction adenocarcinoma as confirmed by a positive HER2 test.[1] HER2 overexpression must be confirmed by a positive HER2 test, immunohistochemistry (IHC) staining of 3+ (strong complete, basolateral or lateral membranous reactivity in ≥ 10% of cancer cells). A negative HER2 test is defined as either an IHC result of 0 (no reactivity or membranous reactivity in < 10% of cancer cells) or 1+ (faint or barely perceptible membranous reactivity in ≥ 10% of cancer cells; cells are reactive only in part of their membrane). Equivocal (2+) IHC HER2 results in ≥ 10% of cancer cells should be additionally examined by FISH or other in situ hybridization as a confirmation method.

Centers for Medicare and Medicaid Services (CMS):
Medicare does not have a National Coverage Determination (NCD) for trastuzumab. Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, section 50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

Local Coverage Determinations (LCDs) exist for trastuzumab (Herceptin) and compliance with these policies is required where applicable. See the LCD for trastuzumab (Herceptin)

Medicare does not have NCDs or LCDs for Perjeta (pertuzumab) at this time.

(Accessed April 2, 2013)

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

CLINICAL EVIDENCE

Human Epidermal Growth Factor Receptor 2 (HER2) Testing in Breast Cancer

In 2006, the American Society of Clinical Oncology and the College of American Pathologists

(ASCO-CAP) convened an expert panel, which conducted a systematic review of the literature and developed recommendations for optimal HER2 testing performance.[2] An algorithm defining positive, equivocal, and negative values for both HER2 protein expression and gene amplification was recommended along with testing validation requirements.

In order to classify a HER2 test as either positive or negative, the laboratory must have performed concordance testing with a validated FISH assay and confirmed that only 5% or less of samples classified as either positive or negative disagree with that validated assay on an ongoing basis. If the laboratory. cannot satisfy this criterion, it should not perform HER2 testing and should send specimens to a reference laboratory.

A positive HER2 results is IHC staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), a FISH result of > 6 HER2 gene copies per nucleus, or a FISH ratio (HER2/CEP17) of 2.0 or greater. A negative HER2 test is defined as either an IHC result of 0 or 1+ for cellular membrane protein expression (no staining or weak, incomplete membrane staining in any proportion of tumor cells), or a FISH result showing HER2/CEP17 ratio of less than 1.8 or an average of < 4 copies of HER2 gene per nucleus.

There is significant variation in the intermediate (equivocal) ranges for both the IHC and FISH assays. The equivocal range for IHC consists of samples scored 2+ with complete membrane staining that is either nonuniform or weak in intensity but with obvious circumferential distribution in > 10% and < 30% of cells. The equivocal range for FISH assays is defined as HER2/CEP 17 ratios from 1.8 to 2.2 or average gene copy numbers between 4.0 and 6.0 for those systems without an internal control probe.

Equivocal IHC samples must be confirmed by FISH analysis of the sample.[8] Equivocal FISH samples are confirmed by counting additional cells or repeating the FISH test. If FISH remains equivocal after additional cells counted or assay repeated, confirmatory IHC is recommended so that HER2 protein expression is known for the sample with true equivocal gene amplification status. In 2011, ASCO-CAP clarified these confirmation results stating that patients with HER2/CEP17 FISH ratio ≥ 2.0 (including those with a ratio between 2.0 and 2.2) or patients with an equivocal (2+) IHC HER2 test who had tumors with uniform intense membrane staining in > 10% and < 30%of cells were also eligible for the trastuzumab adjuvant trials.[4] These strategies for evaluating tumors with borderline or indeterminate HER2 status are further described in the National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines algorithm on HER2 testing.[3] Additionally, the guideline recommends selecting HER2 targeted therapy (e.g., pertuzumab, trastuzumab) if their tumors are either positive for HER2 by ISH or 3+ by IHC.

Human Epidermal Growth Factor Receptor 2 (HER2) Testing in Gastric Cancer

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers. Tests should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.[1]

The 2013 National Comprehensive Cancer Network (NCCN) Gastric Cancer Guideline provides recommendations for HER2 (also known as HER2-neu) testing in those patients for whom trastuzumab therapy is being considered. For patients with unresectable locally advanced, recurrent, or metastatic gastric adenocarcinoma assessment for HER2 overexpression should be performed using immunhistochemistry (IHC) and/or fluorescence in situ hybridization (FISH).[5]

A positive HER2 result is defined as IHC staining of 3+ (strong complete, basolateral or lateral membranous reactivity in ≥ 10% of cancer cells) or FISH positive (HER2:CEP17 ratio ≥ 2). A negative HER2 result is defined as either an IHC result of 0 (no reactivity or membranous reactivity in < 10% of cancer cells) or 1+ (faint or barely perceptible membranous reactivity in ≥ 10% of cancer cells; cells are reactive only in part of their membrane). Equivocal (2+) IHC HER2 results (weak to moderate complete, basolateral or lateral membranous reactivity) in ≥ 10% of cancer cells should be additionally examined by FISH or other in situ hybridization as a confirmation method.[5]

To summarize, NCCN recommends that IHC be requested first then:[5]

- If the IHC score is 3+ then there is no need to request FISH.
- If IHC score is 2+, FISH should be requested and if there is evidence of gene amplification by FISH, trastuzumab can be recommended.
- If IHC score is 0 or 1+, trastuzumab is not recommended.

APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document

HCPCS Code	Description
J9306	Injection, pertuzumab, 1 mg
J9354	Injection, ado-trastuzumab emtansine, 1 mg
J9355	Injection, traztuzumab, 10 mg

REFERENCES

1. Herceptin® [package insert]. South San Francisco, CA: Genentech, Inc. October 2010.
2. Wolff AC, Hammond EH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. J Clin Oncol 2007;25(1): 118-145.
3. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V.1.2013 www.nccn.org. Accessed April 2, 2013.
4. Hammond EH, Hayes DF, and Wolff AC. Clinical Notice for American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations on ER/PgR and HER2 Testing in Breast Cancer. J Clin Oncol 2011;29(15): e458.
5. NCCN Clinical Practice Guidelines in Gastric Cancer. V.1.2013 www.nccn.org. Accessed April 2, 2013.
6. Perjeta™ [package insert]. South San Francisco, CA: Genentech, Inc. June 2012.
7. Kadcyla™ [package insert]. South San Francisco, CA: Genentech, Inc. February 2013.
8. Carlson RW, Moench SJ, Hammond ME, et al. HER2 testing in breast cancer: NCCN Task Force report and recommendations. J Natl Compr Canc Netw. 2006 Jul;4 Suppl 3:S1-22.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
1/1/2014	Policy updated with coding changes effective on 1/1/2014 (added J9306 and J9354, and removed C9292). Policy 2013D0001J archived.
7/1/2013	Policy revised to include HER2 testing requirement for ado-trastuzumab emtansine. Revised drug policy title, clinical evidence and references. Approved by National Pharmacy & Therapeutics Committee 5/21/2013. Policy 2013D0001I archived.
1/1/2013	Policy revised per annual review to include HER2 testing requirement for pertuzumab. Revised coverage rationale and clinical evidence. Added HCPCS code C9292 for pertuzumab. Approved by National Pharmacy & Therapeutics Committee 11/13/2012. Policy 2011D0001F archived
11/8/2011	Policy revised per annual review to include gastric cancer HER2 testing in coverage rationale, clinical recommendations, and research evidence. Revised the following sections: Instructions for Use, CMS and Reference. Approved by National Pharmacy & Therapeutics Committee 11/8/2011. Policy 2009D0001H archived.
11/24/2010	Revised per annual review with updates to CMS and Reference sections. Approved by National Pharmacy & Therapeutics Committee 11/9/2010. Policy 2009D0001G archived.
12/29/2009	Revised per annual review with updates to reference and coding sections. Approved by National Pharmacy & Therapeutics Committee on 12/9/2009. Policy 2008D0001F archived.
11/20/2008	Policy revised in customer claims edit section.
10/8/2008	Policy revised in coverage rationale, clinical recommendations section for FISH ratio.
4/11/2008	Policy revised in coverage rationale, clinical recommendations, and research evidence. Policy 2008D0001E archived.
3/7/2008	Policy revised with changes in the coverage rationale. Policy 2007D0001D archived.
7/27/2007	Policy 2005D0001C archived.
1/11/2007	Policy revised with changes in the coverage rationale. Policy 2005D0001B archived.
12/20/2005	Policy 1999D0001A archived.
6/7/1999	New policy. Approved by National Pharmacy & Therapeutics Committee on 2/9/1999. Policy 1999D0001A.