Clinical Policy: Capecitabine (Xeloda)

Reference Number: CP.PHAR.60
Effective Date: 05.01.11
Last Review Date: 05.26
Line of Business: HIM/ICHRA, Medicaid

Coding Implications
Revision Log

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

Description

Capecitabine (Xeloda®) is nucleoside metabolic inhibitor with antineoplastic activity.

FDA Approved Indication(s)

Xeloda is indicated for the treatment of:

- Colorectal Cancer
  - Adjuvant treatment of patients with Stage III colon cancer as a single agent or as a component of a combination chemotherapy regimen.
  - Perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy.
  - Treatment of patients with unresectable or metastatic colorectal cancer as a single agent or as a component of a combination chemotherapy regimen.
- Breast Cancer
  - Treatment of patients with advanced or metastatic breast cancer as a single agent if an anthracycline-or taxane-containing chemotherapy is not indicated.
  - Treatment of patients with advanced or metastatic breast cancer in combination with docetaxel after disease progression on prior anthracycline-containing chemotherapy.
- Gastric, Esophageal, or Gastroesophageal Junction Cancer
  - Treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen.
  - Treatment of adults with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease as a component of a combination regimen.
- Pancreatic Cancer
  - Adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Xeloda 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. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member must use generic capecitabine, unless contraindicated or clinically significant adverse effects are experienced;
5. Confirmation that a homozygous or compound heterozygous *DPYD* variant is not present, unless immediate treatment is necessary (see *Appendix D)*;
6. Request meets one of the following (a, b, c, or d):*
   a. Monotherapy (unresectable or metastatic disease, or adjuvant treatment): Dose does not exceed 1,250 mg/m^2 twice a day on Days 1 to 14, every 21 days **(if adjuvant treatment: maximum of 8 cycles)**;
   b. In combination with oxaliplatin-containing regimen (unresectable or metastatic disease, or adjuvant treatment): Dose does not exceed 1,000 mg/m^2 twice a day on Days 1 to 14, every 21 days;
   c. For perioperative treatment, one of the following (i or ii):
      i. With concomitant radiation therapy: Dose does not exceed 825 mg/m^2 twice a day;
      ii. Without radiation therapy: Dose does not exceed 1,250 mg/m^2 twice a day;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

B. Breast Cancer (must meet all)**:**
1. Diagnosis of breast cancer and one of the following (a or b):
   a. Disease is recurrent, advanced, metastatic, or unresponsive to preoperative systemic therapy;
   b. Xeloda is prescribed as adjuvant or maintenance therapy;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member must use generic capecitabine, unless contraindicated or clinically significant adverse effects are experienced;
5. Confirmation that a homozygous or compound heterozygous *DPYD* variant is not present, unless immediate treatment is necessary (see *Appendix D)*;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 1,250 mg/m^2 twice a day on Days 1 to 14, every 21 days;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

C. Gastric, Esophageal or Gastroesophageal Junction Cancer (must meet all)**:**
1. Diagnosis of gastric, esophageal, or gastroesophageal junction cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;

4. Member must use generic capecitabine, unless contraindicated or clinically significant adverse effects are experienced;
5. Confirmation that a homozygous or compound heterozygous *DPYD* variant is not present, unless immediate treatment is necessary (see *Appendix D)*;
6. Request meets one of the following (a. b, or c):*
   a. Dose does not exceed 625 mg/m^2 twice a day on Days 1 to 21, every 21 days **(maximum of 8 cycles)**;
   b. Dose does not exceed 1,000 mg/m^2 twice a day on Days 1 to 14, every 21 days;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

D. Pancreatic Cancer (must meet all)**:**
1. Diagnosis of pancreatic cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member must use generic capecitabine, unless contraindicated or clinically significant adverse effects are experienced;
5. Confirmation that a homozygous or compound heterozygous *DPYD* variant is not present, unless immediate treatment is necessary (see *Appendix D)*;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 830 mg/m^2 twice a day on Days 1 to 21, every 28 days **(maximum of 6 cycles)**;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

E. NCCN Recommended Uses (off-label) (must meet all)**:**
1. Prescribed for one of the following diagnoses (a – q):
   a. Ampullary adenocarcinoma;
   b. Anal carcinoma;
   c. Appendiceal neoplasms and cancers;
   d. Cervical cancer;
   e. Gestational trophoblastic neoplasia;
   f. Head and neck cancer (i, ii, or iii):
      i. Cancer of the nasopharynx;
      ii. Advanced head and neck cancer;
      iii. Occult primary tumors;
   g. Hepatobiliary cancer (i, ii, or iii):
      i. Extrahepatic cholangiocarcinoma;
      ii. Gallbladder cancer;
      iii. Intrahepatic cholangiocarcinoma;
   h. Neuroendocrine tumor of the pancreas, gastrointestinal tract, lung, or thymus;

i. Extrapulmonary neuroendocrine carcinoma (i or ii):
   i. Large or small carcinoma;
   ii. Mixed neuroendocrine-non-neuroendocrine neoplasm;
j. Occult primary cancer (cancer of unknown origin);
k. Ovarian or fallopian tube or primary peritoneal cancer;
l. Penile cancer;
m. Small bowel adenocarcinoma;
n. Squamous cell skin cancer;
o. Thymoma or thymic carcinoma;
p. Vaginal cancer;
q. Vulvar cancer;

2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member must use generic capecitabine, unless contraindicated or clinically significant adverse effects are experienced;
5. Confirmation that a homozygous or compound heterozygous DPYD variant is not present, unless immediate treatment is necessary (see *Appendix D*);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace/ICHRA and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace/ICHRA and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace/ICHRA and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Xeloda for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Member must use generic capecitabine, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, request meets one of the following (a - e):
   a. Colorectal cancer, one of the following (i, ii, or iii):
      i. Monotherapy (unresectable or metastatic disease, or adjuvant treatment): New dose does not exceed 2,500 mg/m^2 total daily dose on Days 1 to 14, every 21 days **(if adjuvant treatment: maximum of 8 cycles)**;
      ii. In combination with oxaliplatin-containing regimen (unresectable or metastatic disease, or adjuvant treatment): New dose does not exceed 2,000 mg/m^2 total daily dose on Days 1 to 14, every 21 days;
      iii. For perioperative treatment, one of the following (1 or 2):
         1) With concomitant radiation therapy: New dose does not exceed 1,650 mg/m^2 total daily dose;
         2) Without radiation therapy: New dose does not exceed 2,500 mg/m^2 total daily dose;
   b. Breast cancer: New dose does not exceed 2,500 mg/m^2 total daily dose on Days 1 to 14, every 21 days
   c. Gastric, esophageal, or gastroesophageal junction cancer, one of the following (i or ii):
      i. New dose does not exceed 1,250 mg/m^2 total daily dose on Days 1 to 21, every 21 days (**maximum of 8 cycles)**;
      ii. New dose does not exceed 2,000 mg/m^2 total daily dose on Days 1 to 14, every 21 days;
   d. Pancreatic cancer: New dose does not exceed 1,660 mg/m^2 total daily dose on Days 1 to 21, every 28 days (**maximum of 6 cycles)**;
   e. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace/ICHRA and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the

relevant line of business: HIM.PA.103 for health insurance marketplace/ICHRA and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace/ICHRA and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – HIM.PA.154 for health insurance marketplace/ICHRA and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): severe hypersensitivity reactions to fluorouracil or capecitabine
- Boxed warning(s): serious adverse reactions or death in patients with complete DPD deficiency and increased risk of bleeding with concomitant use of vitamin k antagonists

Appendix D:General Information

- Patients with certain homozygous or compound heterozygous variants in the DPYD gene known to result in complete or near complete absence of DPD activity (complete DPD deficiency) are at increased risk for acute early-onset toxicity and serious, including fatal, adverse reactions (eg, mucositis, diarrhea, neutropenia, and neurotoxicity) when exposed to capecitabine. The FDA updated labeling advising to test for genetic variants of *DPYD* prior to initiating capecitabine, unless immediate treatment is necessary.
  - An FDA-authorized test for the detection of the genetic variants of *DPYD* gene is not currently available. Currently available tests may vary in accuracy and design (e.g., which *DPYD* variant(s) they identify).

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Colorectal Cancer	<u>Adjuvant, unresectable or metastatic treatment</u> • Single agent: 1,250 mg/m^2 PO BID for the first 14 days of each 21-day cycle*	2,500 mg/m^2 total daily dose

Indication	Dosing Regimen	Maximum Dose
	• Combination with oxaliplatin-containing regimen: 1,000 mg/m^2 PO BID for the first 14 days for each 21-day cycle* * *For adjuvant treatment: maximum of 8 cycles; For unresectable or metastatic treatment: until disease progression or unacceptable toxicity* <u>Perioperative treatment</u> • With concomitant radiation therapy: 825 mg/m^2 PO BID • Without radiation therapy: 1,250 mg/m^2 PO BID	
Breast Cancer	<u>Advanced or metastatic treatment</u> • Single agent or combination with docetaxel: 1,000 mg/m^2 or 1,250 mg/m^2 PO BID for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity	2,500 mg/m^2 total daily dose
Gastric, Esophageal, or Gastroesophageal Junction Cancer	<u>Unresectable or metastatic treatment</u> • In combination with platinum-containing chemotherapy: 625 mg/m^2 PO BID on days 1 to 21 of each 21-day cycle (maximum of 8 cycles) OR • In combination with oxaliplatin: 850 mg/m^2 or 1,000 mg/m^2 PO BID for first 14 days of each 21-day cycle until disease progression or unacceptable toxicity <u>HER2-overexpressing metastatic adenocarcinoma</u> • In combination with cisplatin and trastuzumab: 1,000 mg/m^2 PO BID for first 14 days of each 21-day cycle until disease progression or unacceptable toxicity	2,000 mg/m^2 total daily dose
Pancreatic Cancer	• In combination with gemcitabine: 830 mg/m^2 PO BID for the first 21 days of each 28-day cycle (maximum of 6 cycles)	1,660 mg/m^2 total daily dose

VI. Product Availability

Tablets: 150 mg, 500 mg

VII. References

1. Xeloda Prescribing Information. South San Francisco, CA: Genentech, Inc.; October 2025. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/020896s052lbl.pdf. Accessed January 29. 2026.

2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed January 29, 2026.

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
J8522	Capecitabine, oral, 50 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2022 annual review: added "maintenance therapy" and "unresponsive to preoperative systemic therapy" uses of Xeloda in breast cancer per NCCN; collapsed off-label criteria for neuroendocrine tumor of the pancreas into the off-label criteria set; WCG.CP.PHAR.60 was retired and initial approval duration was consolidated to 6 months; references reviewed and updated.	02.22.22	05.22
Template changes applied to other diagnoses/indications.	11.23.22	
2Q 2023 annual review: collapsed off-label criteria for anal carcinoma and added to NCCN recommended (off-label) criteria set; added ampullary adenocarcinoma and extrapulmonary neuroendocrine carcinoma to NCCN recommended (off-label) list; RT4: per updated PI, updated FDA approved indications for colorectal cancer and breast cancer, added gastric/esophageal/gastroesophageal junction cancer and pancreatic cancer criteria (removed from off-label list), removed criterion "member does not have severe renal impairment (creatinine clearance < 30 mL/min)" as severe renal impairment is no longer a contraindication as updated in Appendix C, updated section V; references reviewed and updated.	01.10.23	05.23
2Q 2024 annual review: added NCCN-supported indication of endometrial carcinoma and vulvar cancer into off-label criteria set; references reviewed and updated.	01.18.24	05.24
Added HCPCS code [J8522] and removed HCPCS codes [J8520, J8521].	08.07.24	
2Q 2025 annual review: added NCCN-supported indication of cervical cancer and vaginal cancer into off-label criteria set; for extrapulmonary neuroendocrine carcinoma, revised "and" to "or" for large or small carcinoma; references reviewed and updated.	01.13.25	05.25
2Q 2026 annual review: updated boxed warnings for patients with complete DPD deficiency and added criterion to confirm that a homozygous or compound heterozygous DPYD variant is not present,	03.30.26	05.26

Reviews, Revisions, and Approvals	Date	P&T Approval Date
unless immediate treatment is necessary per updated PI; for off-label indications, added appendiceal neoplasms and cancers and subtypes of head and neck cancer (nasopharynx and occult primary tumor) and removed endometrial carcinoma per NCCN; extended initial approval duration from 6 to 12 months for this maintenance medication for a chronic condition; references reviewed and updated. Added ICHRA line of business.		

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.