Clinical Policy: Capecitabine (Xeloda)

Reference Number: CP.PHAR.60
Effective Date: 05/11
Last Review Date: 06/17

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for capecitabine (Xeloda®/generic).

Policy/Criteria
It is the policy of health plans affiliated with Centene Corporation® that capecitabine (Xeloda/generic) is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Colorectal Cancer (must meet all):

1. Diagnosis of colorectal cancer;
2. Will be used for one of the following indications (a or b):
   a. FDA approved use:
      i. As a single agent for (a or b) when treatment with fluoropyrimidine therapy alone is preferred:
         a) Adjuvant treatment of Dukes' C (stage III) colon cancer after the primary tumor has been completely resected;
         b) As first-line treatment of metastatic colorectal carcinoma;
   b. Off-label NCCN recommended use (one of the following):
      i. In capecitabine and oxaliplatin regimen;
      ii. In combination with bevacizumab;
      iii. With concurrent chemoradiation;
3. Member has none of the following contraindications:
   a. Severe renal impairment (creatinine clearance < 30 mL/min);
   b. Hypersensitivity to 5-fluorouracil.

Approval duration: 6 months

B. Breast Cancer (must meet all):

1. Diagnosis of recurrent or metastatic breast cancer;
2. Will be used for one of the following indications (a or b):
   a. FDA approved use (i or ii):
      i. In combination with docetaxel after failure of anthracycline-containing chemotherapy;
      ii. As monotherapy for disease that is resistant* to (a or b):
         a) Paclitaxel and an anthracycline-containing chemotherapy regimen;
         b) Paclitaxel and further anthracycline therapy is not indicated (e.g., member has received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents);

b. Off-label NCCN recommended use:
   i. As a single agent or in combination with docetaxel for HER2-negative disease with one of the following characteristics:
      a) Concurrent symptomatic visceral disease or visceral crisis;
      b) The disease is HR-negative - or HR-positive and endocrine therapy refractory;
   ii. In combination with trastuzumab or lapatinib (if trastuzumab-exposed disease) for HER2-positive disease with one of the following characteristics:
      a) Concurrent symptomatic visceral disease or visceral crisis;
      b) The disease is HR-negative or HR-positive and endocrine therapy refractory;

3. Member has none of the following contraindications:
   a. Severe renal impairment (creatinine clearance < 30 mL/min);
   b. Hypersensitivity to 5-fluorouracil.

*****Resistance is defined as progressive *disease while on treatment or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen.*

Approval duration: 6 months

C. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

1. Additional NCCN compendium uses for capecitabine, meeting NCCN categories 1, 2a, or 2b, are covered for the following indications per the CP.PHAR.57 Global Biopharm Policy:
   a. Anal carcinoma (squamous cell carcinoma);
   b. Central nervous system cancers:
      i. Limited (1-3) metastatic lesions - brain metastases;
      ii. Multiple (>3) metastatic lesions - brain metastases;
   c. Esophageal and esophagogastric junction cancers (squamous cell carcinoma; adenocarcinoma);
   d. Gastric cancer (adenocarcinoma);
   e. Very advanced and recurrent/persistent head and neck cancer (squamous cell carcinoma with mixed subtypes);
   f. Hepatobiliary cancers:
      i. Extrahepatic cholangiocarcinoma (adenocarcinoma);
      ii. Gallbladder cancer (adenocarcinoma);
      iii. Intrahepatic cholangiocarcinoma (adenocarcinoma);
   g. Neuroendocrine tumors of the pancreas;
   h. Occult primary (adenocarcinoma or carcinoma not otherwise specified);
   i. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer (serous; endometrioid; carcinosarcoma; clear cell; mucinous);
   j. Mucinous carcinoma of the ovary;
   k. Pancreatic cancer (adenocarcinoma);
   l. Penile cancer.

II. Continued Approval

A. All Indications (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Documentation of positive response to therapy (e.g., no disease progression; no unacceptable toxicity).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or

Approval duration: Duration of request or 12 months (whichever is less); or

2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

Background

Description/Mechanism of Action:

Xeloda (capecitabine) is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is convertedto 5-fluorouracil. Enzymes convert capecitabine to 5-fluorouracil (5-FU) *in vivo*. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS). This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Formulations:

Tablet, Oral:
Xeloda: 150 mg, 500 mg
Generic: 150 mg, 500 mg

FDA Approved Indications:

Xeloda (capecitabine) is a nucleoside metabolic inhibitor/oral tablet formulation indicated for:

- Colorectal Cancer
  - Xeloda is indicated as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. Xeloda was non-inferior to 5-fluorouracil and leucovorin (5-FU/LV) for disease-free survival. Physicians should consider results of combination chemotherapy trials, which have shown improvement in disease-free survival and overall survival, when prescribing single-agent Xeloda in the adjuvant treatment of Dukes' C colon cancer.
  - Xeloda is indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival

benefit over 5-FU/LV has not been demonstrated with Xeloda monotherapy. Use of Xeloda instead of 5FU/LV in combinations has not been adequately studied to assure safety or preservation of the survival advantage.

- Breast Cancer
  - Xeloda in combination with docetaxel is indicated for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.
  - Xeloda monotherapy is also indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated (e.g., patients who have received cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents). Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline containing adjuvant regimen.

Appendices
Appendix A: Abbreviation Key
HER2: human epidermal growth factor receptor 2
HR: hormone receptor

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J8520	Capecitabine, oral, 150 mg
J8521	Capecitabine, oral, 500 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Updated references	06/14	06/14
Updated language in Dosing & Administration, Safety, Contraindications, and use in specific populations Added coumadin related question in Figure 1	04/15	06/15
Policy converted to new template. Removed question about monitoring PT/INR. FDA indications retained per PI; all NCCN compendium uses added if not already in the policy. Colorectal cancer - Dukes' C is analogous to stage III per NCCN colon and rectal cancer guidelines.	06/16	06/16
For colorectal cancer, added "when treatment with fluoropyrimidine therapy alone is preferred" to section 2.a. (FDA approved use). Removed as contraindications: dihydropyrimidine dehydrogenase deficiency and hypersensitivity to capecitabine; modified approval duration from 3 to 6	05/17	06/17

Reviews, Revisions, and Approvals	Date	Approval Date
months; re-auth: removed reasons to discontinue; modified approval duration from 6 to 12 months; updated additional NCCN uses and removed lung endocrine tumors (NCCN category 3).		

References

1. Xeloda Prescribing Information. South San Francisco, CA: Genentech, Inc.; December 2016. Available at https://www.gene.com/patients/medicines/xeloda. Accessed May 1, 2017.
2. Capecitabine. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.NCCN.org. Accessed May 1, 2017.
3. National Comprehensive Cancer Network. Colon cancer Version 2.2017. Available at www.NCCN.org. Accessed May 1, 2017.
4. National Comprehensive Cancer Network. Rectal cancer Version 3.2017. Available at www.NCCN.org. Accessed May 1, 2017.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.