09-J1000-42

Original Effective Date: 01/01/12

Reviewed: 01/09/19

Revised: 02/15/19

Subject: Capecitabine (Xeloda®) Tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Position Statement	Dosage/ Administration	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Capecitabine (Xeloda) is an orally administered pro-drug of 5-fluorouracil. Both tumor cells and normal cells metabolize 5-fluorouracil into two metabolites: 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). FdUMP prevents the formation of thymidylate from uracil; thymidylate is the necessary precursor of thymidine triphosphate (dTTP), one of the four deoxyribonucleotides required for synthesis of DNA. A deficiency of this compound results in the inhibition of cellular division. FUTP is incorporated in place of uridine triphosphate (UTP) during RNA synthesis. This interferes with RNA processing and protein synthesis. Interference with DNA and RNA activity results in anti-neoplastic activity.

Capecitabine was the first oral anti-neoplastic agent approve by the US Food and Drug Administration for the treatment of metastatic breast cancer. It is also indicated for the first line treatment of metastatic colon cancer and as adjuvant treatment for colon cancer in persons with Dukes C colon cancer. In addition to its FDA-approved indications, capecitabine treatment is supported by referenced compendia (e.g., National Comprehensive Cancer Network, Micromedex) for off-label uses, including the treatment of anal cancer, brain metastases, cancer of unknown primary (occult primary), esophageal cancer, gastric cancer, gestational trophoblastic neoplasia, hepatobiliary cancer, various types of neuroendocrine tumors, renal cancer, ovarian cancer, pancreatic cancer, penile cancer, rectal cancer, and head and neck cancer.

POSITION STATEMENT:

Capecitabine (Xeloda) meets the definition of medical necessity when **BOTH** of the following are met:

1. Member meets ALL criteria for requested formulation:

a. Capecitabine tablet (generic)
    i. Dosage does not exceed 2500 mg/m^2/day
b. Xeloda® tablet
    i. Member has a failure, contraindication, or intolerance to generic capecitabine
    ii. Dosage does not exceed 2500 mg/m^2/day

2. **ONE** of the following:
    a. Capecitabine will be used to treat **ANY** of the following:
        i. Anal carcinoma
        ii. Appendiceal adenocarcinoma
        iii. Breast cancer
        iv. Brain metastases
        v. Colon cancer
        vi. Esophageal and esophagogastric junction cancer
        vii. Gastric cancer
        viii. Gestational Trophoblastic Neoplasia
        ix. Head and neck cancer
        x. Hepatobiliary cancer (including gallbladder cancer, intrahepatic and extrahepatic cholangiocarcinoma)
        xi. Neuroendocrine tumors (extrapulmonary) with poorly differentiated carcinoma/large or small cell carcinoma
        xii. Neuroendocrine tumor of the gastrointestinal tract with poorly controlled carcinoid syndrome
        xiii. Neuroendocrine tumor of the pancreas
        xiv. Occult primary tumors
        xv. Ovarian cancer (including epithelial ovarian, fallopian tube, primary peritoneal, and mucinous cancer)
        xvi. Pancreatic adenocarcinoma
        xvii. Penile Cancer
        xviii. Rectal cancer
        xix. Renal Cancer
        xx. Small bowel adenocarcinoma
    b. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
    c. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

Approval duration: 1 year (all indications)

DOSAGE/ADMINISTRATION

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved indications

Adjuvant colon cancer treatment in persons with Dukes' C colon cancer

First-line of metastatic colorectal cancer when used as monotherapy and treatment with fluoropyrimidine therapy alone is preferred

Metastatic breast cancer as monotherapy in persons resistant to both paclitaxel and an anthracycline-containing regimen or in combination with docetaxel following failure of prior anthracycline-containing therapy

Capecitabine should be administered with water 30 minutes after a meal. When used as monotherapy, the recommended dose is 1,250 mg/m^2 twice daily for 14 days followed by a 1 week rest period in a 3 week cycle. Adjuvant therapy is recommended for a total of six months. When used in combination with docetaxel, the recommended dose is 1,250 mg/m^2 twice daily for 14 days followed by a one week rest period, combined with docetaxel 75 mg/m^2 as a 1 hour IV infusion every three weeks.

Dose Adjustments: reduce the dose by 25% in members with moderate renal impairment. Monitor in persons with mild to moderate hepatic impairment. Geriatric patients are more likely to experience adverse reactions and should be monitored closely. See prescribing information for adjustments due to adverse reactions.

Drug Availability: capecitabine is supplied as a 150- or 500 mg tablet.

PRECAUTIONS:

BOXED WARNING:

Individuals receiving capecitabine and oral coumarin-derivative anticoagulants (e.g., warfarin) should have their anticoagulant response (INR or prothrombin time) monitored frequently to adjust the anticoagulant accordingly. Altered coagulation parameters and/or bleeding, including death have occurred. The drug interaction may occur within days to several months after initiation of therapy or after stopping therapy with capecitabine. Individuals > 60 years of age with a diagnosis of cancer are more at risk.

CONTRAINDICATIONS

Severe renal impairment

Hypersensitivity

WARNINGS/PRECAUTIONS

Cardiotoxicity: Common in patients with a prior history of coronary artery disease.

Coagulopathy: May result in bleeding, death. Monitor anticoagulant response (e.g., INR) and adjust anticoagulant dose accordingly.

Dehydration and Renal Failure: Interrupt treatment until dehydration is corrected. Potential risk of acute renal failure secondary to dehydration. Monitor and correct dehydration.

Diarrhea: May be severe. Interrupt capecitabine treatment immediately until diarrhea resolves or decreases to grade 1. Recommend standard antidiarrheal treatments.

Dihydropyrimidine dehydrogenase (DPD) deficiency: Withhold or permanently discontinue in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No dose has been proven safe in patients with absent DPD activity.

Hematologic: Do not treat members with neutrophil counts $<1.5 \times 10^9$/L or thrombocyte counts $<100 \times 10^9$/L. If grade 3-4 neutropenia or thrombocytopenia occurs, stop therapy until condition resolves.

Hyperbilirubinemia (Grade 2 to 4): Interrupt capecitabine treatment immediately until the hyperbilirubinemia resolves or decreases in intensity.

Mucocutaneous and Dermatologic Toxicity: Severe mucocutaneous reactions, Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported. Permanently discontinue if severe mucocutaneous reactions occur. Hand-and-Foot Syndrome may occur. Interrupt capecitabine treatment until the event resolves or decreases in intensity.

Pregnancy: Can cause fetal harm. Advise women of the potential risk to the fetus.

BILLING/CODING INFORMATION:

HCPCS Coding

J8520	Capecitabine, oral, 150 mg
J8521	Capecitabine, oral, 500 mg
WW089	Capecitabine, 150 mg oral
WW096	Capecitabine, 500 mg oral

ICD-10 Diagnosis Codes That Support Medical Necessity

C00.0 – C00.9	Malignant neoplasm of lip
C01	Malignant neoplasm of base of tongue
C02.0	Malignant neoplasm of dorsal surface of tongue
C02.1	Malignant neoplasm of border of tongue
C02.2 – C02.4	Malignant neoplasm of ventral surface of tongue, anterior two-thirds of tongue, part unspecified, lingual tonsil
C02.8	Malignant neoplasm of overlapping sites of tongue
C02.9	Malignant neoplasm of tongue, unspecified
C03.0 – C03.9	Malignant neoplasm of upper gum, lower gum, gum unspecified
C04.0 – C04.9	Malignant neoplasm of floor of mouth
C05.0 – C05.9	Malignant neoplasm of palate
C06.0 – C06.9	Malignant neoplasm of other and unspecified parts of mouth

C09.0 – C09.9	Malignant neoplasm of tonsil
C10.0 – C10.9	Malignant neoplasm of oropharynx
C11.0 – C11.9	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of pyriform sinus
C13.0 – C13.9	Malignant neoplasm of hypopharynx
C14.0 – C14.8	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15.3 – C15.9	Malignant neoplasm of esophagus
C16.0 – C16.9	Malignant neoplasm of stomach
C17.0 – C17.2	Malignant neoplasm of duodenum, jejunum, ileum
C17.8 – C17.9	Malignant neoplasm of overlapping sites of small intestine or of unspecified site of small intestine
C18.0 – C18.9	Malignant neoplasm of colon
C19 – C21.8	Malignant neoplasm of rectosigmoid junction, rectum, anus and anal canal
C22.1	Intrahepatic bile duct carcinoma
C23 – C24.9	Malignant neoplasm of gallbladder and other and unspecified parts of biliary tract
C25.0 – C25.2	Malignant neoplasm of head, body, or tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7 – C25.9	Malignant neoplasm of other parts of pancreas, overlapping sites of pancreas, or unspecified part of pancreas
C30.0	Malignant neoplasm of nasal cavity
C31.0 – C31.1	Malignant neoplasm of maxillary or ethmoidal sinus
C32.0 – C32.9	Malignant neoplasm of larynx
C44.00 – C44.09	Unspecified malignant neoplasm of skin of lip
C48.1 – C48.2	Malignant neoplasm of specified or unspecified parts of peritoneum
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C50.011 – C50.929	Malignant neoplasm of breast
C56.1 – C57.9	Malignant neoplasm of ovary, fallopian tube, broad ligament, parametrium and uterine adnexa, unspecified
C60.0 – C60.9	Malignant neoplasm of penis
C63.7	Malignant neoplasm of other specified male genital organs
C63.8	Malignant neoplasm of overlapping sites of male genital organs
C63.9	Malignant neoplasm of male genital organs , unspecified
C64.1 - C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1 - C65.9	Malignant neoplasm of unspecified renal pelvis
C76.0	Malignant neoplasm of head, face, and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C78.00 – C78.02	Secondary malignant neoplasm of lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C79.89	Secondary malignant neoplasm of other specified sites

C7A.00 – C7A.8	Malignant neuroendocrine tumors
C7B.00 – C7B.09	Secondary carcinoid tumor
C7B.8	Other secondary neuroendocrine tumors
C80.0 – C80.1	Disseminated malignant neoplasm, unspecified; Malignant (primary) neoplasm, unspecified
D37.01 – D37.09	Neoplasm of uncertain behavior of lip, tongue, salivary glands and pharynx
D37.1 – D37.9	Neoplasm of uncertain behavior of other digestive organs
D38.0	Neoplasm of uncertain behavior of larynx
D38.5 – D38.6	Neoplasm of uncertain behavior of other respiratory organs or unspecified respiratory organ
D39.2 – D39.9	Neoplasm of uncertain behavior of placenta, and other female genital organs
E16.0 – E16.8	Other disorders of pancreatic internal secretion
E34.0	Carcinoid syndrome

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage Products: No National Coverage Determination (NCD) was found at the time of the last guideline revised date. The following Local coverage determination (LCD) was found at fcso.com:L33826, Oral Anti-cancer Drugs.

DEFINITIONS:

DPD: Dihydropyrimidine dehydrogenase (DPD) is an enzyme involved in the breakdown of the pyrimidines, uracil and thymine. A deficiency in DPD is a result of mutations in the DPYD gene. The deficiency causes excess uracil and thymine; however it is unknown how excess pyrimidines are related to signs and symptoms of the disorder. Fluoropyrimidine toxicity may result in individuals with deficiency of DPD because the medications are broken down by the enzyme.

RELATED GUIDELINES:

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, 05-86000-26

Bevacizumab (Avastin®) Injection, 09-J0000-66

Brachytherapy-Oncologic Applications, 04-77260-20

Carboplatin (Paraplatin®) IV, 09-J0000-93

Docetaxel (Taxotere®) IV, 09-J0000-95

Genetic Testing for Hereditary Breast or Ovarian Cancer, 05-82000-30

Genetic Testing for Inherited Susceptibility to Colon Cancer Including Microsatellite Instability, 08-82000-31

Gonadotropin Releasing Hormone Analogs and Antagonists, 09-J0000-48

Intensity-Modulated Radiation Therapy (IMRT), 04-77260-22

Oxaliplatin (Eloxatin®) IV, 09-J1000-00

Positron Emission Tomography (PET Scan) Oncologic Applications, 04-78000-17

Tumor Markers, 05-86000-22

OTHER:

Table 1: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/09/19.

GUIDELINE UPDATE INFORMATION:

01/01/12	New Medical Coverage Guideline.
01/15/14	Review and revision to guideline; consisting of updating the position statement, dosage/administration section, precautions section, references, coding, and program exceptions.
07/15/14	Revision to guideline; consisting of adding language requiring failure of generic capecitabine.
01/15/15	Review and revision to guideline; consisting of position statement, coding, references.
11/01/15	Revision: ICD-9 Codes deleted.
01/15/16	Review and revision to guideline; consisting of updating position statement, dosing, warnings, coding, references.
01/15/17	Review and revision to guideline; consisting of updating position statement, coding, and references.
01/15/18	Review and revision to guideline; consisting of updating position statement and references.
02/15/19	Review and revision to guideline; consisting of updating position statement, coding and references.