CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020896Orig1s044,045,046,047,048,049,050,051

Trade Name:	Xeloda tablets
Generic or Proper Name:	capecitabine
Sponsor:	Genentech, Inc.
Approval Date:	December 14, 2022
Indication:	S-044: Adjuvant treatment of patients with Stage III colon cancer as a single agent or as a component of a combination chemotherapy regimen; S-045: Treatment of patients with advanced or metastatic breast cancer in combination with docetaxel after disease progression on prior anthracycline containing chemotherapy; S-046: Treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen; S-047: Treatment of patients with advanced or metastatic breast cancer as a single agent if an anthracycline- or taxane-containing chemotherapy is not indicated; S-048: Treatment of patients with unresectable or metastatic colorectal cancer as a single agent or as a component of a combination chemotherapy regimen; S-049: Adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen; S-050: Perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy; S-051: 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;

CENTER FOR DRUG EVALUATION AND RESEARCH

020896Orig1s044,045,046,047,048,049,050,051

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 020896/S-044, S-045, S-046, S-047, S-048, S-049, S-050, S-051

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Gigi Lee, BScPharm, RPh, MSc
Associate Program Director, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Lee:

Please refer to your supplemental new drug applications (sNDAs) dated and received February 15, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xeloda (capecitabine) tablets.

In connection with Project Renewal, these Prior Approval sNDAs provide for the following updates:

- Addition of new indications and updates to the current indications, and their associated recommended dosage regimens including the option for a lower starting dose for patients with metastatic breast cancer:
    - S-044: Adjuvant treatment of patients with Stage III colon cancer as a single agent or as a component of a combination chemotherapy regimen;
    - S-045: Treatment of patients with advanced or metastatic breast cancer in combination with docetaxel after disease progression on prior anthracycline-containing chemotherapy;
    - S-046: Treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen;
    - S-047: Treatment of patients with advanced or metastatic breast cancer as a single agent if an anthracycline- or taxane-containing chemotherapy is not indicated;
    - S-048: Treatment of patients with unresectable or metastatic colorectal cancer as a single agent or as a component of a combination chemotherapy regimen;

- S-049: Adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen;

- S-050: Perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy;

- S-051: 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;

- Revisions to the Warnings and Precautions and Adverse Reaction sections to incorporate relevant safety information;

- Updates to the description of the risks of capecitabine in patients with dihydropyrimidine dehydrogenase (DPD) deficiency;

- Edits to other sections to conform to current labeling guidances.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on September 16, 2022, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 020896/S-044-051**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for these applications because necessary studies are impossible or highly impracticable. Colorectal, breast, gastric, esophageal, and pancreatic cancers are adult-related conditions and they rarely or never occur in pediatric patients.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Clara Lee, Health Scientist, at Clara.Lee@fda.hhs.gov or (240) 402-4809.

Sincerely,

{See appended electronic signature page}

Jennifer Gao, MD
Associate Director
Oncology Center of Excellence

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER J GAO
12/14/2022 04:45:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020896Orig1s044,045,046,047,048,049,050,051

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XELODA® safely and effectively. See full prescribing information for XELODA®.

XELODA® (capecitabine) tablets, for oral use
Initial U.S. Approval: 1998

WARNING: INCREASED RISK OF BLEEDING WITH CONCOMITANT USE OF VITAMIN K ANTAGONISTS
See full prescribing information for complete boxed warning.
Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking XELODA concomitantly with oral vitamin K antagonists. (5.1, 7.2)
Monitor international normalized ratio (INR) more frequently and adjust the dose of the vitamin K antagonist as appropriate. (7.2)

----------RECENT MAJOR CHANGES----------

Boxed Warning	(12/2022)
Indications and Usage, Colorectal Cancer (1.1)	(12/2022)
Indications and Usage, Breast Cancer (1.2)	(12/2022)
Indications and Usage, Gastric, Esophageal, or Gastroesophageal Junction Cancer (1.3)	(12/2022)
Indications and Usage, Pancreatic Cancer (1.4)	(12/2022)
Dosage and Administration (2.1-2.7)	(12/2022)
Contraindications (4)	(12/2022)
Warnings and Precautions (5.1-5.12)	(12/2022)

---------- INDICATIONS AND USAGE----------
XELODA (capecitabine) is a nucleoside metabolic inhibitor indicated for:
Colorectal Cancer
- adjuvant treatment of patients with Stage III colon cancer as a single agent or as a component of a combination chemotherapy regimen. (1.1)
- perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy. (1.1)
- treatment of patients with unresectable or metastatic colorectal cancer as a single agent or as a component of a combination chemotherapy regimen. (1.1)

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. (1 2)
- treatment of patients with advanced or metastatic breast cancer in combination with docetaxel after disease progression on prior anthracycline-containing chemotherapy. (1.2)

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. (1.3)
- 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. (1.3)

Pancreatic Cancer
- adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen. (1.4)

----------DOSAGE AND ADMINISTRATION----------
Adjuvant Treatment of Colon Cancer
- Single agent: 1,250 mg/m^2 twice daily orally for the first 14 days of each 21-day cycle for a maximum of 8 cycles. (2.1) In combination with Oxaliplatin-Containing Regimens: 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle for a maximum of 8 cycles in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle. (2.1)

Perioperative Treatment of Rectal Cancer
- With Concomitant Radiation Therapy: 825 mg/m^2 orally twice daily (2.1)
- Without Radiation Therapy: 1,250 mg/m^2 orally twice daily (2.1)

Unresectable or Metastatic Colorectal Cancer:
- Single agent: 1,250 mg/m^2 twice daily orally for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity. (2.1)
- In Combination with Oxaliplatin: 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle. (2.1)

Advanced or Metastatic Breast Cancer:
- Single agent: 1,000 mg/m^2 or 1,250 mg/m^2 twice daily orally for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity. (2.2)
- In combination with docetaxel: 1,000 mg/m^2 or 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle, until disease progression or unacceptable toxicity in combination with docetaxel at 75 mg/m^2 administered intravenously on day 1 of each cycle (2.2)

Unresectable or Metastatic Gastric, Esophageal, or Gastroesophageal Junction Cancer
- 625 mg/m^2 orally twice daily on days 1 to 21 of each 21-day cycle for a maximum of 8 cycles in combination with platinum-containing chemotherapy. (2.3)
  OR
- 850 mg/m^2 or 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle. (2.3)

HER2-overexpressing metastatic adenocarcinoma of the gastroesophageal junction or stomach
- 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with cisplatin and trastuzumab. (2.3)

Pancreatic cancer
- 830 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle for maximum of 6 cycles in combination with gemcitabine 1,000 mg/m^2 administered intravenously on days 1, 8, and 15 of each cycle. (2.4)

Refer to Sections 2.5 and 2.6 for information related to dosage modifications for adverse reactions and renal impairment (2.5 and 2.6).

---------- DOSAGE FORMS AND STRENGTHS----------
Tablets: 150 mg and 500 mg (3)

---------- CONTRAINDICATIONS ----------
History of severe hypersensitivity reactions to fluorouracil or capecitabine (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency: Patients with certain homozygous or compound heterozygous variants in the *DPYD* gene are at increased risk for acute early-onset toxicity and serious, including fatal, adverse reactions due to XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). XELODA is not recommended for use in patients known to have certain homozygous or compound heterozygous *DPYD* variants that result in complete absence of DPD activity. Withhold or permanently discontinue based on clinical assessment. No XELODA dose has been proven safe in patients with complete absence of DPD activity. (5.2)
- Cardiotoxicity: May be more common in patients with a prior history of coronary artery disease. Withhold XELODA for cardiotoxicity as appropriate. The safety of resumption of XELODA in patients with cardiotoxicity that has resolved has not been established. (2 5, 5.3)
- Diarrhea: Withhold XELODA and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence. (2.5, 5.4)
- Dehydration: Optimize hydration before starting XELODA. Monitor hydration status and kidney function at baseline and as clinically indicated. Withhold XELODA and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence. (2 5, 5.5)
- Renal Toxicity: Monitor renal function at baseline and as clinically indicated. Optimize hydration before starting XELODA. Withhold XELODA and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence. (2.5, 5.6)
- Serious Skin Toxicities: Monitor for new or worsening serious skin reactions. Permanently discontinue XELODA in patients who experience a severe cutaneous adverse reaction. (5.7)
- Palmar-Plantar Erythrodysesthesia Syndrome: Withhold XELODA then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence. (2.5, 5.8)
- Myelosuppression: Monitor complete blood count at baseline and before each cycle. XELODA is not recommended in patients with baseline neutrophil counts <1.5 x 10^9/L or platelet counts <100 x 10^9/L. For grade 3 or 4 myelosuppression, withhold XELODA and then resume at same

or reduced dose, or permanently discontinue, based on occurrence. (2.5, 5.9)

- Hyperbilirubinemia: Patients with Grade 3-4 hyperbilirubinemia may resume treatment once the event is Grade 2 or less (≤3 x ULN), using the percent of current dose as shown in column 3 of Table 1 (2.5, 5.10)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.11, 8.1, 8.3)

---------- **ADVERSE REACTIONS**----------

- Most common adverse reactions in patients who received XELODA as a single agent for the adjuvant treatment for colon cancer (≥30%) were palmar-plantar erythrodysesthesia syndrome, diarrhea, and nausea. (6.1)
- Most common adverse reactions (≥30%) in patients with metastatic colorectal cancer who received XELODA as a single agent were anemia, diarrhea, palmar-plantar erythrodysesthesia syndrome, hyperbilirubinemia, nausea, fatigue, and abdominal pain. (6.1)
- Most common adverse reactions (≥30%) in patients with metastatic breast cancer who received XELODA with docetaxel were diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, nausea, alopecia, vomiting, edema, and abdominal pain. (6.1)
- Most common adverse reactions (≥30%) in patients with metastatic breast cancer who received XELODA as a single agent were lymphopenia, anemia, diarrhea, hand-and-foot syndrome, nausea, fatigue, vomiting, and dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

---------- **DRUG INTERACTIONS**----------

- Allopurinol: Avoid concomitant use of allopurinol with XELODA. (7.1)
- Leucovorin: Closely monitor for toxicities when XELODA is coadministered with leucovorin. (7.1)
- CYP2C9 substrates: Closely monitor for adverse reactions when CYP2C9 substrates are coadministered with XELODA. (7.2)
- Vitamin K antagonists: Monitor INR more frequently and dose adjust oral vitamin K antagonist as appropriate
- Phenytoin: Closely monitor phenytoin levels in patients taking XELODA concomitantly with phenytoin and adjust the phenytoin dose as appropriate. (7.2)
- Nephrotoxic drugs: Closely monitor for signs of renal toxicity when XELODA is used concomitantly with nephrotoxic drugs. (7.3)

---------- **USE IN SPECIFIC POPULATIONS** ----------

- Lactation: Advise not to breastfeed. (8.2)
- Hepatic Impairment: Monitor patients with hepatic impairment more frequently for adverse reactions. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: INCREASED RISK OF BLEEDING WITH CONCOMITANT USE OF VITAMIN K ANTAGONISTS

Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking XELODA concomitantly with oral vitamin K antagonists, such as warfarin *[see Warnings and Precautions (5.1), Drug Interactions (7.2)]*.

Clinically significant increases in prothrombin time (PT) and international normalized ratio (INR) have been reported in patients who were on stable doses of a vitamin K antagonist at the time XELODA was introduced. These events occurred within several days and up to several months after initiating XELODA and, in a few cases, within 1 month after stopping XELODA. These events occurred in patients with and without liver metastases.

Monitor INR more frequently and adjust the dose of the vitamin K antagonist as appropriate *[see Drug Interactions (7.2)]*.

1 INDICATIONS AND USAGE

1.1 Colorectal Cancer

XELODA is indicated for the:

- 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.

1.2 Breast Cancer

XELODA is indicated for the:

- 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.

1.3 Gastric, Esophageal, or Gastroesophageal Junction Cancer

XELODA is indicated for the:

- 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.

1.4 Pancreatic Cancer

XELODA is indicated for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Colorectal Cancer

Adjuvant Treatment of Colon Cancer

Single Agent

The recommended dosage of XELODA is 1,250 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle for a maximum of 8 cycles.

In Combination with Oxaliplatin-Containing Regimens

The recommended dosage of XELODA is 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle for a maximum of 8 cycles in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.

Refer to the oxaliplatin prescribing information for additional dosing information as appropriate.

Perioperative Treatment of Rectal Cancer

The recommended dosage of capecitabine is 825 mg/m^2 orally twice daily when administered with concomitant radiation therapy and 1,250 mg/m^2 orally twice daily when administered without radiation therapy as part of a peri-operative combination regimen.

Unresectable or Metastatic Colorectal Cancer

Single Agent

The recommended dosage of XELODA is 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle until disease progression or unacceptable toxicity.

In Combination with Oxaliplatin

The recommended dosage of XELODA is 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.

Refer to the Prescribing Information for oxaliplatin for additional dosing information as appropriate.

2.2 Recommended Dosage for Breast Cancer

Advanced or Metastatic Breast Cancer

Single Agent

The recommended dosage of XELODA is 1,000 mg/m^2 or 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle until disease progression or unacceptable toxicity. Individualize the dose and dosing schedule of XELODA based on patient risk factors and adverse reactions.

In Combination with Docetaxel

The recommended dosage of XELODA is 1,000 mg/m^2 or 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle until disease progression or unacceptable toxicity in combination with docetaxel 75 mg/m^2 administered intravenously on day 1 of each cycle.

Refer to the Prescribing Information for docetaxel for additional dosing information as appropriate.

2.3 Recommended Dosage for Gastric, Esophageal, or Gastroesophageal Junction Cancer

The recommended dosage of XELODA for unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer is:

- 625 mg/m^2 orally twice daily on days 1 to 21 of each 21-day cycle for a maximum of 8 cycles in combination with platinum-containing chemotherapy.

OR

- 850 mg/m^2 or 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle. Individualize the dose and dosing schedule of XELODA based on patient risk factors and adverse reactions.

The recommended dosage of XELODA for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma is 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with cisplatin and trastuzumab.

Refer to the Prescribing Information for agents used in combination for additional dosing information as appropriate.

2.4 Recommended Dosage for Pancreatic Cancer

The recommended dosage of XELODA is 830 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle until disease progression, unacceptable toxicity, or for a maximum 6 cycles in combination with gemcitabine 1,000 mg/m^2 administered intravenously on days 1, 8, and 15 of each cycle.

Refer to Prescribing Information for gemcitabine for additional dosing information as appropriate.

2.5 Dosage Modifications for Adverse Reactions

Monitor patients for adverse reactions and modify dosages of XELODA as described in Table 1. Do not replace missed doses of XELODA; instead resume XELODA with the next planned dosage.

When XELODA is administered with docetaxel, withhold XELODA and docetaxel until the requirements for resuming both XELODA and docetaxel are met. Refer to the Prescribing Information for docetaxel for additional dosing information as appropriate.

Table 1 Recommended Dosage Modifications for Adverse Reactions

Severity	Dosage Modification	Resume at Same or Reduced Dose (Percent of Current Dose)
Grade 2		
1st appearance	Withhold until resolved to grade 0-1.	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Permanently discontinue.	-
Grade 3		
1st appearance	Withhold until resolved to grade 0-1.	75%
2nd appearance		50%
3rd appearance	Permanently discontinue.	-
Grade 4		
1st appearance	Permanently discontinue OR Withhold until resolved to grade 0-1.	50%

Hyperbilirubinemia

Patients with Grade 3-4 hyperbilirubinemia may resume treatment once the event is Grade 2 or less (less than three times the upper limit of normal), using the percent of current dose as shown in column 3 of Table 1 *[see Warnings and Precautions (5.10)]*.

2.6 Dosage Modification For Renal Impairment

Reduce the dose of XELODA by 25% for patients with creatinine clearance (CLcr) of 30 to 50 mL/min as determined by Cockcroft-Gault equation. A dosage has not been established in patients with severe renal impairment (CLcr <30 mL/min) *[see Use in Specific Populations (8.6)]*.

2.7 Administration

Round the recommended dosage for patients to the nearest 150 mg dose to provide whole XELODA tablets.

Swallow XELODA tablets whole with water within 30 minutes after a meal. Do not chew, cut, or crush XELODA tablets *[see Warnings and Precautions (5.12)]*.

Take XELODA at the same time each day approximately 12 hours apart.

Do not take an additional dose after vomiting and continue with the next scheduled dose.

Do not take a missed dose and continue with the next scheduled dose.

XELODA is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

3 DOSAGE FORMS AND STRENGTHS

Tablets, film-coated:

- 150 mg: biconvex, oblong, light-peach colored, with “XELODA” on one side and “150” on the other
- 500 mg: biconvex, oblong, peach colored, with “XELODA on one side and “500” on the other

4 CONTRAINDICATIONS

XELODA is contraindicated in patients with history of severe hypersensitivity reaction to fluorouracil or capecitabine *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Bleeding With Concomitant Use of Vitamin K Antagonists

Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking XELODA concomitantly with vitamin K antagonists, such as warfarin.

Clinically significant increases in PT and INR have been reported in patients who were on stable doses of oral vitamin K antagonists at the time XELODA was introduced. These events occurred within several days and up to several months after initiating XELODA and, in a few cases, within 1 month after stopping XELODA. These events occurred in patients with and without liver metastases.

Monitor INR more frequently and adjust the dose of the vitamin K antagonist as appropriate *[see Drug Interactions (7.1)]*.

5.2 Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency

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 due to XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity (partial DPD deficiency) may also have increased risk of serious, including fatal, adverse reactions.

XELODA is not recommended for use in patients known to have certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency.

Withhold or permanently discontinue XELODA based on clinical assessment of the onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe reactions, which may indicate complete DPD deficiency. No XELODA dose has been proven safe for patients with complete DPD deficiency. There are insufficient data to recommend a specific dose in patients with partial DPD deficiency.

Consider testing for genetic variants of *DPYD* prior to initiating XELODA to reduce the risk of serious adverse reactions if the patient’s clinical status permits and based on clinical judgement *[see Clinical Pharmacology (12.5)]*. Serious adverse reactions may still occur even if no *DPYD* variants are identified.

An FDA-authorized test for the detection of genetic variants of *DPYD* to identify patients at risk of serious adverse reactions due to increased systemic exposure to XELODA is not currently available. Currently available tests used to identify *DPYD* variants may vary in accuracy and design (e.g., which *DPYD* variant(s) they identify).

5.3 Cardiotoxicity

Cardiotoxicity can occur with XELODA. Myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy have been reported with XELODA. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

Withhold XELODA for cardiotoxicity as appropriate *[see Dosage and Administration (2.5)]*. The safety of resumption of XELODA in patients with cardiotoxicity that has resolved have not been established.

5.4 Diarrhea

Diarrhea, sometimes severe, can occur with XELODA. In 875 patients with metastatic breast or colorectal cancer who received XELODA as a single agent, the median time to first occurrence of grade 2 to 4 diarrhea was 34 days (range: 1 day to 1 year). The median duration of grade 3 to 4 diarrhea was 5 days.

Withhold XELODA and then resume at same or reduced dose or permanently discontinue based on severity and occurrence *[see Dosage and Administration (2.5)]*.

5.5 Dehydration

Dehydration can occur with XELODA. Patients with anorexia, asthenia, nausea, vomiting, or diarrhea may be at an increased risk of developing dehydration with XELODA. Optimize hydration before starting XELODA. Monitor hydration status and kidney function at baseline and as clinically indicated. Withhold XELODA and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence *[see Dosage and Administration (2.5)]*.

5.6 Renal Toxicity

Serious renal failure, sometimes fatal, can occur with XELODA. Renal impairment or coadministration of XELODA with other products known to cause renal toxicity may increase the risk of renal toxicity *[see Drug Interactions (7.3)]*.

Monitor renal function at baseline and as clinically indicated. Optimize hydration before starting XELODA. Withhold XELODA and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence *[see Dosage and Administration (2.5)]*.

5.7 Serious Skin Toxicities

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome and toxic epidermal necrolysis (TEN), which can be fatal, can occur with XELODA *[see Adverse Reactions (6.2)]*.

Monitor for new or worsening serious skin reactions. Permanently discontinue XELODA for severe cutaneous adverse reactions.

5.8 Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-plantar erythrodysesthesia syndrome (PPES) can occur with XELODA.

In patients with metastatic breast or colorectal cancer who received XELODA as a single agent, the median time to onset of grades 1 to 3 PPES was 2.6 months (range: 11 days to 1 year).

Withhold XELODA and then resume at same or reduced dose or permanently discontinue based on severity and occurrence *[see Dosage and Administration (2.5)]*.

5.9 Myelosuppression

Myelosuppression can occur with XELODA.

In the 875 patients with metastatic breast or colorectal cancer who received XELODA as a single agent, 3.2% had grade 3 or 4 neutropenia, 1.7% had grade 3 or 4 thrombocytopenia, and 2.4% had grade 3 or 4 anemia.

In the 251 patients with metastatic breast cancer who received XELODA with docetaxel, 68% had grade 3 or 4 neutropenia, 2.8% had grade 3 or 4 thrombocytopenia, and 10% had grade 3 or 4 anemia.

Necrotizing enterocolitis (typhlitis) has been reported. Consider typhlitis in patients with fever, neutropenia and abdominal pain.

Monitor complete blood count at baseline and before each cycle. XELODA is not recommended if baseline neutrophil count $<1.5 \times 10^9$/L or platelet count $<100 \times 10^9$/L. For grade 3 to 4 myelosuppression, withhold XELODA and then resume at same or reduced dose, or permanently discontinue, based on occurrence *[see Dosage and Administration (2.5)]*.

5.10 Hyperbilirubinemia

Hyperbilirubinemia can occur with XELODA. In the 875 patients with metastatic breast or colorectal cancer who received XELODA as a single agent, grade 3 hyperbilirubinemia occurred in 15% of patients and grade 4 hyperbilirubinemia occurred in 3.9%. Of the 566 patients who had hepatic metastases at baseline and the 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 23% and 12%, respectively. Of these 167 patients with grade 3 or 4 hyperbilirubinemia, 19% had postbaseline increased alkaline phosphatase and 28% had postbaseline increased transaminases at any time (not necessarily concurrent). The majority of these patients with increased transaminases or alkaline phosphatase had liver metastases at baseline. In addition, 58% and 35% of the 167 patients with grade 3 or 4 hyperbilirubinemia had pre- and postbaseline increased alkaline phosphatase or transaminases (grades 1 to 4), respectively. Only 8% (n=13) and 3% (n=5) had grade 3 or 4 increased alkaline phosphatase or transaminases.

In the 596 patients who received XELODA for metastatic colorectal cancer, the incidence of grade 3 or 4 hyperbilirubinemia was similar to that observed for the pooled population of patients with metastatic breast and colorectal cancer. The median time to onset for grade 3 or 4 hyperbilirubinemia was 64 days and median total bilirubin increased from 8 µm/L at baseline to 13 µm/L during treatment with XELODA. Of the 136 patients with grade 3 or 4 hyperbilirubinemia, 49 patients had grade 3 or 4 hyperbilirubinemia as their last measured value, of which 46 had liver metastases at baseline.

In the 251 patients with metastatic breast cancer who received XELODA with docetaxel, grade 3 hyperbilirubinemia occurred in 7% and grade 4 hyperbilirubinemia occurred in 2%.

Withhold XELODA and then resume at a same or reduced dose, or permanently discontinue, based on occurrence *[see Dosage and Administration (2.5)]*. Patients with Grade 3-4 hyperbilirubinemia may resume treatment once the event is Grade 2 or less than three times the upper limit of normal, using the percent of current dose as shown in Table 1 *[see Dosage and Administration (2.5)]*.

5.11 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and its mechanism of action, XELODA can cause fetal harm when administered to a pregnant woman. Insufficient data is available on XELODA use in pregnant women to evaluate a drug-associated risk. In animal reproduction studies, administration of capecitabine to pregnant animals during the period of organogenesis caused embryolethality and teratogenicity in mice and embryolethality in monkeys at 0.2 and 0.6 times the human exposure (AUC) in patients who received a dosage of 1,250 mg/m^2 twice daily, respectively.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with XELODA and for 6 months following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with XELODA and for 3 months following the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.12 Eye Irritation, Skin Rash, and Other Adverse Reactions from Exposure to Crushed Tablets

In instances of exposure to crushed XELODA tablets, the following adverse reactions have been reported: eye irritation and swelling, skin rash, diarrhea, paresthesia, headache, gastric irritation, vomiting and nausea. Advise patients not to cut or crush tablets.

If XELODA tablets must be cut or crushed, this should be done by a professional trained in safe handling of cytotoxic drugs using appropriate equipment and safety procedures *[see Dosage and Administration (2.7)]*. The safety and effectiveness have not been established for the administration of crushed XELODA tablets.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cardiotoxicity *[see Warnings and Precautions (5.3)]*
- Diarrhea *[see Warnings and Precautions (5.4)]*
- Dehydration *[see Warnings and Precautions (5.5)]*
- Renal Toxicity *[see Warnings and Precautions (5.6)]*
- Serious Skin Toxicities *[see Warnings and Precautions (5.7)]*
- Palmar-Plantar Erythrodysesthesia Syndrome *[see Warnings and Precautions (5.8)]*
- Myelosuppression *[see Warnings and Precautions (5.9)]*

- Hyperbilirubinemia *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Treatment of Colon Cancer

Single Agent

The safety of XELODA as a single agent was evaluated in patients with Stage III colon cancer in X-ACT *[see Clinical Studies (14.1)]*. Patients received XELODA 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle (N=995) or leucovorin 20 mg/m^2 intravenously followed by fluorouracil 425 mg/m^2 as an intravenous bolus on days 1 to 5 of each 28-day cycle (N=974). Among patients who received XELODA, the median duration of treatment was 5.4 months.

Deaths due to all causes occurred in 0.8% of patients who received XELODA on study or within 28 days of receiving study drug. Permanent discontinuation due to an adverse reaction occurred in 11% of patients who received XELODA.

Most common adverse reactions (>30%) were palmar-plantar erythrodysesthesia syndrome, diarrhea, and nausea.

Tables 2 and 3 summarize the adverse reactions and laboratory abnormalities in X-ACT.

Table 2 Adverse Reactions (≥10%) in Patients Who Received XELODA for Adjuvant Treatment of Colon Cancer in X-ACT

Adverse Reaction	XELODA (N=995)		Fluorouracil + Leucovorin (N=974)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	60	17	9	<1
Gastrointestinal				
Diarrhea	47	12	65	14
Nausea	34	2	47	2
Stomatitis	22	2	60	14
Vomiting	15	2	21	2
Abdominal pain	14	3	16	2

Adverse Reaction	XELODA (N=995)		Fluorouracil + Leucovorin (N=974)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General				
Fatigue	16	<1	16	1
Asthenia	10	<1	10	1
Lethargy	10	<1	9	<1

Clinically relevant adverse reactions in <10% of patients are presented below:

Eye: conjunctivitis

Gastrointestinal: constipation, upper abdominal pain, dyspepsia

General: pyrexia

Metabolism and Nutrition: anorexia

Nervous System: dizziness, dysgeusia, headache

Skin & Subcutaneous Tissue: rash, alopecia, erythema

Table 3 Grade 3 or 4 Laboratory Abnormalities (>1%) in Patients Who Received XELODA as a Single Agent for Adjuvant Treatment of Colon Cancer in X-ACT

Laboratory Abnormality	XELODA (N=995)	Fluorouracil + Leucovorin (N=974)
	Grade 3 or 4 (%)	Grade 3 or 4 (%)
Bilirubin increased	20	6
Lymphocytes decreased	13	13
Neutrophils/granulocytes decreased	2.4	26
Calcium decreased	2.3	2.2
Neutrophils decreased	2.2	26
ALT increased	1.6	0.6
Calcium increased	1.1	0.7
Hemoglobin decreased	1	1.2
Platelets decreased	1	0.7

In Combination with Oxaliplatin-Containing Regimens

The safety of XELODA for the perioperative treatment of adults with Stage III colon cancer as a component of a combination chemotherapy regimen was derived from published literature *[see Clinical Studies (14.1)]*. The safety of XELODA for the adjuvant treatment of patients with Stage III colon cancer as a component of a combination chemotherapy regimen was similar to those in patients treated with XELODA as a single agent, with the exception of an increased incidence of neurosensory toxicity.

Perioperative Treatment of Rectal Cancer

The safety of XELODA for the perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy was derived from published literature *[see Clinical Studies (14.1)]*. The safety of XELODA for the perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy was similar to those in patients treated with XELODA as a single agent, with the exception of an increased incidence of diarrhea.

Metastatic Colorectal Cancer

Single Agent

The safety of XELODA as a single agent was evaluated in a pooled metastatic colorectal cancer population (Study SO14695 and Study SO14796) *[see Clinical Studies (14.1)]*. Patients received XELODA 1,250 mg/m^2 orally twice a day for the first 14 days of a 21-day cycle (N=596) or leucovorin 20 mg/m^2 intravenously followed by fluorouracil 425 mg/m^2 as an intravenous bolus on days 1 to 5 of each 28-day cycle (N=593). Among the patients who received XELODA, the median duration of treatment was 4.6 months.

Deaths due to all causes occurred in 8% of patients who received XELODA on study or within 28 days of receiving study drug. Permanent discontinuation due to an adverse reaction or intercurrent illness occurred in 13% of patients who received XELODA.

Most common adverse reactions (>30%) were anemia, diarrhea, palmar-plantar erythrodysesthesia syndrome, hyperbilirubinemia, nausea, fatigue, and abdominal pain.

Table 4 shows the adverse reactions occurring in this pooled colorectal cancer population.

Table 4 Adverse Reactions (≥10%) in Patients Who Received XELODA in Pooled Metastatic Colorectal Cancer Population (Study SO14695 and Study SO14796)

Adverse Reaction	XELODA (N=596)			Fluorouracil + Leucovorin (N=593)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Blood and Lymphatic System						
Anemia	80	2	<1	79	1	<1
Neutropenia	13	1	2	46	8	13
Gastrointestinal						
Diarrhea	55	13	2	61	10	2
Nausea	43	4	–	51	3	<1
Abdominal pain	35	9	<1	31	5	–
Vomiting	27	4	<1	30	4	<1
Stomatitis	25	2	<1	62	14	1
Constipation	14	1	<1	17	1	–
Gastrointestinal motility disorder	10	<1	–	7	<1	–

Adverse Reaction	XELODA (N=596)			Fluorouracil + Leucovorin (N=593)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Oral discomfort	10	–	–	10	–	–
Skin and Subcutaneous Tissue						
Palmar-plantar erythrodysesthesia syndrome	54	17	NA	6	1	NA
Dermatitis	27	1	–	26	1	–
Hepatobiliary						
Hyperbilirubinemia	48	18	5	17	3	3
General						
Fatigue*	42	4	–	46	4	–
Pyrexia	18	1	–	21	2	–
Edema	15	1	–	9	1	–
Pain	12	1	–	10	1	–
Metabolism and Nutrition						
Decreased appetite	26	3	<1	31	2	<1
Respiratory Thoracic and Mediastinal						
Dyspnea	14	1	–	10	<1	1
Eye						
Eye irritation	13	–	–	10	<1	–
Nervous System						
Peripheral sensory neuropathy	10	–	–	4	–	–
Headache	10	1	–	7	–	–
Musculoskeletal						
Back pain	10	2	–	9	<1	–

– Not observed
* Includes weakness
NA = Not Applicable

Clinically relevant adverse reactions in <10% of patients are presented below:

Eye: abnormal vision

Gastrointestinal: upper gastrointestinal tract inflammatory disorders, gastrointestinal hemorrhage, ileus

General: chest pain

Infections: viral

Metabolism and Nutrition: dehydration

Musculoskeletal: arthralgia

Nervous System: dizziness (excluding vertigo), insomnia, taste disturbance

Psychiatric: mood alteration, depression

Respiratory, Thoracic, and Mediastinal: cough, pharyngeal disorder

Skin and Subcutaneous Tissue: skin discoloration, alopecia

Vascular: venous thrombosis

In Combination with Oxaliplatin

The safety of XELODA for the treatment of patients with unresectable or metastatic colorectal cancer as a component of a combination chemotherapy regimen was derived from published literature *[see Clinical Studies (14.1)]*. The safety of XELODA for the treatment of patients with unresectable or metastatic colorectal cancer as a component of a combination chemotherapy regimen was similar to those in patients treated with XELODA as a single agent, with the exception of an increased incidence of peripheral neuropathy.

Metastatic Breast Cancer

In Combination with Docetaxel

The safety of XELODA in combination with docetaxel was evaluated in patients with metastatic breast cancer in Study SO14999 *[see Clinical Studies (14.2)]*. Patients received XELODA 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle with docetaxel 75 mg/m^2 as 1-hour intravenous infusion on day 1 of each 21-day cycle for at least 6 weeks or docetaxel 100 mg/m^2 as a 1-hour intravenous infusion on day 1 of each 21-day cycle for at least 6 weeks. Among patients who received XELODA, the mean duration of treatment was 4.2 months.

Permanent discontinuation due to an adverse reaction occurred in 26% of patients who received XELODA. Dosage interruptions due to an adverse reaction occurred in 79% of patients who received XELODA and dosage reductions due to an adverse reaction occurred in 65%.

Most common adverse reactions (>30%) were diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, nausea, alopecia, vomiting, edema, and abdominal pain.

Table 5 summarizes the adverse reactions in Study SO14999.

Table 5 Adverse Reactions (≥10%) in Patients Who Received XELODA with Docetaxel for Metastatic Breast Cancer in Study SO14999

Adverse Reaction	XELODA with Docetaxel (N=251)			Docetaxel (N=255)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal						
Diarrhea	67	14	<1	48	5	<1
Stomatitis	67	17	<1	43	5	–
Nausea	45	7	–	36	2	–
Vomiting	35	4	1	24	2	–
Abdominal pain	30	3	<1	24	2	–
Constipation	20	2	–	18	–	–
Dyspepsia	14	–	–	8	1	–
Skin and Subcutaneous Tissue						
Palmar-plantar erythrodysesthesia syndrome	63	24	NA	8	1	NA
Alopecia	41	6	–	42	7	–
Nail disorder	14	2	–	15	–	–
Cardiac						
Edema	33	<2	–	34	<3	1

Adverse Reaction	XELODA with Docetaxel (N=251)			Docetaxel (N=255)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
General						
Pyrexia	28	2	–	34	2	–
Asthenia	26	4	<1	25	6	–
Fatigue	22	4	–	27	6	–
Weakness	16	2	–	11	2	–
Pain in Limb	13	<1	–	13	2	–
Blood and Lymphatic System						
Neutropenic fever	16	3	13	21	5	16
Nervous System						
Taste disturbance	16	<1	–	14	<1	–
Headache	15	3	–	15	2	–
Paresthesia	12	<1	–	16	1	–
Dizziness	12	–	–	8	<1	–
Musculoskeletal and Connective Tissue						
Arthralgia	15	2	–	24	3	–
Myalgia	15	2	–	25	2	–
Back Pain	12	<1	–	11	3	–
Respiratory, Thoracic and Mediastinal						
Dyspnea	14	2	<1	16	2	–
Cough	13	1	–	22	<1	–
Sore Throat	12	2	–	11	<1	–
Metabolism and Nutrition						
Anorexia	13	<1	–	11	<1	–
Appetite decreased	10	–	–	5	–	–
Dehydration	10	2	–	7	<1	<1

Adverse Reaction	XELODA with Docetaxel (N=251)			Docetaxel (N=255)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Eye						
Lacrimation increased	12	–	–	7	<1	–

– Not observed
NA = Not Applicable

Clinically relevant adverse reactions in <10% of patients are presented below:

Blood and Lymphatic System: agranulocytosis, prothrombin decreased

Cardiac: supraventricular tachycardia

Eye: conjunctivitis, eye irritation

Gastrointestinal: ileus, necrotizing enterocolitis, esophageal ulcer, hemorrhagic diarrhea, dry mouth

General: chest pain (non-cardiac), lethargy, pain, influenza-like illness

Hepatobiliary: jaundice, abnormal liver function tests, hepatic failure, hepatic coma, hepatotoxicity

Immune System: hypersensitivity

Infection: hypoesthesia, neutropenic sepsis, sepsis, bronchopneumonia, oral candidiasis, urinary tract infection

Metabolism and Nutrition: weight decreased

Musculoskeletal and Connective Tissue: bone pain

Nervous System: insomnia, peripheral neuropathy, ataxia, syncope, taste loss, polyneuropathy, migraine

Psychiatric: depression

Renal and Urinary: renal failure

Respiratory, Thoracic and Mediastinal: upper respiratory tract infection, pleural effusion, epistaxis, rhinorrhea

Skin and Subcutaneous Tissue: pruritis, rash erythematous, dermatitis, nail discoloration, onycholysis

Vascular: lymphedema, hypotension, venous phlebitis and thrombophlebitis, postural hypotension, flushing

Table 6 summarizes the laboratory abnormalities in this trial.

Table 6 Laboratory Abnormalities (≥20%) in Patients Who Received XELODA with Docetaxel for Metastatic Breast Cancer in Study SO14999

Laboratory Abnormality	XELODA with Docetaxel (N=251)			Docetaxel (N=255)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Lymphocytopenia	99	48	41	98	44	40
Leukopenia	91	37	24	88	42	33
Neutropenia	86	20	49	87	10	66
Anemia	80	7	3	83	5	<1
Thrombocytopenia	41	2	1	23	1	2
Hepatobiliary						
Hyperbilirubinemia	20	7	2	6	2	2

Single Agent

The safety of XELODA as a single agent was evaluated in patients with metastatic breast cancer in Study SO14697 *[see Clinical Studies (14.2)]*. Patients received XELODA 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle. The mean duration of treatment was 3.7 months.

Permanent discontinuation due to an adverse reaction or intercurrent illness occurred in 8% of patients.

Most common adverse reactions (>30%) were lymphopenia, anemia, diarrhea, hand-and-foot syndrome, nausea, fatigue, vomiting, and dermatitis.

Table 7 summarizes the adverse reactions in Study SO14697.

Table 7 Adverse Reactions (≥10%) in Patients Who Received XELODA for Metastatic Breast Cancer in Study SO14697

Adverse Reaction	XELODA (n=162)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Blood and Lymphatic System			
Lymphopenia	94	44	15
Anemia	72	3	1

Adverse Reaction	XELODA (n=162)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	26	2	2
Thrombocytopenia	24	3	1
Gastrointestinal			
Diarrhea	57	12	3
Nausea	53	4	–
Vomiting	37	4	–
Stomatitis	24	7	–
Abdominal pain	20	4	–
Constipation	15	1	–
Skin and Subcutaneous Tissue			
Hand-and-foot syndrome	57	11	NA
Dermatitis	37	1	–
General			
Fatigue	41	8	–
Pyrexia	12	1	–
Metabolism and Nutrition			
Anorexia	23	3	–
Hepatobiliary			
Hyperbilirubinemia	22	9	2
Nervous System			
Paresthesia	21	1	–
Eye			
Eye irritation	15	–	–

– = Not observed
NA = Not Applicable

Pooled Safety Population

Clinically relevant adverse reactions in <10% of patients who received XELODA as a single agent are presented below.

Blood & Lymphatic System: leukopenia, coagulation disorder, bone marrow depression, pancytopenia

Cardiac: tachycardia, bradycardia, atrial fibrillation, myocarditis, edema

Ear: vertigo

Eye: conjunctivitis

Gastrointestinal: abdominal distension, dysphagia, proctalgia, gastric ulcer, ileus, gastroenteritis, dyspepsia

General: chest pain, influenza-like illness, hot flushes, pain, thirst, fibrosis, hemorrhage, edema, pain in limb

Hepatobiliary: hepatic fibrosis, hepatitis, cholestatic hepatitis, abnormal liver function tests

Immune System: drug hypersensitivity

Infections: bronchitis, pneumonia, keratoconjunctivitis, sepsis, fungal infections

Metabolism and Nutrition: cachexia, hypertriglyceridemia, hypokalemia, hypomagnesemia, dehydration

Musculoskeletal and Connective Tissue: myalgia, arthritis, muscle weakness

Nervous System: insomnia, ataxia, tremor, dysphasia, encephalopathy, dysarthria, impaired balance, headache, dizziness

Psychiatric: depression, confusion

Renal and Urinary: renal impairment

Respiratory, Mediastinal and Thoracic: cough, epistaxis, respiratory distress, dyspnea

Skin and Subcutaneous Tissue: nail disorder, sweating increased, photosensitivity reaction, skin ulceration, pruritus, radiation recall syndrome

Vascular: hypotension, hypertension, lymphedema, pulmonary embolism

Unresectable or Metastatic Gastric, Esophageal, or Gastroesophageal Junction Cancer

The safety of XELODA for the treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen was derived from published literature *[see Clinical Studies (14.3)]*. The safety of XELODA for the treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen was consistent with the known safety profile of XELODA.

The safety of XELODA for the treatment of patients 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 was derived from the published

literature *[see Clinical Studies (14.3)]*. The safety of XELODA for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma was consistent with the known safety profile of XELODA.

Pancreatic Cancer

The safety of XELODA for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen was derived from the published literature *[see Clinical Studies (14.4)]*. The safety of XELODA for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen was consistent with the known safety profile of XELODA.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of XELODA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye: lacrimal duct stenosis, corneal disorders including keratitis

Hepatobiliary: hepatic failure

Immune System Disorders: angioedema

Nervous System: toxic leukoencephalopathy

Renal & Urinary: acute renal failure secondary to dehydration including fatal outcome

Skin & Subcutaneous Tissue: cutaneous lupus erythematosus, severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN), persistent or severe PPES can eventually lead to loss of fingerprints

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XELODA

Allopurinol

Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites *[see Clinical Pharmacology (12.3)]*, which may decrease efficacy. Avoid concomitant use of allopurinol with XELODA.

Leucovorin

The concentration of fluorouracil is increased and its toxicity may be enhanced by leucovorin, folic acid, or folate analog products. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.

Instruct patients not to take products containing folic acid or folate analog products unless directed to do so by their healthcare provider.

7.2 Effect of Xeloda on Other Drugs

CYP2C9 Substrates

XELODA increased exposure of CYP2C9 substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates. Closely monitor for adverse

reactions of CYP2C9 substrates where minimal concentration changes may lead to serious adverse reactions when used concomitantly with XELODA (e.g., anticoagulants, antidiabetic drugs).

Vitamin K Antagonists

XELODA increases exposure of vitamin K antagonist *[see Clinical Pharmacology (12.3)], which m*ay alter coagulation parameters and/or bleeding and could result in death *[see Warning and Precautions (5.1)]*. These events may occur within days of treatment initiation and up to 1 month after discontinuation of XELODA.

Monitor INR more frequently and refer to the prescribing information of oral vitamin K antagonist for dosage adjustment, as appropriate, when XELODA is used concomitantly with vitamin K antagonist.

Phenytoin

XELODA may increases exposure of phenytoin, which may increase the risk of adverse reactions related to phenytoin. Closely monitor phenytoin levels and refer to the prescribing information of phenytoin for dosage adjustment, as appropriate, when XELODA is used concomitantly with phenytoin.

7.3 Nephrotoxic Drugs

Due of the additive pharmacologic effect, concomitant use of XELODA with other drugs known to cause renal toxicity may increase the risk of renal toxicity *[see Warnings and Precautions (5.6)]*. Closely monitor for signs of renal toxicity when XELODA is used concomitantly with nephrotoxic drugs (e.g. platinum salts, irinotecan, methotrexate, intravenous bisphosphonates).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, XELODA can cause fetal harm when administered to a pregnant woman. Available human data with XELODA use in pregnant women is not sufficient to inform the drug-associated risk. In animal reproduction studies, administration of capecitabine to pregnant animals during the period of organogenesis caused embryolethality and teratogenicity in mice and embryolethality in monkeys at 0.2 and 0.6 times the exposure (AUC) in patients receiving the recommended dose of 1,250 mg/m^2 twice daily, respectively *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Oral administration of capecitabine to pregnant mice during the period of organogenesis at a dose of 198 mg/kg/day caused malformations and embryo lethality. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values that were approximately 0.2 times the AUC values in patients administered the recommended daily dose. Malformations in mice included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. Oral administration of capecitabine to pregnant monkeys during the period of organogenesis at a dose of 90 mg/kg/day, caused fetal lethality. This dose produced 5'-DFUR AUC values that were approximately 0.6 times the AUC values in patients administered the recommended daily dose.

8.2 Lactation

Risk Summary

There is no information regarding the presence of capecitabine or its metabolites in human milk, or on its effects on milk production or the breastfed child. Capecitabine metabolites were present in the milk of lactating mice *(see Data)*. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with XELODA and for 1 week after the last dose.

Data

Lactating mice given a single oral dose of capecitabine excreted significant amounts of capecitabine metabolites into the milk.

8.3 Females and Males of Reproductive Potential

XELODA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating XELODA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with XELODA and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with XELODA and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on animal studies, XELODA may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of XELODA in pediatric patients have not been established.

Safety and effectiveness were assessed, but not established in two single arm studies in 56 pediatric patients aged 3 months to <17 years with newly diagnosed gliomas. In both trials, pediatric patients received an investigational pediatric formulation of capecitabine concomitantly with and following completion of radiation therapy (total dose of 5580 cGy in 180 cGy fractions). The relative bioavailability of the investigational formulation to XELODA was similar.

The adverse reaction profile was consistent with that of adults, with the exception of laboratory abnormalities which occurred more commonly in pediatric patients. The most frequently reported laboratory abnormalities (per-patient incidence ≥ 40%) were increased ALT (75%), lymphocytopenia (73%), hypokalemia (68%), thrombocytopenia (57%), hypoalbuminemia (55%), neutropenia (50%), low hematocrit (50%), hypocalcemia (48%), hypophosphatemia (45%) and hyponatremia (45%).

8.5 Geriatric Use

Of 7938 patients with colorectal cancer who were treated with XELODA, 33% were older than 65 years. Of the 4536 patients with metastatic breast cancer who were treated with XELODA, 18% were older than 65 years.

Of 1951 patients with gastric, esophageal, or gastrointestinal junction cancer who were treated with XELODA, 26% were older than 65 years.

Of 364 patients with pancreatic cancer who received adjuvant treatment with XELODA, 47% were 65 years or older.

No overall differences in efficacy were observed comparing older versus younger patients with colorectal cancer, gastric, esophageal or gastrointestinal junction cancer, or pancreatic cancer using the approved recommended dosages and treatment regimens.

Older patients experience increased gastrointestinal toxicity due to XELODA compared to younger patients. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil *[see Drug Interactions (7.1)]*.

8.6 Renal Impairment

The exposure of capecitabine and its inactive metabolites (5-DFUR and FBAL) increases in patients with CLcr <50 mL/min as determined by Cockcroft-Gault *[see Clinical Pharmacology (12.3)]*. Reduce the dosage for patients with CLcr of 30 to 50 mL/min *[see Dosage and Administration (2.6)]*. There is limited experience with XELODA in patients with CLcr <30 mL/min, and a dosage has not been established in those patients. If no treatment alternative exists, XELODA could be administered to such patients on an individual basis applying a reduced starting dose, close monitoring of a patient's clinical and biochemical data and dose modifications guided by observed adverse reactions.

8.7 Hepatic Impairment

The exposure of capecitabine increases in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the safety and pharmacokinetics of XELODA is unknown *[see Clinical Pharmacology (12.3)]*. Monitor patients with hepatic impairment more frequently for adverse reactions.

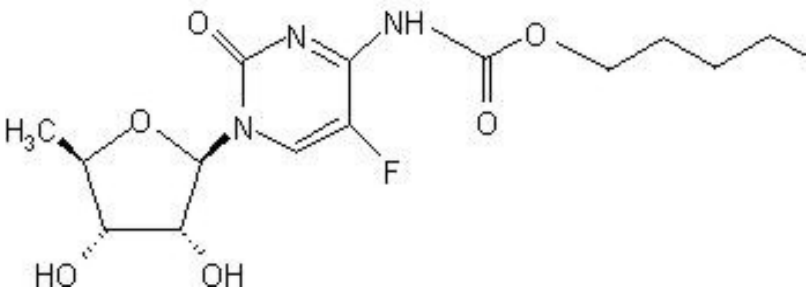
10 OVERDOSAGE

Administer uridine triacetate within 96 hours for management of XELODA overdose.

Although no clinical experience using dialysis as a treatment for XELODA overdose has been reported, dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low–molecular-weight metabolite of the parent compound.

11 DESCRIPTION

Capecitabine is a nucleoside metabolic inhibitor. The chemical name is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular formula of $C_{15}H_{22}FN_3O_6$ and a molecular weight of 359.35. Capecitabine has the following structural formula:



Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20ºC.

XELODA (capecitabine) is supplied as biconvex, oblong film-coated tablets for oral use. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine. The inactive ingredients in XELODA include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Capecitabine is metabolized to fluorouracil in vivo. Both normal and tumor cells metabolize fluorouracil 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, N^{5-10}-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. 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.

12.2 Pharmacodynamics

Population-based exposure-effect analyses demonstrated a positive association between AUC of fluorouracil and grade 3-4 hyperbilirubinemia.

12.3 Pharmacokinetics

The AUC of capecitabine and its metabolite 5'-DFCR increases proportionally over a dosage range of 500 mg/m^2/day to 3,500 mg/m^2/day (0.2 to 1.4 times the approved recommended dosage). The AUC of capecitabine's metabolites 5'-DFUR and fluorouracil increased greater than proportional to the dose. The interpatient variability in the C_{max} and AUC of fluorouracil was greater than 85%.

Absorption

Following oral administration of XELODA 1,255 mg/m^2 orally twice daily (the recommended dosage when used as single agent), the median T_{max} of capecitabine and its metabolite fluorouracil was approximately 1.5 hours and 2 hours, respectively.

Effect of Food

Following administration of a meal (breakfast medium-rich in fat and carbohydrates), the mean C_{max} and $AUC_{0\text{-}INF}$ of capecitabine was decreased by 60% and 34%, respectively. The mean C_{max} and $AUC_{0\text{-}INF}$ of fluorouracil were also decreased by 37 % and 12%, respectively. The T_{max} of both capecitabine and fluorouracil was delayed by 1.5 hours.

Distribution

Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent. Capecitabine was primarily bound to human albumin (approximately 35%).

Following oral administration of XELODA 7 days before surgery in patients with colorectal cancer, the median ratio of concentration for the active metabolite fluorouracil in colorectal tumors to adjacent tissues was 2.9 (range: 0.9 to 8.0).

Elimination

The elimination half-lives of capecitabine and fluorouracil were approximately 0.75 hour.

Metabolism

Capecitabine undergoes metabolism by carboxylesterase and is hydrolyzed to 5'-DFCR. 5'-DFCR is subsequently converted to 5'-DFUR by cytidine deaminase. 5'-DFUR is then hydrolized by thymidine phosphorylase (dThdPase) enzymes to the active metabolite fluorouracil.

Fluorouracil is subsequently metabolized by dihydropyrimidine dehydrogenase to 5-fluoro-5, 6-dihydro-fluorouracil (FUH_2). The pyrimidine ring of FUH_2 is cleaved by dihydropyrimidinase to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, FUPA is cleaved by β-ureido-propionase to α-fluoro-β-alanine (FBAL).

Excretion

Following administration of radiolabeled capecitabine, 96% of the administered capecitabine dose was recovered in urine (3% unchanged and 57% as metabolite FBAL) and 2.6% in feces.

Specific Populations

Following therapeutic doses of XELODA, no clinically meaningful difference in the pharmacokinetics of 5'-DFUR, fluorouracil or FBAL were observed based on sex (202 females and 303 males) and race (455 White, 22 Black, and 28 Other). No clinically meaningful difference on the pharmacokinetics of 5'-DFUR and fluorouracil were observed based on age (range: 27 to 86 years); however, the AUC of FBAL increased by 15% following a 20% increase in age.

Racial or Ethnic Groups

Following administration of XELODA 825 mg/m^2 orally twice daily for 14 days (0.66 times the recommended dosage), the C_{max} and AUC of capecitabine decreased by 36% and 24%, respectively in Japanese patients (n=18) compared to White patients (n=22). The C_{max} and AUC of FBAL decreased by approximately 25% and 34%, respectively in Japanese patients compared to White patients; however, the clinical significance of these differences is unknown. No clinically significant differences in the pharmacokinetics of 5'-DFCR, 5'-DFUR or fluorouracil were observed.

Patients with Renal Impairment

Table 8 Effect of Renal Impairment on the Pharmacokinetics of Capecitabine, 5'-DFUR, and FBAL

Renal Impairment [a]	**Changes in AUC [b]**			
	Capecitabine	**5'-DFUR[c]**	**FBAL[c]**	**5-FU**
CLcr 30 to 50 mL/min	Increased by 25%	Increased by 42%	Increased by 85%	No relevant change
CLcr <30 mL/min	Increased by 25%	Increased by 71%	Increased by 258%	Increased by 24%

[a] Compared to patients with CLcr >80 mL/min

[b] Following administration of XELODA 1,250 mg/m^2 orally twice daily; day 1 observations

[c] Capecitabine metabolite

CLcr= Creatine Clearance, AUC= Area under the plasma concentration-time curve

Patients with Hepatic Impairment

$AUC_{0\text{-}INF}$ and C_{max} of capecitabine's active principle, fluorouracil, were not affected in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. The $AUC_{0\text{-}INF}$ and C_{max} of capecitabine increased by 60%. The effect of severe hepatic impairment on the pharmacokinetics of capecitabine and its metabolites are unknown.

Drug Interaction Studies

Clinical Studies

Effect of Capecitabine on Warfarin: In four patients with cancer, chronic administration of XELODA 1,250 mg/m^2 twice daily with a single dose of warfarin 20 mg increased the mean AUC of S-warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8-fold, and the maximum observed mean INR value was increased by 91%.

Effect of Capecitabine on Celecoxib: Concomitant administration of multiple doses of capecitabine (XELODA 1,000 mg/m^2 twice daily for 14 days) increased celecoxib (sensitive CYP2C9 substrate) AUC by 28%, C_{max} by 24% and C_{trough} by 30%.

Effect of Antacids on Capecitabine: When an aluminum hydroxide- and magnesium hydroxide-containing antacid was administered immediately after a XELODA dose of 1,250 mg/m^2 in patients with cancer, AUC and C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, fluorouracil, FBAL) of XELODA.

Effect of Allopurinol on Capecitabine: Concomitant use with allopurinol may decrease conversion of capecitabine to the active metabolites, FdUMP and FUTP.

Effect of Capecitabine on Docetaxel and Effect of Docetaxel on Capecitabine: XELODA had no effect on the pharmacokinetics of docetaxel (C_{max} and AUC) and docetaxel has no effect on the pharmacokinetics of capecitabine and the fluorouracil precursor 5'-DFUR.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Capecitabine and its metabolites (5'-DFUR, 5'-DFCR, fluorouracil, and FBAL) did not inhibit CYP1A2, CYP2A6, CYP3A4, CYP2C19, CYP2D6, or CYP2E1 in vitro.

12.5 Pharmacogenomics

The *DPYD* gene encodes the enzyme DPD, which is responsible for the catabolism of >80% of fluorouracil. Approximately 3-5% of White populations have partial DPD deficiency and 0.2% of White populations have complete DPD deficiency, which may be due to certain genetic no function or decreased function variants in *DPYD* resulting in partial to complete or near complete absence of enzyme activity. DPD deficiency is estimated to be more prevalent in Black or African American populations compared to White populations. Insufficient information is available to estimate the prevalence of DPD deficiency in other populations.

Patients who are homozygous or compound heterozygous for no function *DPYD* variants (i.e., carry two no function *DPYD* variants) or are compound heterozygous for a no function *DPYD* variant plus a decreased function *DPYD* variant have complete DPD deficiency and are at increased risk for acute early-onset of toxicity and serious life-threatening, or fatal adverse reactions due to increased systemic exposure to XELODA. Partial DPD deficiency can result from the presence of either two decreased function *DPYD* variants or one normal function plus

either a decreased function or a no function *DPYD* variant. Patients with partial DPD deficiency may also be at an increased risk for toxicity from XELODA.

Four *DPYD* variants have been associated with impaired DPD activity in White populations, especially when present as homozygous or compound heterozygous variants: c.1905+1G>A (*DPYD* *2A), c.1679T>G (*DPYD* *13), c.2846A>T, and c.1129-5923C>G (Haplotype B3). *DPYD**2A and *DPYD**13 are no function variants, and c.2846A>T and c.1129-5923C>G are decreased function variants. The decreased function *DPYD* variant c.557A>G is observed in individuals of African ancestry. This is not a complete listing of all *DPYD* variants that may result in DPD deficiency *[see Warnings and Precautions (5.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate studies investigating the carcinogenic potential of capecitabine have not been conducted. Capecitabine was not mutagenic in vitro to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). Capecitabine was clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo to mouse bone marrow (micronucleus test). Fluorouracil causes mutations in bacteria and yeast. Fluorouracil also causes chromosomal abnormalities in the mouse micronucleus test in vivo.

In studies of fertility and general reproductive performance in female mice, oral capecitabine doses of 760 mg/kg/day (about 2,300 mg/m^2/day) disturbed estrus and consequently caused a decrease in fertility. In mice that became pregnant, no fetuses survived this dose. The disturbance in estrus was reversible. In males, this dose caused degenerative changes in the testes, including decreases in the number of spermatocytes and spermatids. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.7 times the corresponding values in patients administered the recommended daily dose.

14 CLINICAL STUDIES

14.1 Colorectal Cancer

Adjuvant Treatment of Colon Cancer

Single Agent
The efficacy of XELODA was evaluated in X-ACT (NCT00009737), a multicenter, randomized, controlled clinical trial. Eligible patients were between 18 and 75 years of age with histologically-confirmed Dukes' Stage C colon cancer with at least one positive lymph node and to have undergone (within 8 weeks prior to randomization) complete resection of the primary tumor without macroscopic or microscopic evidence of remaining tumor. Patients were also required to have no prior cytotoxic chemotherapy or immunotherapy (except steroids) and have an ECOG performance status of 0 or 1 (KPS $\geq$70%), ANC $\geq$1.5x10^9/L, platelets $\geq$100x10^9/L, serum creatinine $\leq$1.5 ULN, total bilirubin $\leq$1.5 ULN, AST/ALT $\leq$2.5 ULN and CEA within normal limits at time of randomization.

Patients (n=1987) were randomized to XELODA 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle for a total of 8 cycles or fluorouracil 425 mg/m^2 and leucovorin 20 mg/m^2 intravenously on days 1 to 5 of each 28-day cycle for a total of 6 cycles. The XELODA dose was

reduced in patients with baseline CLcr of 30 to 50 mL/min. The major efficacy outcome measure was disease-free survival (DFS).

The baseline demographics are shown in Table 9. The baseline characteristics were well-balanced between arms.

Table 9 Baseline Demographics in X-ACT

	XELODA (N=1004)	**Fluorouracil + Leucovorin (N=983)**
Age (median, years)	62	63
Range	(25-80)	(22-82)
Sex		
Male, %	54	54
Female, %	46	46
ECOG Performance Status		
0, %	85	85
1, %	15	15
Staging – Primary Tumor		
PT1, %	1	0.6
PT2, %	9	9
PT3, %	76	76
PT4, %	14	0
Other, %	0.1	14
Staging – Lymph Node		
pN1, %	69	71
pN2, %	30	29
Other, %	0.4	0.1

Efficacy results are summarized in Table 10 and Figures 1 and 2. The median follow-up at the time of the analysis was 6.9 years. Because the upper 2-sided 95% confidence limit of hazard ratio for DFS was less than 1.20, XELODA was non-inferior to fluorouracil + leucovorin. The choice of the non-inferiority margin of 1.20 corresponds to the retention of approximately 75% of the fluorouracil + leucovorin effect on DFS. The hazard ratio for XELODA compared to fluorouracil + leucovorin with respect to overall survival was 0.86 (95% CI 0.74, 1.01). The 5-year overall survival rates were 71% for XELODA and 68% for fluorouracil + leucovorin.

Table 10 Efficacy Results in X-ACTa (All Randomized Population)

Efficacy Parameters	XELODA (N=1004)	Fluorouracil + Leucovorin (N=983)
5-year Disease-free Survival Rate[b]	59%	55%
Hazard Ratio	0.88	
(95% CI)	(0.77, 1.01)	
p-value[c]	p = 0.068	

[a] Approximately 93.4% had 5-year DFS information
[b] Based on Kaplan-Meier estimates
[c] Wald chi-square test

Figure 1 Kaplan-Meier Estimates of Disease-Free Survival in X-ACT (All Randomized Population)

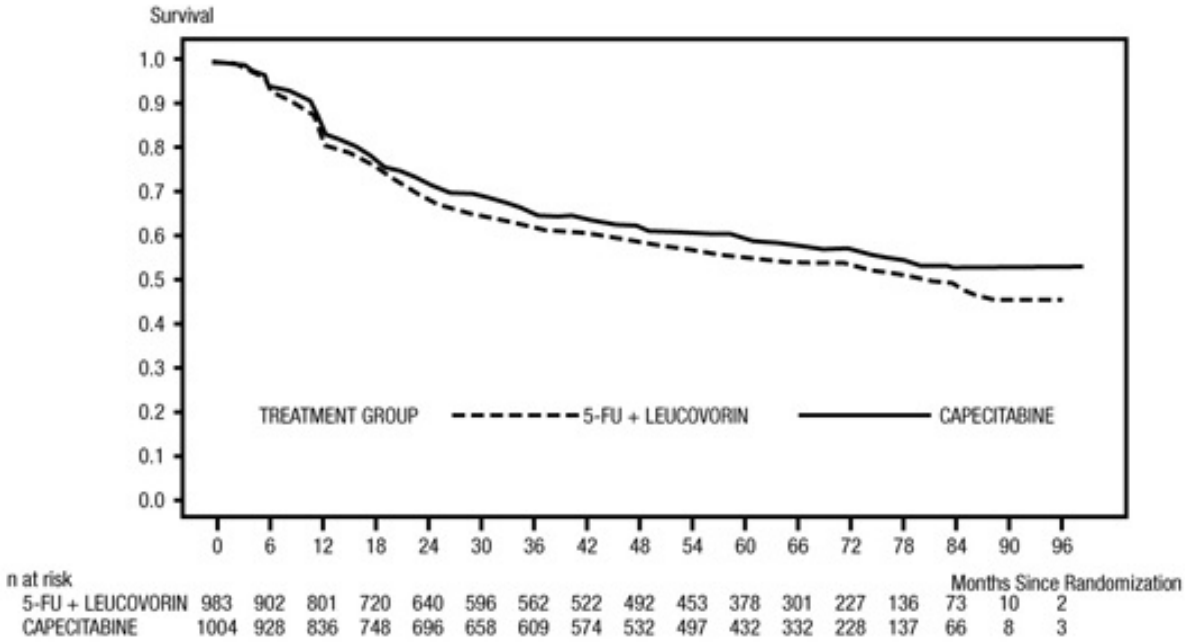
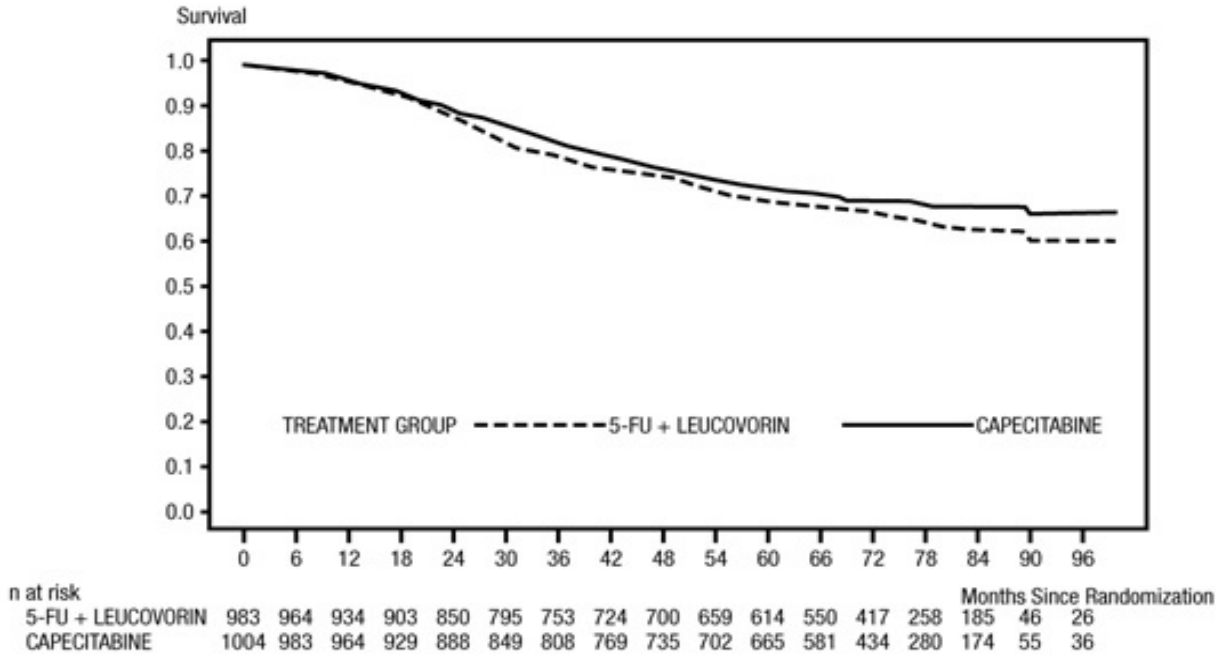


Figure 2 Kaplan-Meier Estimates of Overall Survival in X-ACT (All Randomized Population)



In Combination with Oxaliplatin-Containing Regimens

The efficacy of XELODA in combination with oxaliplatin for the adjuvant treatment of patients with Stage III colon cancer as a component of a combination chemotherapy regimen was derived from studies in the published literature, including NO16968 [NCT00069121], a multicenter, open-label, randomized trial, where the major efficacy outcome measure was disease free survival.

Perioperative Treatment of Rectal Cancer

The efficacy of XELODA for the perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy was derived from studies in the published literature, including Rektum-III [NCT01500993], a randomized, open-label, multicenter, non-inferiority trial, where the major efficacy outcome measure was overall survival.

Metastatic Colorectal Cancer

The efficacy of XELODA as a single agent was evaluated in two open-label, multicenter, randomized, controlled clinical trials (Study SO14695 and Study SO14796). Eligible patients received first-line treatment for metastatic colorectal cancer. Patients were randomized to XELODA 1,250 mg/m^2 twice daily for first 14 days of a 21-day cycle or leucovorin 20 mg/m^2 intravenously followed by fluorouracil 425 mg/m^2 as an intravenous bolus on days 1 to 5 of each 28-day cycle.

The efficacy outcome measures were overall survival, time to progression and response rate (complete plus partial responses). Responses were defined by the World Health Organization criteria and submitted to a blinded independent review committee (IRC). Differences in assessments between the investigator and IRC were reconciled by the sponsor, blinded to

treatment arm, according to a specified algorithm. Survival was assessed based on a non-inferiority analysis.

The baseline demographics are shown in Table 11.

Table 11 Baseline Demographics for Study SO14695 and Study SO14796

	Study SO14695		**Study SO14796**	
	XELODA (N=302)	**Fluorouracil + Leucovorin (N=303)**	**XELODA (N=301)**	**Fluorouracil + Leucovorin (N=301)**
Age (median, years)	64	63	64	64
Range	(23-86)	(24-87)	(29-84)	(36-86)
Sex				
Male, %	60	65	57	57
Female, %	40	35	43	43
Karnofsky PS (median)	90	90	90	90
Range	(70-100)	(70-100)	(70-100)	(70-100)
Colon, %	74	77	66	65
Rectum, %	26	23	34	35
Prior radiation therapy, %	17	21	14	14
Prior adjuvant fluorouracil, %	28	36	19	14

Efficacy results for Study SO14695 and Study SO14796 are shown in Table 12 and Table 13.

Table 12 Efficacy Results for First-Line Treatment of Metastatic Colorectal Cancer (Study SO14695)

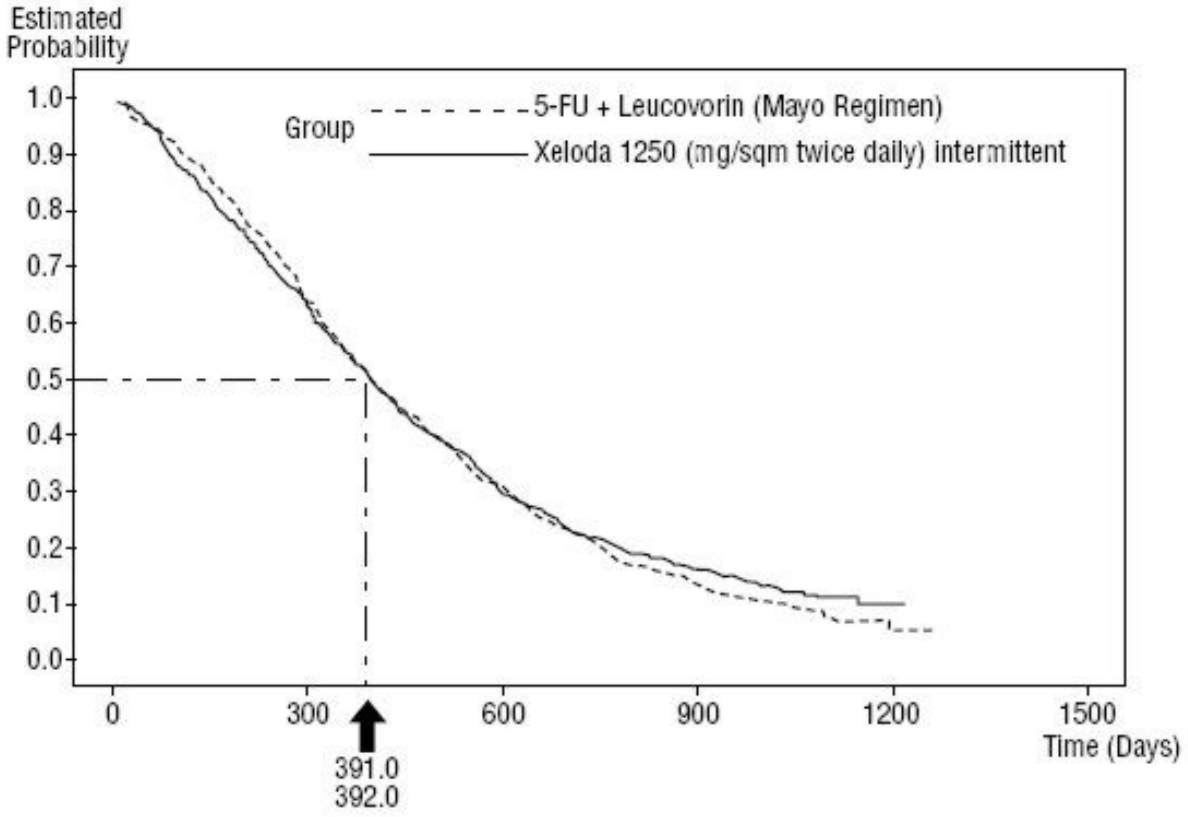
	XELODA (N=302)	**Fluorouracil + Leucovorin (N=303)**
Overall Response Rate		
% (95% CI)	21 (16, 26)	11 (8, 15)
p-value	0.0014	
Time to Progression		
Median, months (95% CI)	4.2 (3.9, 4.5)	4.3 (3.4, 5.0)
Hazard Ratio	0.99	
95% CI	(0.84, 1.17)	
Overall Survival		
Median, months (95% CI)	12.5 (10.5, 14.3)	13.4 (12.0, 14.7)
Hazard Ratio	1.00	
95% CI	(0.84, 1.18)	

Table 13 Efficacy Results for First-Line Treatment of Metastatic Colorectal Cancer (Study SO14796)

	XELODA (N=301)	**Fluorouracil + Leucovorin (N=301)**
Overall Response Rate		
% (95% CI)	21 (16, 26)	14 (10, 18)
p-value	0.027	
Time to Progression		
Median, months (95% CI)	4.5 (4.2, 5.5)	4.3 (3.4, 5.1)
Hazard Ratio	0.97	
95% CI	(0.82, 1.14)	
Overall Survival		
Median, months (95% CI)	13.3 (12.1, 14.8)	12.1 (11.1,14.1)
Hazard Ratio	0.92	
95% CI	(0.78, 1.09)	

Efficacy results of the pooled population from Study SO14695 and Study SO14796 are shown in Figure 3. Statistical analyses were performed to determine the percent of the survival effect of fluorouracil + leucovorin that was retained by XELODA. The estimate of the survival effect of fluorouracil + leucovorin was derived from a meta-analysis of ten randomized studies from the published literature comparing fluorouracil to regimens of fluorouracil + leucovorin that were similar to the control arms used in these Studies SO14695 and SO14796. The method for comparing the treatments was to examine the worst case (95% confidence upper bound) for the difference between fluorouracil + leucovorin and XELODA, and to show that loss of more than 50% of the fluorouracil + leucovorin survival effect was ruled out. It was demonstrated that the percent of the survival effect of fluorouracil + leucovorin maintained was at least 61% for Study SO14796 and 10% for Study SO14695. The pooled result is consistent with a retention of at least 50% of the effect of fluorouracil + leucovorin. It should be noted that these values for preserved effect are based on the upper bound of the fluorouracil + leucovorin vs XELODA difference.

Figure 3 Kaplan-Meier Curve for Overall Survival of Pooled Data (Studies SO14695 and SO14796)



In Combination with Oxaliplatin

The efficacy of XELODA for the treatment of patients with unresectable or metastatic colorectal cancer as a component of a combination chemotherapy regimen was derived from studies in the published literature, including NO16966 [NCT00069095], a randomized, non-inferiority, 2x2 factorial trial, where the major efficacy outcome measure was progression free survival.

14.2 Metastatic Breast Cancer

In Combination With Docetaxel

The efficacy of XELODA in combination with docetaxel was evaluated in an open-label, multicenter, randomized trial (Study SO14999). Eligible patients had metastatic breast cancer resistant to, or recurring during or after an anthracycline-containing therapy, or relapsing during or recurring within 2 years of completing an anthracycline-containing adjuvant therapy were enrolled. Patients were randomized to XELODA 1,250 mg/m^2 twice daily for the first 14 days of a 21-day cycle and docetaxel 75 mg/m^2 as a 1-hour intravenous infusion on day 1 of day of a 21-day cycle or docetaxel 100 mg/m^2 as a 1-hour intravenous infusion on day 1 of a 21-day cycle. The efficacy outcome measures were time to disease progression, overall survival, and response rate.

Patient demographics are provided in Table 14.

Table 14 Baseline Demographics in Metastatic Breast Cancer (Study SO14999)

	XELODA + Docetaxel (N=255)	**Docetaxel (N=256)**
Age (median, years)	52	51
Karnofsky Performance Status (median)	90	90
Site of Disease		
Lymph nodes, %	47	49
Liver, %	45	48
Bone, %	42	46
Lung, %	37	39
Skin, %	29	29
Prior Chemotherapy		
Anthracycline[1], %	100	100
Fluorouracil, %	77	74
Paclitaxel, %	10	9
Resistance to an Anthracycline		
No resistance, %	7	7
Progression on anthracycline therapy, %	26	29
Stable disease after 4 cycles of anthracycline therapy, %	16	16
Relapsed within 2 years of completion of anthracycline-adjuvant therapy, %	31	29
Experienced a brief response to anthracycline therapy, with subsequent progression while on therapy or within 12 months after last dose, %	20	20
No. of Prior Chemotherapy Regimens for Treatment of Metastatic Disease		
0, %	35	31
1, %	48	53
2, %	17	15
3, %	0	1

[1]Includes 10 patients in combination and 18 patients in single agent arms treated with an anthracenedione

Efficacy results are shown in Table 15, Figure 4 and Figure 5.

Table 15 Efficacy Results in Metastatic Breast Cancer (Study SO14999)

Efficacy Parameter	**XELODA + Docetaxel (N=255)**	**Docetaxel (N=256)**
Time to Disease Progression		
Median, months	6.1	4.2
95% CI	(5.4, 6.5)	(3.5, 4.5)
Hazard Ratio	0.643	
p-value	0.0001	
Overall Survival		
Median, months	14.5	11.6
95% CI	(12.3, 16.3)	(9.8, 12.7)
Hazard Ratio	0.775	
p-value	0.0126	
Response Rate[1]	32%	22%

[1] The response rate reported represents a reconciliation of the investigator and IRC assessments performed by the sponsor according to a predefined algorithm.

Figure 4 Kaplan-Meier Estimates for Time to Disease Progression in Metastatic Breast Cancer (Study SO14999)

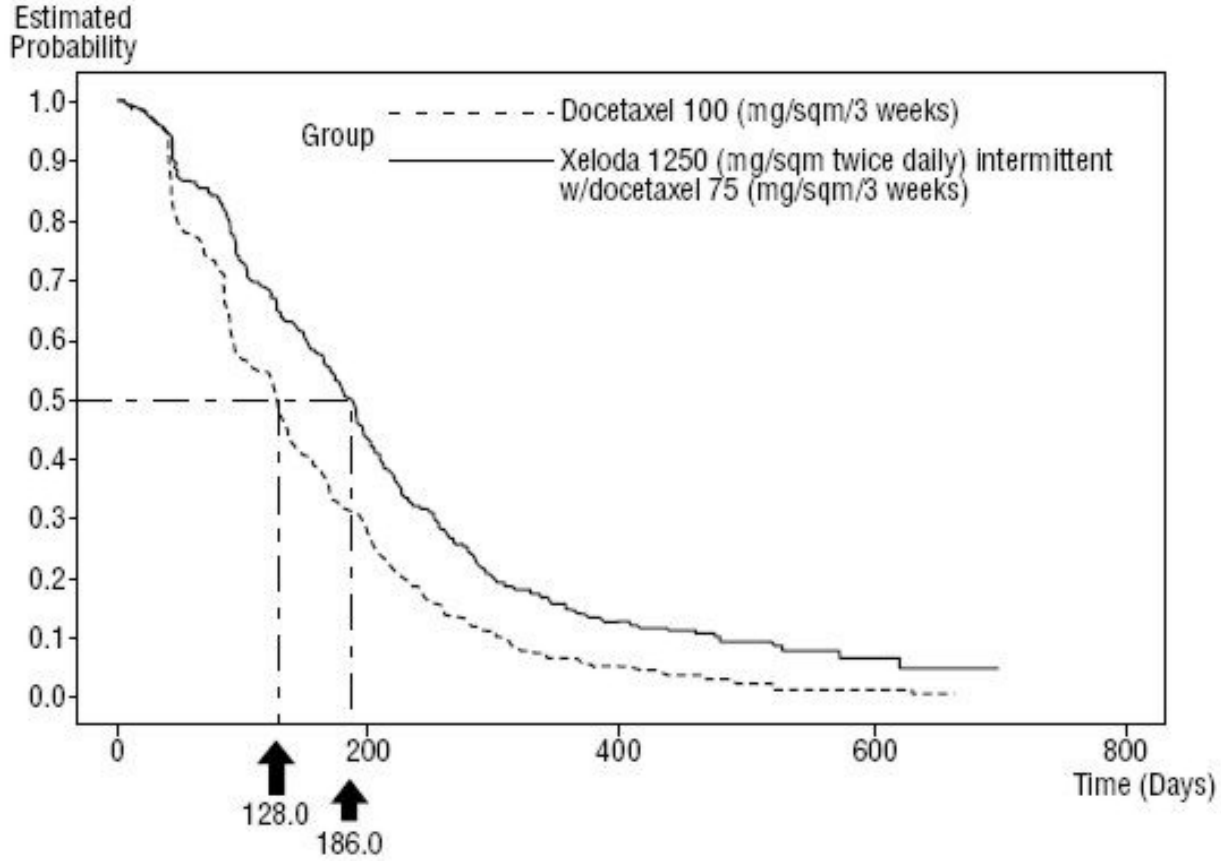
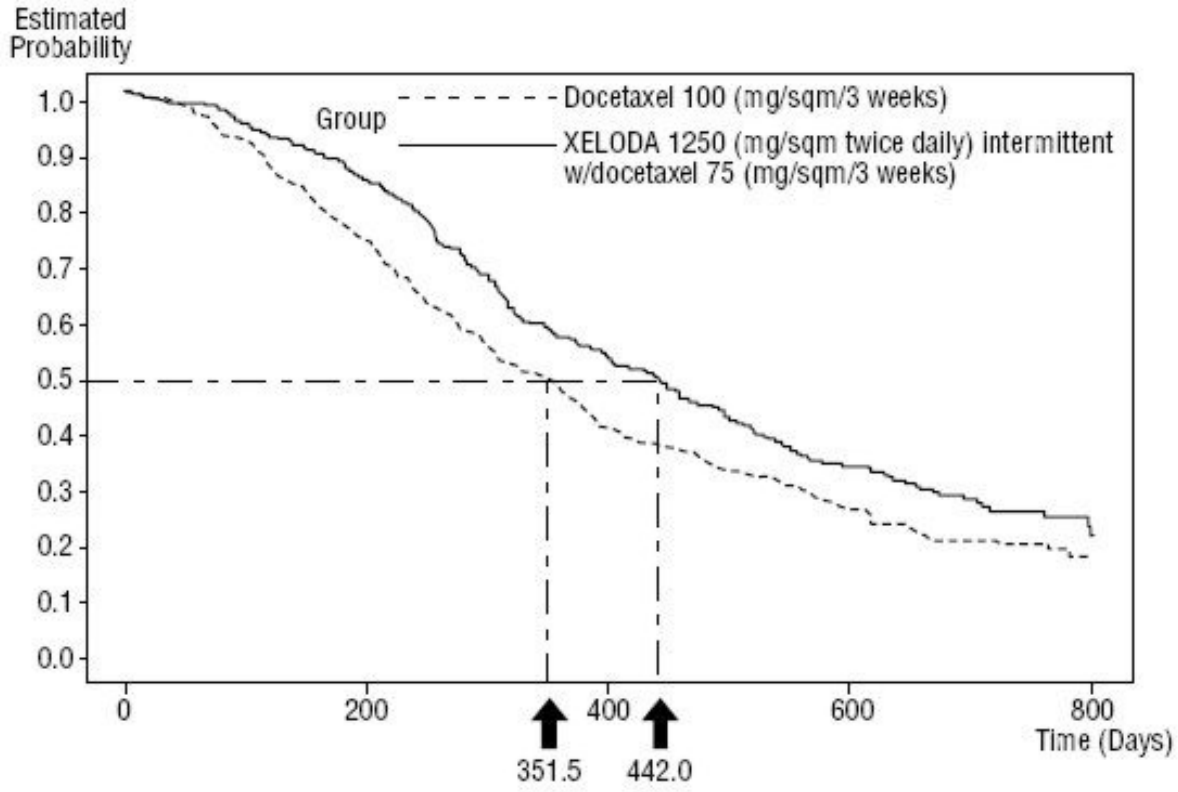


Figure 5 Kaplan-Meier Estimates of Survival in Metastatic Breast Cancer (Study SO14999)



Single Agent

The efficacy of XELODA as a single agent was evaluated in an open-label single-arm trial (Study SO14697). Eligible patients had 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/m^2 of doxorubicin or doxorubicin equivalents). Resistance was 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 chemotherapy regimen. Patients received XELODA 1,255 mg/m^2 orally twice daily for first 14-days of a 21-day treatment cycle. The major efficacy outcome measure was tumor response rate in patients with measurable disease, with response defined as a ≥50% decrease in sum of the products of the perpendicular diameters of bidimensionally measurable disease for at least 1 month.

The baseline demographics are shown in Table 16.

Table 16 Baseline Demographics in Metastatic Breast Cancer (Study SO14697)

	Patients With Measurable Disease (N=135)	**All Patients (N=162)**
Age (median, years)	55	56
Karnofsky Performance Status	90	90
No. Disease Sites		
1-2, %	32	37
3-4, %	46	43
>5, %	22	21
Dominant Site of Disease		
Visceral[1], %	75	68
Soft Tissue, %	22	22
Bone, %	3	10
Prior Chemotherapy		
Paclitaxel, %	100	100
Anthracycline[2], %	90	91
Fluorouracil, %	81	82
Resistance to Paclitaxel, %	76	77
Resistance to an Anthracycline[2], %	41	41
Resistance to both Paclitaxel and an Anthracycline[2], %	32	31

[1]Lung, pleura, liver, peritoneum
[2]Includes 2 patients treated with an anthracenedione

Efficacy for Study SO14697 are shown in Table 17.

Table 17 Efficacy Results in Metastatic Breast Cancer (Study SO14697)

Efficacy Parameter	**Resistance to Both Paclitaxel and an Anthracycline (N=43)**
Response Rate[1] (95% CI)	25.6% (13.5, 41.2)
Complete Response	0%
Partial Response[1]	11%
Duration of Response[1] Median, months[2] (Range)	5.1 (2.1-7.7)

[1] Includes 2 patients treated with an anthracenedione
[2] From date of first response

For the subgroup of 43 patients who were doubly resistant, the median time to progression was 3.4 months and the median survival was 8.4 months. The objective response rate in this population was supported by a response rate of 18.5% (1 CR, 24 PRs) in the overall population of 135 patients with measurable disease, who were less resistant to chemotherapy (see Table 15). The median time to progression was 3.0 months and the median survival was 10.1 months.

14.3 Gastric, Esophageal, or Gastroesophageal Junction Cancer

The efficacy of XELODA for treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen was derived from studies in the published literature. XELODA was evaluated in REAL-2, a randomized non-inferiority, 2x2 factorial trial, where the major efficacy outcome measure was overall survival, and an additional randomized trial conducted by the North Central Cancer Treatment Group, where the major efficacy outcome measure was objective response rate.

The efficacy of XELODA for the 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 was derived from studies in the published literature. XELODA was evaluated in the ToGA trial [NCT01041404], an open-label, multicenter, randomized trial where the primary efficacy measure was overall survival.

14.4 Pancreatic Cancer

The efficacy of XELODA for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen was derived from a study in the published literature. XELODA was evaluated in ESPAC-4 trial, a two-group, open-label, multicenter, randomized trial, where the major efficacy outcome measure was overall survival.

15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

XELODA (capecitabine) tablets are supplied as follows:

- 150 mg, biconvex, oblong, film-coated, light peach tablets with "XELODA" on one side and "150" on the other; available in bottles of 60 tablets (NDC 0004-1100-20), individually packaged in a carton.

- 500 mg, biconvex, oblong, film-coated, peach tablets with "XELODA" on one side and "500" on the other; available in bottles of 120 tablets (NDC 0004-1101-50), individually packaged in a carton.

Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*. KEEP TIGHTLY CLOSED.

XELODA is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Increased Risk of Bleeding with Concomitant Use of Vitamin K Antagonists

Advise patients on vitamin K antagonists, such as warfarin, that they are at an increased risk of severe bleeding while taking XELODA. Advise these patients that INR should be monitored more frequently, and dosage modifications of the vitamin K antagonist may be required, while taking and after discontinuation of XELODA. Advise these patients to immediately contact their healthcare provider if signs or symptoms of bleeding occur *[see Warnings and Precautions (5.1)]*.

Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency

Inform patients of the potential for serious and life-threatening adverse reactions due to DPD deficiency and discuss with your patient whether they should be tested for genetic variants of *DPYD* that are associated with an increased risk of serious adverse reactions from the use of XELODA. Advise patients to immediately contact their healthcare provider if symptoms of severe mucositis, diarrhea, neutropenia, and neurotoxicity occur *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.5)]*.

Cardiotoxicity

Advise patients of the risk of cardiotoxicity and to immediately contact their healthcare provider for new onset of chest pain, shortness of breath, dizziness, or lightheadedness *[see Warnings and Precautions (5.3)]*.

Diarrhea

Inform patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal stools) or greater or experiencing severe bloody diarrhea with severe abdominal pain and fever to stop taking XELODA. Advise patients on the use of antidiarrheal treatments (e.g., loperamide) to manage diarrhea *[see Warnings and Precautions (5.4)]*.

Dehydration

Instruct patients experiencing grade 2 or higher dehydration to stop taking XELODA immediately and to contact their healthcare provider. Advise patients to not restart XELODA until rehydrated and any precipitating causes have been corrected or controlled *[see Warnings and Precautions (5.5)]*.

Renal Toxicity

Instruct patients experiencing decreased urinary output or other signs and symptoms of renal toxicity to immediately contact their healthcare provider *[see Warnings and Precautions (5.6)]*.

Serious Skin Toxicities

Instruct patients skin rash, blistering, or peeling to immediately contact their healthcare provider *[see Warnings and Precautions (5.7)]*.

Palmar-Plantar Erythrodysesthesia Syndrome

Instruct patients experiencing grade 2 palmar-plantar erythrodysesthesia syndrome or greater to stop taking XELODA immediately and to contact their healthcare provider. Inform patients that initiation of symptomatic treatment is recommended and hand-and-foot syndrome can lead to loss of fingerprints which could impact personal identification *[see Warnings and Precautions (5.8)]*.

Myelosuppression

Inform patients who develop a fever of 100.5°F or greater or other evidence of potential infection to immediately contact their healthcare provider *[see Warnings and Precautions (5.9)]*.

Hyperbilirubinemia

Inform patients who develop jaundice or icterus to immediately contact their healthcare provider *[see Warnings and Precautions (5.10)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with XELODA and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with XELODA and for 3 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with XELODA and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that XELODA may impair fertility *[see Use in Specific Populations (8.3)]*.

Hypersensitivity and Angioedema

Advise patients that XELODA may cause severe hypersensitivity reactions and angioedema. Advise patients who have known hypersensitivity to capecitabine or 5-fluorouracil to inform their healthcare provider *[see Contraindications (4)]*. Instruct patients who develop hypersensitivity reactions or mucocutaneous symptoms (e.g., urticaria, rash, erythema, pruritus, or swelling of the face, lips, tongue or throat which make it difficult to swallow or breathe) to stop taking XELODA and immediately contact their healthcare provider or to go to an emergency room. *[see Adverse Reactions (6)]*.

Nausea and Vomiting

Instruct patients experiencing grade 2 nausea (food intake significantly decreased but able to eat intermittently) or greater to stop taking XELODA and to immediately contact their healthcare provider for management of nausea *[see Adverse Reactions (6.1)]*.

Instruct patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater to stop taking XELODA immediately and to contact their healthcare provider for management of vomiting *[see Adverse Reactions (6.1)]*.

Stomatitis

Inform patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth or tongue, but able to eat) or greater to stop taking XELODA immediately and to contact their healthcare provider *[see Adverse Reactions (6.1)]*.

Important Administration Instructions

Advise patients to swallow XELODA tablets whole with water within 30 minutes after a meal. Advise patients and caregivers not to chew, crush, or cut XELODA tablets. Advise patients if they cannot swallow XELODA tablets whole to inform their healthcare provider *[see Dosage and Administration (2.7), Warnings and Precautions (5.12)]*.

Drug interactions

Instruct patients not to take products containing folic acid or folate analog products (e.g., leucovorin, levoleucovorin) unless directed to do so by their healthcare provider. Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products *[see Drug Interactions (7.1, 7.2, 7.3)]*.

Distributed by:

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A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Patient Information
XELODA® (zeh-LOE-duh)
(capecitabine)
tablets

What is the most important information I should know about XELODA?

XELODA can cause serious side effects, including:

- **Increased risk of bleeding when taking XELODA with blood thinner medicines, such as warfarin**. **Taking XELODA with these medicines can cause changes in how fast your blood clots and can cause bleeding that can lead to death**. This can happen as soon as a few days after you start taking XELODA, or later during treatment, and possibly within 1 month after you stop taking XELODA. This can happen in people whose cancer has spread to the liver (liver metastasis) **and** in people whose cancer has not spread to the liver.
  - Before taking XELODA, tell your healthcare provider if you are taking warfarin or another blood thinner medicine.
  - If you take warfarin or another blood thinner that is like warfarin during treatment with XELODA, your healthcare provider should do blood tests more often, to check how fast your blood clots during and after you stop treatment with XELODA. Your healthcare provider may change your dose of the blood thinner medicine if needed.
  - **Tell your healthcare provider right away if you develop any signs or symptoms of bleeding.**

See **"What are the possible side effects of XELODA?"** for more information about side effects.

What is XELODA?

XELODA is a prescription medicine used to treat:

- A kind of cancer called colon or rectal (colorectal) cancer. XELODA may be used:
  - alone or in combination with other chemotherapy medicines in people with colon cancer that has spread to lymph nodes in the area close to the colon (Stage III colon cancer), to help prevent your cancer from coming back after you have had surgery.
  - adults with rectal cancer, around the time of your surgery, as a part of chemotherapy and radiation (chemoradiation) treatment when your rectal cancer has spread to nearby tissues (locally advanced).
  - alone or in combination with other chemotherapy medicines, when your colorectal cancer cannot be removed by surgery or has spread to other areas of your body (metastatic).
- A kind of cancer called breast cancer. XELODA may be used in people with breast cancer that is advanced or has spread to other parts of the body (metastatic):
  - alone if you are not able to receive an anthracycline medicine or taxane-containing chemotherapy.
  - in combination with docetaxel when you have received anthracycline containing chemotherapy and it is no longer working.
- Kinds of cancer called stomach (gastric), esophageal, or gastroesophageal junction (GEJ) cancer. XELODA may be used in adults:
  - in combination with other chemotherapy medicines when your cancer of the stomach, esophagus, or GEJ cannot be removed by surgery or has spread to other parts of the body (metastatic).
  - when your cancer of the stomach, esophagus, or GEJ is metastatic adenocarcinoma, **and:**
    - is HER2-positive, **and**
    - you have not received treatment with XELODA in combination with other treatments for your metastatic cancer.
- A kind of cancer called pancreatic cancer. XELODA may be used to treat adults in combination with other chemotherapy medicines, to help prevent your pancreatic cancer from coming back after you have had surgery.

It is not known if XELODA is safe and effective in children.

Do not take XELODA if you:

- have had a severe allergic reaction to fluorouracil or capecitabine. See the end of this leaflet for a complete list of ingredients in XELODA.

Talk to your healthcare provider before taking XELODA if you are not sure.

Before taking XELODA, tell your healthcare provider about all your medical conditions, including if you:
See **"What is the most important information I should know about XELODA?"**

- have had heart problems.
- have kidney or liver problems.
- are pregnant or plan to become pregnant. XELODA can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with XELODA.

- Use an effective method of birth control (contraception) during treatment and for 6 months after your last dose of XELODA. Talk to your healthcare provider about birth control choices that may be right for you during treatment with XELODA.
- Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with XELODA.

Males who have female partners who are able to become pregnant should use effective birth control during treatment and for 3 months after your last dose of XELODA.

- are breastfeeding or plan to breastfeed. It is not known if XELODA passes into your breast milk. Do not breastfeed during treatment with XELODA and for 1 week after your last dose of XELODA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XELODA may affect the way other medicines work, and other medicines may affect the way XELODA works.

How should I take XELODA?

- Take XELODA exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much XELODA to take and when to take it. The number of days that you will take XELODA during each treatment cycle and the number of days in each treatment cycle depends on the type of cancer you are being treated for.
- Take XELODA 2 times a day at the same time each day, about 12 hours apart.
- Take XELODA within 30 minutes after finishing a meal.
- Swallow XELODA tablets whole with water. **Do not** chew, cut, or crush XELODA tablets. See "Eye irritation, skin rash and other side effects with exposure to crushed XELODA tablets" in the section called "**What are the possible side effects of XELODA?**"
- If you cannot swallow XELODA tablets whole, tell your healthcare provider.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with XELODA if you develop side effects.
- **Do not** take products that contain folic acid or folate analog products, for example, leucovorin or levoleucovorin, during treatment with XELODA, unless your healthcare provider instructs you to take it.
- If you vomit after taking a dose of XELODA, do not take another dose at that time. Wait and take your next dose of XELODA at your scheduled time.
- If you miss a dose of XELODA, just skip the dose and then take your next dose at your scheduled time.
- If you take too much XELODA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of XELODA?

XELODA can cause serious side effects including:

- See **"What is the most important information I should know about XELODA?"**
- **Serious side effects in people with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.** People with certain changes in a gene called "DPYD" may have a deficiency of the DPD enzyme. Some of these people may not produce enough DPD enzyme, and some of these people may not produce the DPD enzyme at all.
  - People who do not produce any DPD enzyme are at increased risk of sudden side effects that come on early during treatment with XELODA and can be serious, and sometimes lead to death. **Call your healthcare provider right away if you develop any of the following symptoms and they are severe**, including:
    - sores of the mouth, tongue, throat and esophagus (mucositis)
    - diarrhea
    - low white blood cell counts
    - nervous system problems.
  - People with some DPD enzyme may have an increased risk of serious side effects with XELODA treatment that can sometimes lead to death.

  Your healthcare provider should talk with you about DPYD testing to look for DPD deficiency.
- **Heart problems.** XELODA can cause heart problems including: heart attack and decreased blood flow to the heart, chest pain, irregular heartbeats, changes in the electrical activity of your heart seen on an electrocardiogram (ECG), problems with your heart muscle, heart failure, and sudden death. You may have an increased risk of heart problems with XELODA if you have a history of narrowing or blockage of the coronary arteries (coronary artery disease). **Stop taking XELODA and call your healthcare provider or go to the nearest hospital emergency room right away if you get any new symptoms of a heart problem including:**
  - chest pain
  - shortness of breath
  - dizziness
  - lightheadedness
- **Diarrhea.** Diarrhea is common with XELODA and can sometimes be severe. Stop taking XELODA and call your healthcare provider right away if the number of bowel movements you have in a day increases by 4 or more bowel movements than what is usual for you, or if you have bowel movements at night. Ask your healthcare provider about what medicines you can take to treat your diarrhea. Stop taking XELODA if you have severe bloody diarrhea with severe abdominal pain and fever and call you healthcare provider right away.

- **Loss of too much body fluid (dehydration) and kidney failure.** Dehydration can happen with XELODA and may affect how well your kidneys work. If you take XELODA with certain other medicines that can cause kidney problems, you may have an increased risk of serious kidney failure that can sometimes lead to death. Your risk of kidney failure may also be increased if you have kidney problems before taking XELODA.

  Nausea, and vomiting are common with XELODA. If you lose your appetite, feel weak, and have nausea, vomiting, or diarrhea, you can quickly become dehydrated.

  Stop taking XELODA and call your healthcare provider right away if you:

  - vomit 2 or more times in a day.
  - are only able to eat or drink a little now and then, or not at all due to nausea.
  - have diarrhea. See "diarrhea" above.

  You may need to receive fluids through your vein (intravenous) to treat your dehydration or receive treatment for kidney failure.
- **Severe skin and mouth reactions.**
  - XELODA can cause severe skin reactions that may lead to death. Tell your healthcare provider right away if you develop a skin rash, blister and peeling of your skin. Your healthcare provider may tell you to stop taking XELODA if you have a serious skin reaction. Do not take XELODA again if this happens.
  - XELODA can also cause "hand and foot" syndrome. Hand and foot syndrome is common with XELODA and can cause you to have numbness and changes in sensation in your hands and feet, or cause redness, pain, swelling of your hands and feet. Stop taking XELODA and call your healthcare provider right away if you have any of these symptoms and you are not able to do your usual activities.
  - Hand and foot syndrome can lead to a loss of fingerprints which could impact your identification.
  - You may get sores in your mouth or on your tongue when taking XELODA. Stop taking XELODA and call your healthcare provider right away if you get painful redness, swelling, or ulcers in your mouth or tongue, or if you are having problems eating.
- **Decreased white blood cells, platelets, and red blood cell counts. Decreased white blood cells, platelets, and red blood cell counts can happen with XELODA and can sometimes be severe.** Your healthcare provider will do blood tests during treatment with XELODA to check your blood cell counts.

  If your white blood cell count is very low, you are at increased risk for infection. Call your healthcare provider right away if you develop a fever of 100.5°F or greater or have other signs and symptoms of infection.
- **Increased level of bilirubin in your blood and liver problems.** Increased bilirubin in your blood is common with XELODA and can also sometimes be severe. Your healthcare provider will check you for these problems during treatment with XELODA. Tell your healthcare provider right away if you develop yellowing of your skin or the white part of your eyes.
- **Eye irritation, skin rash and other side effects with exposure to crushed XELODA tablets.** If you come into contact with (you are exposed to) crushed XELODA tablets, you may develop side effects including:
  - eye irritation and swelling
  - skin rash
  - diarrhea
  - feeling like pins and needles in your hands
  - headache
  - stomach irritation
  - nausea and vomiting

  Do not chew, cut, or crush XELODA tablets. See **"How should I take XELODA tablets**."

  If for any reason your tablets must be cut or crushed, this must be done by your pharmacist or healthcare provider.

Your healthcare provider may decide to decrease your dose, or temporarily or permanently stop XELODA if you have serious side effects with XELODA.

The most common side effects in people with colon cancer who take XELODA alone to help prevent it from coming back include: hand and foot syndrome, diarrhea, and nausea.

The most common side effects in people with metastatic colorectal carcinoma who take XELODA alone include:

- decreased red blood cell count
- diarrhea
- hand and foot syndrome
- increased bilirubin level in your blood
- nausea
- tiredness
- stomach-area (abdominal) pain

The most common side effects in people with metastatic breast cancer who take XELODA in combination with docetaxel include:

- diarrhea
- mouth sores or mouth inflammation
- hair loss
- swelling

- hand and foot syndrome
- nausea and vomiting
- stomach-area (abdominal) pain

The most common side effects in people with metastatic breast cancer who take XELODA alone include:

- decreased white blood cell and red blood cell count
- diarrhea
- hand and foot syndrome
- nausea and vomiting
- tiredness
- skin inflammation, including rash

Severe allergic reactions can happen with XELODA. See "**Do not take XELODA if you**:" **Stop taking XELODA and call your healthcare provider right away or go to an emergency room if you have any of the following symptoms of a severe allergic reaction to XELODA:**

- red itchy welts on your skin (hives)
- rash
- skin redness
- itching
- swelling of your face, lips, tongue or throat
- trouble swallowing or breathing

XELODA may cause fertility problems in females and males. This may affect the ability to have a child. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of XELODA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XELODA?

- Store XELODA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep XELODA in a tightly closed container.
- Ask your healthcare provider or pharmacist how to safely throw away any unused XELODA.

Keep XELODA and all medicines out of the reach of children.

General information about the safe and effective use of XELODA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XELODA for a condition for which it was not prescribed. Do not give XELODA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about XELODA that is written for health professionals.

What are the ingredients in XELODA?

Active ingredient: capecitabine

Inactive ingredients: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

Distributed by: Genentech, Inc. A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990

For more information, go to http://www.gene.com/patients/medicines/xeloda or call 1-877-436-3683.

This Patient Informa ion has been approved by the U.S. Food and Drug Administration. Revised: 12/2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020896Orig1s044,045,046,047,048,049,050,051

MULTI-DISCIPLINE REVIEW

Project Renewal Assessment Aid

NDA 020896

XELODA (capecitabine) tablets

Version date: August 2021 (ONLY for Project Renewal sNDA reviews)

Disclaimer: The FDA's recommendations and opinions are limited to this Assessment Aid and do not extend to other documents regarding this application. In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Product Introduction and Relevant U.S. Regulatory History

XELODA (capecitabine) tablets is a fluoropyrimidine submitted under New Drug Application (NDA) 020896. It initially received accelerated approval on April 30, 1998, under Subpart H of Part 314, as a single agent 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. The accelerated approval was based on response rate in a single phase 2 trial conducted in patients considered to have refractory breast cancer.

On August 4, 2008, the NDA holder submitted a supplement (NDA 020896/S26) proposing revisions to the labeling to, among other things, conform with the format described under the Physician Labeling Rule (PLR). Revisions to the labeling were made to conform to the Physician's Labeling Rule (PLR) format specified in 21 CFR 201.57. This supplement was approved on February 5, 2011.

Several updates to the labeling have occurred since the original approval of XELODA. These updates either added a new disease indication and/or safety information for the safe use of XELODA. A summary of these relevant labeling updates include:

- On April 30, 2001, updated labeling was approved to provide safety information and dose modification for renal impairment (S-006). It also added a new indication for use of XELODA as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred (S-009), based on improvement in overall response rate (ORR). A survival benefit of XELODA monotherapy over 5-fluorouracil and leucovorin (5FU/LV) was not demonstrated but an oral regimen may be preferred by some patients. Additionally, use of XELODA instead of 5FU/LV-based combination chemotherapy was not adequately studied to assure safety or preservation of the survival advantage shown for the combination regimens.
- On September 7, 2001, labeling was updated to reflect results of the confirmatory trial required following the initial accelerated approval. The phase 3 trial compared XELODA in combination with docetaxel versus docetaxel monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy (S-010). Approval was based on improved time to progression (TTP), ORR and overall survival (OS). Additionally, safety information was added regarding coagulopathy with concomitant use of warfarin (S-011).
- On June 15, 2005, labeling was updated with a new indication for XELODA monotherapy in patients with Duke's C colon cancer following complete resection of primary tumor as adjuvant treatment when fluoropyrimidine therapy alone is preferred. The approval of XELODA was based on non-inferior DFS (S-016) compared to 5FU/LV in the XELODA Adjuvant Colon Cancer Trial (X-ACT).
- On February 5, 2011, additional follow-up of patients on X-ACT resulted in updates to labeling (S-026), and the XELODA labeling was updated to conform to PLR format.

- On December 10, 2013, labeling was updated to include pediatric use from studies conducted in pediatric patients with newly diagnosed non-disseminated diffused intrinsic brainstem gliomas (S-032).

This Project Renewal Assessment Aid for XELODA (NDA 020896) provides a summary of the key proposed FDA recommendations for updates to the information related to approved uses for XELODA to align with 21 CFR 201.56 and 201.57 and applicable guidances,[1,2] as well as proposed recommendations for adding or modifying an indication(s) or other condition(s) of use based on certain data and information, including published literature, FDA's finding of safety and effectiveness of listed drugs, and information to which the Applicant would need to obtain a right of reference.

In addition, the FDA's independent assessment to support proposed recommendations for labeling modifications included published literature review, FDA Adverse Event Reporting System data, and assessment of the existing XELODA labeling for adherence to current regulations and guidances. FDA's key proposed recommended labeling modifications are described below. Rationale for additional proposed labeling updates is provided in annotated comments to the Applicant, including references where appropriate, within the proposed draft labeling.

1.2 Information to Support the Proposed Changes to Labeling

The published literature cited in the annotated labeling support the FDA's proposed updates to the XELODA product labeling. The Applicant should submit any additional data or information relevant to the labeling updates proposed in the above-referenced supplement(s). Because some of the evidence supporting the updates is derived from information for which the Applicant does not own or have a right of reference, the Applicant must submit the supplements pursuant to section 505(b)(2) of the FD&C Act.

Based on the evaluation of information identified through this process and as further assessed by the FDA in conjunction with a review of additional published literature (as annotated in the proposed labeling), the following key labeling modifications, including new indications or modifications to existing indications and to dosage and administration, are proposed for inclusion in the XELODA labeling.

Any additional new indication(s) that the Applicant would like to propose that are not reflected in this Assessment Aid are outside the scope of Project Renewal and should be discussed separately with the appropriate FDA oncology review division.

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[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/indications-and-usage-section-labeling-human-prescription-drug-and-biological-products-content-AND.

[2] https://www.fda.gov/media/72142/download.

2. PROPOSED REVISIONS TO INDICATIONS AND DOSAGE AND ADMINISTRATION

2.1 Colorectal Cancer

XELODA is indicated for the:

- 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.

Recommended Dosage for Colorectal Cancer

Adjuvant Treatment of Colon Cancer

Single Agent

The recommended dosage of XELODA is 1,250 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle for a maximum of 8 cycles.

In Combination with Oxaliplatin-Containing Regimens

The recommended dosage of XELODA is 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle for a maximum of 8 cycles in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.

Refer to the oxaliplatin prescribing information for additional dosing information as appropriate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2020, there were an estimated 104,610 new cases of colon cancer with approximately 53,200 deaths from the disease, accounting for 9% of all cancer deaths in the United States (Siegel 2020). • With the availability of screening, majority of colon cancer are diagnosed in either the localized or regional stages, with approximately 70% of patients diagnosed with potentially curable disease (Andre 2009). The 5-year	Colon cancer is common, and majority of patients are diagnosed when their disease is potentially curable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	relative survival of CRC diagnosed at a localized stage is approximately 90%.	
Current Treatment Options	• Adjuvant chemotherapy as either single agents or in combination are treatment options in eligible patients with colorectal cancer. • 5-Fluorouracil plus leucovorin (FU/LV) has been shown to improve overall survival (OS) over observation as adjuvant therapy in patients with resected colon cancer. • Combination chemotherapy also improved overall survival (OS). The MOSAIC trial demonstrated superiority of leucovorin [folinic acid], fluorouracil, and oxaliplatin (FOLFOX) to FU/LV in patients with resected stage II and III colon cancer (Haller 2011). • Capecitabine 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 (DFS). Physicians should consider results of combination chemotherapy trials, which have shown improvement in DFS and OS, when prescribing single-agent XELODA in the adjuvant treatment of Dukes' C colon cancer.* • Capecitabine's currently approved dose is: 1250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycle. • Adjuvant treatment in patients with Dukes' C colon cancer is recommended for a total of 6 months [i.e., 1250 mg/m^2 orally twice daily for 2 weeks followed by a 1-week rest period, given	There is a need to develop systemic therapies that are both effective and well tolerated to improve the overall outcomes and survivorship of patients with potentially curable colon cancer who are at high risk of recurrence. FOLFOX is a commonly used adjuvant regimen for colon cancer given improvement in DFS and OS. Duration of adjuvant therapy is typically 6 months, although 3 months is reasonable in low-risk stage III disease. In patients for whom oxaliplatin therapy is inappropriate, it is reasonable to use 5FU/LV as this has been shown to improve OS over observation alone. Single agent capecitabine is FDA approved for use as a single agent in the adjuvant treatment of colon cancer. It has been shown to be non-inferior to 5FU/LV and provides an

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	as 3-week cycles for a total of 8 cycles (24 weeks)].	oral drug option.
Benefit	• Capecitabine was initially approved in 2005 for use as a single agent as adjuvant treatment for colon cancer based on a multicenter, randomized clinical trial. Patients were randomized to capecitabine 1250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle for a total of 8 cycles OR fluorouracil in combination with leucovorin. The primary outcome measure was non-inferiority for DFS. The hazard ratio for capecitabine compared to fluorouracil and leucovorin with respect to DFS was 0.88 (95% CI: 0.77, 1.01; p=0.068). • Capecitabine has also demonstrated efficacy in the adjuvant treatment of colon cancer when used as a component of a combination chemotherapy regimen (capecitabine + oxaliplatin, also known as XELOX) as evidenced by an improvement in DFS compared to bolus FU/LV in Trial NO16968. • Trial NO16968, a multicenter, randomized trial compared XELOX with bolus FU/LV as adjuvant therapy for patients with stage III colon cancer who had undergone curative resection (Schmoll 2007). The primary end point was disease-free survival (DFS). This trial enrolled 1886 patients, with 944 patients randomized to the XELOX treatment arm. The XELOX regimen consisted of a 2-hour IV infusion of oxaliplatin 130 mg/m^2 on day 1 and oral capecitabine 1,000 mg/m^2 twice daily given for 14 days of a 3-week cycle, for a total of eight cycles (24 weeks). • After 57 months of follow-up for the primary	Capecitabine is currently indicated for use as a single agent in the adjuvant treatment of Dukes' C colon cancer. Duke's stage C indicates positive lymph nodes. Duke's system of staging has largely been replaced by the American Joint Committee on Cancer (AJCC) staging. Duke's stage C corresponds to AJCC Stage III disease, which is defined as T4N0M0 or Any T, N1-2, M0 disease. The data for AJCC stage II colon cancer was discussed and the evidence was considered insufficient to support inclusion of these patients in this indication. Trial NO16968 demonstrated an improvement in DFS of XELOX compared to bolus 5FU/LV, which supports expanding the current indication to include capecitabine in combination with oxaliplatin. In patients with stage III

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	analysis, 31.3% in the XELOX treatment arm had relapsed, developed a new primary colon cancer, or died compared to 37.5% in the FU/LV group (hazard ratio [HR] 0.80; 95% CI, 0.69 to 0.93; P = .0045). The 3-year DFS rate was 70.9% with XELOX and 66.5% with FU/LV. The 5-year OS for XELOX and FU/LV were 77.6% and 74.2%, respectively. The HR for OS was 0.87 (95% CI, 0.72 to 1.05; P = .1486).	colon cancer who are being considered for multi-agent chemotherapy combination, XELOX is another adjuvant chemotherapy option and provides an oral dosing option for a fluoropyrimidine. The dosing information in the capecitabine USPI was updated to reflect the dosing for the XELOX regimen.
Risk and Risk Management	• The known and currently labeled major AEs for capecitabine in adjuvant colon cancer include hand-foot syndrome, diarrhea, nausea, stomatitis, fatigue, and vomiting. • No new safety signals emerged for capecitabine in Trial NO16968 (Bailey 2015). The toxicities attributable to capecitabine were consistent with the drug's known safety profile. The higher grades of neurosensory toxicity and hand-foot syndrome reported for XELOX are expected, with the former attributable to oxaliplatin and the latter to capecitabine.	The safety profile attributable to capecitabine in the XELOX regimen for adjuvant treatment of colon cancer is acceptable for the intended population, and is manageable with current labeling. Hand-foot syndrome or palmar-plantar erythrodysesthesia syndrome (PPES) is included under Warnings and Precautions. No REMS is indicated at this time.

Perioperative Treatment of Rectal Cancer

The recommended dosage of capecitabine is 825 mg/m^2 orally twice daily when administered with concomitant radiation therapy and 1,250 mg/m^2 orally twice daily when administered without radiation therapy as part of a peri-operative combination regimen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately one-third of all newly diagnosed colorectal (CRC) is composed of rectal cancer; an estimated 43,340 Americans will be diagnosed with rectal cancer in 2020 (Siegel 2020). • Much of the statistics on rectal cancer such as deaths and survival by stage are reported as a composite CRC data, rather than reported separately, since large number of deaths from rectal cancer are misclassified as colon (Siegel 2020; Andre 2009). • Incidence of rectal cancer has been rising in young adults compared to trends reported for 1975-2010 (Siegel 2020a; Gastrointestinal Tumor Study Group 1985). Based on observed trends, the estimated rates of rectal cancer in 2030 will increase by 124.2% and 46.0%, respectively, for patients aged 20-34 and 35-49 years. The cause of this increased trend is presently unknown. • Locally advanced rectal cancer (LARC) is defined as stage II (T3-4, node negative) or stage III (node positive) disease, and prognosis has improved with screening and advances in both surgical and perioperative management. In appropriately treated patients, the 5- and 10-year overall survival (OS) is estimated at 60% and 50%, respectively.	Locally advanced rectal cancer (LARC) is a serious and life-threatening condition. The risk of pelvic recurrence is higher compared to colon cancer, and locally recurrent rectal cancer carries a poor prognosis. Even in appropriately treated patients, local recurrence and distant metastasis remain an issue, with over one-third of patients dying within 5 years of initial treatment.
Current Treatment Options	• LARC is particularly challenging to manage given the anatomical constraints of the pelvis and the risks for recurrence, both local and distant. Over the last two decades, there has been a paradigm shift in the management of LARC and combined-modality management has become the standard of care (SOC). • Following surgical resection, the benefit of adjuvant radiation (RT) is to reduce local	Successive trials by different groups have built on curative surgery. First, the addition of RT demonstrated improved local control and then addition of chemotherapy to RT improved cancer-specific survival and OS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	recurrence without improved survival. Treatment with combined radiation therapy and chemotherapy (also known as chemoradiotherapy or CRT) improves outcomes in terms of locoregional recurrence compared to radiation therapy (Krook 1991; O'Connell 1994). CRT has also demonstrated a reduction in cancer-related and overall deaths by 36% and 29%, respectively (O'Connell 1994). The two trials that support CRT employed different regimens but backbone chemotherapy for both trials was bolus fluorouracil (5FU) plus semustine. • In an attempt to improve the efficacy of chemotherapy, O'Connell et al. conducted a trial which omitted semustine and delivered infusional 5FU throughout the duration of RT. Compared to CRT with bolus 5FU, CRT with infusional 5FU did not significantly reduce local tumor recurrence; the benefit was in increased time to relapse and improved survival. This strategy then became the SOC. • The EORTC Radiotherapy Group showed that a combination of 5FU and leucovorin (LV) could be given safely during pelvic radiotherapy in patients with LARC (Bosset 1993). The same group assessed whether perioperative chemotherapy improves OS in patients who receive preoperative RT, and concluded that there were no difference in OS with either strategy (Bosset 2006). Thus, neoadjuvant or adjuvant CRT are equivalent SOC options with intravenous 5FU-based chemotherapy as the systemic backbone.	These findings have led to CRT with 5FU-based chemotherapy delivered in the neoadjuvant or adjuvant setting being the SOC for LARC. Owing to the heterogeneous nature of LARC, accurate prognostic information for individual patients can be difficult to estimate and there are many instances where patient outcomes do not match those for their tumor stage. Thus, there remains an unmet medical need to improve the outcomes of patients with LARC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Investigating the efficacy and safety of substituting fluorouracil with the oral prodrug capecitabine, investigators from 35 institutions in Germany conducted a non-inferiority trial of adjuvant CRT, randomizing (1:1) 401 patients with stage II/III LARC to either capecitabine- or fluorouracil-based CRT (Hofheinz 2012). The protocol was later amended to allow for a neoadjuvant cohort where patients in the capecitabine group received CRT (5040 cGy + capecitabine 1650 mg/m2 daily) followed by surgery and 5 cycles of capecitabine (2500 mg/m2 daily for 14 days) and patients in the fluorouracil group received CRT (5040 cGy + infusional 5FU 1000 mg/m2 on days 1–5 and 29–33) followed by surgery and 4 cycles of bolus 5FU (500 mg/m2 for 5 days). • The primary endpoint of OS was met; 5-year OS for the capecitabine CRT group was non-inferior to the 5FU CRT group (76% [95% CI 67–82] vs 67% [58–74], p=0.0004). Local recurrences were similar between groups (6% in the capecitabine group vs 7% in the 5FU group, p=0.67), but fewer patients developed distant metastases in the capecitabine group (19% vs 28%, p=0.04). This finding translated to a higher DFS in the capecitabine versus 5FU group (HR 1.4 [95% CI 1.02-2.02]; log-rank p=0.035). Exploratory analysis of neoadjuvant versus adjuvant cohorts trended to favor use of capecitabine. The investigators concluded that capecitabine could replace 5FU in neoadjuvant or adjuvant CRT regimens for patients with LARC (Hofheinz 2012).	RCTs have shown non-inferiority of capecitabine compared to 5FU when combined with RT for several endpoints including OS. Thus the fluoropyrimidine chemotherapy backbone for perioperative CRT may consist of either capecitabine or 5FU.
Risk and Risk Management	• Diarrhea was the most common adverse event (AE) reported in the German trial (Hofheinz 2012). Rates of all-grade diarrhea during chemotherapy were almost identical between groups (24% in the capecitabine group vs 22%	The safety profile of capecitabine as a component of CRT is acceptable for the intended population, and is

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in the fluorouracil group, p=0.67); however, during CRT diarrhea was significantly higher in the capecitabine group (45% vs 32%; p=0.009). • Patients treated with capecitabine had more hand-foot skin reactions, but these were mostly mild to moderate in severity (Hofheinz 2012). • Leukopenia was more frequent with patients on 5FU than with capecitabine (Hofheinz 2012).	manageable with current labeling. Diarrhea and hand-foot syndrome are included under Warnings and Precautions. Most physicians administering CRT to patients with LARC are well versed with identification and management of toxicities associated with capecitabine.

Unresectable or Metastatic Colorectal Cancer

Single Agent

The recommended dosage of XELODA is 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle until disease progression or unacceptable toxicity.

In Combination with Oxaliplatin

The recommended dosage of XELODA is 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.

Refer to the Prescribing Information for oxaliplatin for additional dosing information as appropriate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Colon and rectal cancer (CRC) combined is the 3rd leading cause of cancer deaths, accounting for 9% of all cancer deaths in the United States (Siegal 2020a).	Metastatic colon cancer is a serious and life-threatening condition with only about 1 in 5 patients surviving from their disease in 5 years, with the highest CRC deaths among the elderly.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Approximately 22% of CRC are diagnosed with metastatic disease, with an estimated 5-year relative survival of 22% for this stage (Siegal 2020a). CRC deaths is highest among people aged 65–74.	
Current Treatment Options	• Systemic chemotherapy, with or without targeted agents, is the mainstay of treatment for metastatic colon cancer. Key considerations for choice of therapy may include goals of treatment, prior therapy received, and toxicity profile of the treatment regimen. • For patients who can tolerate intensive therapy, treatment options include multi-agent combination regimens (i.e. FOLFOX, leucovorin + 5FU + irinotecan [FOLFIRI], leucovorin + oxaliplatin + irinotecan + 5FU [FOLFOXIRI], irinotecan + oxaliplatin [IROX]). In patients for whom less intensive therapy is preferred, such as frail patients, options include FU/LV or single-agent capecitabine. • Capecitabine is currently *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.* • The current recommended dose of capecitabine is 1250 mg/m2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles.	Treatment options include multi-agent combination regimens for patients who can tolerate them. In patients for whom less intensive therapy is preferred, such as frail patients, options include single-agent chemotherapy. There is an unmet medical need to improve the outcomes of patients with unresectable or metastatic colon cancer.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Capecitabine monotherapy is indicated as first-line treatment for patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Since capecitabine's initial approval of this indication, additional data is available that now also supports its use as part of a combination chemotherapy regimen. • A randomized trial (NO16966), initially designed as a two-arm, non-inferiority study evaluated XELOX vs. FOLFOX4 (modified leucovorin, 5FU, oxaliplatin) as first-line therapy in metastatic CRC (Cassidy 2008, Cassidy 2011). The study was subsequently amended to a 2x2 factorial design with further randomization to bevacizumab or placebo. The capecitabine in the XELOX regimen of this study was dosed at 1,000 mg/m2 twice daily given for 14 days of a 3-week cycle. • FOLFOX4 is currently used as a standard of care treatment option, and therefore is a reasonable comparator arm. • Total enrollment in NO16966 was 2034 patients; 634 and 1400 patients enrolled before and after protocol amendment, respectively. The primary endpoint of the study was PFS with a margin for noninferiority set at ≤ 1.23, corresponding to retention of at least 50% of the benefit that oxaliplatin plus FU/LV has shown over FU/LV alone in the first-line treatment of metastatic CRC (Cassidy 2008, Cassidy 2011). • NO16966 met its primary endpoint of demonstrating non-inferiority of XELOX vs. FOLFOX4 (HR, 1.04; 97.5% CI, 0.93 to 1.16). OS was a key secondary efficacy end point, although the study was not powered for OS so this was considered exploratory. The HR for	Capecitabine monotherapy is indicated as first line treatment of patients with metastatic colorectal cancer. Since the approval of monotherapy capecitabine for use in colorectal cancer, additional data now also demonstrates the benefit of capecitabine used as a component of a combination chemotherapy regimen for patients with metastatic colorectal cancer. XELOX has demonstrated non-inferiority for PFS to a SOC regimen, FOLFOX4. FOLFOX4 is a reasonable comparator arm to use for this non-inferiority study, as it is considered a clinical standard of care treatment. The dosages for monotherapy use and combination chemotherapy use differ and are each supported by the respective clinical trials that also support these indications. The dosing information in the capecitabine USPI was updated to reflect the dosing for the XELOX regimen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	OS was 0.99 (97.5% CI, 0.88 to 1.12) (Cassidy 2008, Cassidy 2011). • Exploratory subgroup analyses of XELOX vs. FOLFOX4 without bevacizumab were supportive of the primary endpoint results, demonstrating that the median PFS in the XELOX and FOLFOX4 arms without bevacizumab were similar. OS was also similar for XELOX (19.8 months) and FOLFOX4 (19.6 months) (Cassidy 2008, Cassidy 2011). • While the overall rates of grade 3/4 adverse events were fairly similar with both XELOX and FOLFOX4, grade 4 adverse events were less common with XELOX (25% and 12%, respectively); this difference was predominantly due to grade 4 neutropenia (Cassidy 2008, Cassidy 2011). XELOX was associated with higher rates of grade 3 diarrhea and hand-foot syndrome, which are known adverse events already included in section 5 of the XELODA USPI.	
Risk and Risk Management	• The known and currently labeled major adverse events for capecitabine in metastatic colon cancer include anemia, diarrhea, hand-foot syndrome, hyperbilirubinemia, nausea, fatigue, and abdominal pain. • No new safety signals emerged for capecitabine in NO16966. The toxicities attributable to capecitabine were consistent with the drug's known safety profile. The higher grades of diarrhea and hand-foot syndrome reported for XELOX are expected.	The safety profile attributable to capecitabine in the XELOX regimen for treatment of metastatic colon cancer is acceptable for the intended population, and is manageable with current labeling. Diarrhea and hand-foot syndrome are included under Warnings and Precautions. No risk evaluation and mitigation (REMS) is indicated at this time.

The Applicant's Position

The Applicant agrees with all FDA proposed updates as outlined in the subsection 2.1 Colorectal Cancer.

The FDA's Assessment

The FDA agrees with the Applicant's position.

NO16968 [NCT00069121] was an adequate and well-controlled multicenter, open-label, randomized trial based on a critical evaluation of the stated methods from the published literature. The clinical meaningfulness and objectivity of disease-free survival as the major efficacy outcome measure and the observed results provides confidence in the effect demonstrated. This trial is supported by a well-established safety profile and mechanism of action, with confirmatory evidence of anti-tumor effects of capecitabine demonstrated in clinical trials across other cancer types. Within this context, the review team's determination is that there is substantial evidence of effectiveness of capecitabine in combination with oxaliplatin for the adjuvant treatment of patients with stage III colon cancer as a component of a combination chemotherapy regimen.

Rektum-III [NCT01500993] was an adequate and well-controlled multicenter, open-label, randomized, non-inferiority trial based on a critical evaluation of the stated methods from the published literature. The clinical meaningfulness and objectivity of overall survival as the major efficacy outcome measure and the observed results provides confidence in the effect demonstrated. This trial is supported by a well-established safety profile and mechanism of action, with confirmatory evidence of anti-tumor effects of capecitabine demonstrated in clinical trials across other cancer types. Within this context, the review team's determination is that there is substantial evidence of effectiveness of capecitabine for the perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy.

NO16966 [NCT00069095] was an adequate and well-controlled randomized, non-inferiority, 2x2 factorial trial, based on a critical evaluation of the stated methods from the published literature. The clinical meaningfulness and objectivity of progression free survival as the major efficacy outcome measure and the observed results provides confidence in the effect demonstrated. This trial is supported by a well-established safety profile and mechanism of action, with confirmatory evidence of anti-tumor effects of capecitabine demonstrated in clinical trials across other cancer types. Within this context, the review team's determination is that there is substantial evidence of effectiveness of capecitabine for the treatment of patients with unresectable or metastatic colorectal cancer as a component of a combination chemotherapy regimen.

2.2 Breast Cancer

XELODA is indicated for the:

- 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.

Recommended Dosage for Breast Cancer

Advanced or Metastatic Breast Cancer

Single Agent

The recommended dosage of XELODA is 1,000 mg/m^2 or 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle until disease progression or unacceptable toxicity. Individualize the dose and dosing schedule of XELODA based on patient risk factors and adverse reactions.

In Combination with Docetaxel

The recommended dosage of XELODA is is 1,000 mg/m^2 or 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle until disease progression or unacceptable toxicity in combination with docetaxel 75 mg/m^2 administered intravenously on day 1 of each cycle.

Refer to the Prescribing Information for docetaxel for additional dosing information as appropriate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The current indication for Xeloda for patients with breast cancer is: • 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	Breast cancer is a serious and life-threatening disease and is a leading cause of cancer and death in U.S. women.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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.	
Current Treatment Options	• Capecitabine's currently approved dose as monotherapy is: 1250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycle. • Capecitabine's currently approved dose in combination with docetaxel is: 1250 mg/m2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m2 total daily dose) for 2 weeks followed by a 1-week rest period given as a 3-week cycle.	• Capecitabine is currently approved for use as monotherapy or in combination with docetaxel for the treatment of patients with metastatic breast cancer at a dose of 1250 mg/m2 administered orally twice daily for 2 weeks on, 1 week off.
Benefit	• Capecitabine was initially approved in 2001 for use in combination with docetaxel based on the results of a phase 1 study, where a range of doses of docetaxel administered in 3 week cycles was combined with an intermittent regimen of capecitabine (2 weeks of treatment on, 1 week off) at a dose of 1250 mg/m2 BID. Capecitabine in combination with docetaxel resulted in statistically significant improvements in time to disease progression, overall survival, and objective response rate compared to monotherapy with docetaxel. • Capecitabine was approved in 1998 as monotherapy based on an open-label,	• Capecitabine is approved for patients with metastatic breast cancer in combination with docetaxel or as monotherapy at a starting dose of 1250 mg/m2 BID for 2 weeks on/1 week off given in 3-week cycles. • Several single arm trials have demonstrated improved safety with comparable response rates to historical control when capecitabine is administered at the lower starting dose of 1000 mg/m2 BID at the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	single-arm trial in 162 patients with stage IV breast cancer. Capecitabine was administered at a dose of 1250 mg/m2 twice daily for 2 weeks followed by a 1 week rest period given as 3-week cycles. The response rate was 25.6% (95% CI: 13.5, 41.2) and the median duration of response was 154 days (range 63-233). • Capecitabine was initially FDA approved at a dose of 1250 mg/m2 BID administered for 2 weeks followed by a 1 week off period in 3-week cycles. However, the tolerability of fluoropyrimidines varies with geographic region and patients from the United States have shown poorer tolerability than other global populations. • In several clinical trials incorporating the 1250 mg/m2 BID dose, a large proportion of patients required a 25% dose reduction (Blum 2001, Reichardt 2003, Fumoleau 2004, Miller 2005, Blum 1999). Rates of dose reduction (≥25% reduction) ranged from 27 to 65% in these trials. • In a randomized phase III trial from 34 centers between July 2001 and June 2005 in the first line metastatic breast cancer setting, 325 women were randomized to capecitabine 1000 mg/m2 BID for 14 of 21 days administered intermittently (n=107), capecitabine 650 mg/m2 BID for 21 of 21 days administered continuously (n=107), or CMF (cyclophosphamide, methotrexate, and 5-FU) administered on days 1 and 8 every 28 days (n=109) (Stockler 2011). The primary endpoint was quality-adjusted PFS, and OS and ORR were secondary endpoints. Intermittent and continuous capecitabine were to be compared first, and if found to be similar, combined for	same schedule as the approved dose. • A randomized phase III study using CMF as an active control arm provides supportive evidence of the efficacy of capecitabine at 1000 mg/m2 BID and fewer serious adverse events compared to CMF. Only 10% of patients (11 out of 107) on the study attempted dose escalation to 1250 mg/m2, and 6 out of the 11 patients experienced adverse events within 2 cycles requiring subsequent dose reduction. • There are no randomized clinical trial data directly comparing the 1250 mg/m2 BID dose to the 1000 mg/m2 BID dose and it is unlikely that such a trial would proceed due to a perceived lack of equipoise. However, evidence across several independently conducted clinical trials, including single arm trials comparing safety and objective response rate to historical control, and randomized trials incorporating the 1000 mg/m2 BID dose, support the improved safety of the lower dose with no clear or substantive loss of efficacy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	comparison to CMF. Median follow up was 3.3 years. Baseline characteristics were balanced between the 3 treatment arms. Objective response rate was similar between the three arms (capecitabine 1000 mg/m2 22%, capecitabine 650 mg/m2 20%, CMF 18%). PFS was similar between capecitabine 1000 mg/m2 and 650 mg/m2 (HR 0.97, 95% CI 0.73-1.28, median 6 mo both arms). PFS was also similar between capecitabine combined and CMF (HR 0.86, 95% CI 0.67-1.10, median 6 mo both arms). Quality-adjusted PFS was similar between capecitabine combined and CMF (mean 8.8 vs 7.6 mo, 95% CI for difference -.07 to 3.0, p=0.20). The trial was terminated prematurely due to slow accrual. However, the OS analyses included 237 deaths (73%) among the 323 women. OS was similar between the two capecitabine arms (HR 0.86, 95% CI 0.62-1.12). When comparing OS between capecitabine combined and CMF, OS was longer in the capecitabine combined arm (HR 0.72, 95% CI 0.55-0.92, median 22 mo capecitabine vs. 18 mo CMF). Serious adverse events were less frequent in patients who received capecitabine compared to patients who received CMF (21% vs. 35%). The average duration of treatment was longer in patient who received capecitabine (12.1 cycles and 9 mo) compared to patients who received CMF (5.5 cycles or 6 mo). Patients who received capecitabine also were more likely to continue chemotherapy beyond 6 and 12 mo compared to patients who received CMF. Patients who started treatment at 1000 mg/m2 twice daily were permitted to have a dose increase to 1250 mg/m2 twice	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	daily if they did not experience adverse events after 2 cycles. Ten percent (11 out of 107) of women attempted dose escalation, with 6 women experiencing an adverse event requiring dose reduction within 2 cycles. • Two retrospective analyses have evaluated lower capecitabine starting doses in patients with breast cancer. In the first analysis that evaluated whether a lower starting dose improved tolerability without compromising efficacy in patients who had several prior treatments, a starting dose of 2000 mg/m2 per day total (equivalent of 1000 mg/m2 BID) did not have poorer response rates or shorter times to progression (Hennessy 2005). In the second analysis in the first line setting, no difference in time to treatment failure was found according to the capecitabine starting dose (Debled 2009). • Several single arm studies have evaluated a capecitabine monotherapy starting dose of 1000 mg/m2 BID and have demonstrated less toxicity (e.g., less diarrhea, vomiting, and stomatitis) compared to historical control studies. Response rates in these single arm studies were noted to be comparable to RR for the 1250 mg/m2 BID dose. The RR for capecitabine when used in combination with docetaxel or as monotherapy in patients with breast cancer are listed in the current Xeloda PI as 32% and 25.6%, respectively. In a study of 73 patients treated with capecitabine at both doses, in the 1,250 mg/m2 cohort, 11 of 30 patients achieved tumor regression (ORR 36.7% [95% CI: 19.9, 56.1]) compared to a ORR of 34.9% (95% CI: 21, 50.9) in the 43	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients receiving 1000 mg/m2 (Bajetta 2005). In a second study, among 30 evaluable patients, the 5 patients receiving the higher dose had a RR of 60% compared to a RR of 56% at the lower dose (Rossi 2007). In a third study of 57 patients receiving the 1,000 mg/m2 dose, the ORR was 28% (El-Helw 2005). In a fourth study, the ORR in 161 patients receiving the 1,000 mg/m2 dose was 26.1% (Kaufmann 2010).	
Risk and Risk Management	• The known and currently labeled major AEs for capecitabine used in combination with docetaxel in metastatic breast cancer include diarrhea, stomatitis, nausea, vomiting, alopecia, edema, and abdominal pain. • The known and currently labeled major AEs for capecitabine administered as monotherapy in patients with metastatic breast cancer include diarrhea, hand-foot syndrome, nausea, vomiting, dermatitis, stomatitis, paresthesia, anorexia, and abdominal pain. • The currently approved 1250 mg/m2 dose of capecitabine has resulted in a high proportion of dose reductions in several clinical trials in patients with metastatic breast cancer. • Several non-randomized studies have supported improved tolerability of the lower starting dose of capecitabine at 1000 mg/m2 as evidenced by less diarrhea, vomiting, and stomatitis, compared to the 1250 mg/m2 dose.	The safety profile attributable to capecitabine at a dose of 1250 mg/m2 BID results in a high proportion of dose reductions in trials of patients with metastatic breast cancer. The lower starting dose of 1000 mg/m2 BID appears to improve tolerability, as evidenced by lower rates of key toxicities.

The Applicant's Position

The Applicant agrees with all FDA proposed updates as outlined in the subsection 2.2 Breast Cancer.

The FDA's Assessment

The FDA agrees with the Applicant's position.

FDA reviewed evidence in the published literature on the safety and tolerability of a starting dose of 1,000 mg/m^2 for patients with advanced or metastatic breast cancer. The FDA review team's determination is that there is substantial evidence of safety and tolerability of Xeloda starting dose of 1,000 mg/m^2 for patients with advanced or metastatic breast cancer.

FDA proposed this labeling update and sent the benefit/risk table above to the Applicant on October 7, 2022 as an Information Request. The Applicant submitted their response to the NDA on October 17, 2022, agreeing to FDA's proposal.

2.3 Gastric, Esophageal, or Gastroesophageal Junction Cancer

XELODA is indicated for the:

- 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.

Recommended Dosage for Gastric Cancer, Esophageal, or Gastroesophageal Junction Cancer

The recommended dosage of XELODA for unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer is:

- 625 mg/m^2 orally twice daily on days 1 to 21 of each 21-day cycle for a maximum of 8 cycles in combination with platinum-containing chemotherapy.

OR

- 850 mg/m^2 or 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle. Individualize the dose and dosing schedule of XELODA based on patient risk factors and adverse reactions.

The recommended dosage of XELODA for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma is 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with cisplatin and trastuzumab.

Refer to the Prescribing Information for agents used in combination for additional dosing information as appropriate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cancers of the esophagus and stomach combined account for approximately 2.5% of all cancers diagnosed in the United States, with an estimated lifetime risk of 0.5% and 0.8% for developing esophageal and stomach cancers, respectively (Siegal 2020b). • Globally, the epidemiology of gastroesophageal cancers show wide geographic variability (Bray 2018); and trends may further vary by histologic subtype (i.e., squamous cell carcinoma [SCC] or adenocarcinoma) (Torre 2016). • Since 2000, the incident rate for both cancers in the US has declined overall. The decline for stomach cancer is more evident, from ~9 to ~7 per 100,000 (Siegal 2020b). While the overall incidence of esophageal cancer has declined, from 4.5 to ~4.0 per 100,000, rates of esophageal adenocarcinoma and GEJ adenocarcinoma are rising. In the US, esophageal adenocarcinoma is now more common than SCC, with a roughly a 6:4 distribution (Siegal 2020b). • The 5-year relative survival for esophageal cancer is ~20%, it is slightly better for stomach cancer at 32%. Prognosis for advanced or metastatic disease for these cancers are uniformly dismal with only ~5% of patients surviving through 5 years. Collectively, these cancers represent about 4.5% of all cancer deaths in the US (Siegal 2020b).	Cancers of the esophagus, GE junction and stomach are serious and life-threatening conditions. Although survival has improved over the decades, majority of patients are still diagnosed with either inoperable or metastatic disease, where the prognosis remains poor. Additionally, patients with advanced/metastatic stage are commonly symptomatic from their disease, negatively impacting quality of life and limiting their treatment options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Generally, systemic therapy for inoperable advanced or metastatic esophageal and gastroesophageal junction (GEJ) adenocarcinoma, squamous cell carcinoma (SCC) of the esophagus and gastric adenocarcinoma may be used interchangeably. • Currently, there is no systemic treatment for advanced/metastatic disease that can be considered as the standard, but some regimens are preferred over others. Regimen choice is made in the context of patient's comorbidities and performance status, as well as treatment toxicity profile. For patients who are younger or with limited comorbidities or with good performance status and can be evaluated frequently for toxicity, 3-drug cytotoxic regimen are utilized while those patients who are frail or have limited access to health services, a 2-drug cytotoxic regimen is preferred to avoid excessive toxicity. • Prior to the late 1990's, chemotherapy for advanced disease in these upper GI cancers was based on cisplatin alone because comparable response rates could be obtained with the single-agent with less toxicity. Platinum doublet with cisplatin and fluorouracil (CF) was established as a standard of care for patients with esophageal cancer based on trial results where the combination was compared to cisplatin alone, with improvement in response rates of ~16% for platinum doublet chemotherapy (Bleiberg 1997). Although patients from this study all had esophageal SCC, results were extrapolated in practice to esophageal adenocarcinoma including of the GEJ.	There is an unmet medical need to improve the outcomes of patients with locally advanced or metastatic esophageal, GEJ and gastric cancers. No definite systemic regimen has been established as the standard of care but several treatment options exist which provide clinically meaningful benefit to patients, including improvements in OS. However, improvement of outcomes from these regimens may come at the cost of greater toxicity. Treatment regimens which may lead to greater toxicity, such as 3-drug cytotoxic chemotherapy, are generally reserved for patients who are medically fit and can be evaluated frequently and promptly managed for toxicity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Efforts to increase efficacy of platinum doublet focused on the addition of a third cytotoxic agent. Moreover, these studies tended to focus on adenocarcinoma, enrolling patients with either GEJ or gastric adenocarcinoma. For instance, the triplet regimen, docetaxel + cisplatin + 5FU (DCF), was compared to CF chemotherapy in the phase III portion of Study V-325, which enrolled ~2% of patients with histology other than adenocarcinoma (Van Cutsem 2006). The study met its primary endpoint of time-to-progression (5.6 vs 3.7 months, respectively; HR 0.68; p<0.001) but this was at the cost of increased toxicity (69% vs 59% grade 3/4 toxicities, respectively). Nonetheless, DCF is used in medically fit patients because it improved OS (HR 0.77; p=0.02). • Another way to improve outcomes from doublet chemotherapy was to add a biologic/targeted agent. This strategy, however, is generally reserved for select patients with known biologic targets such as patients with human epidermal growth factor receptor 2 positive (HER2+) gastric or GEJ adenocarcinoma.	
Benefit	• Single agent capecitabine has demonstrated activity as measured by response rates ranging from 6% to 32% in phase II pilot studies (Hong 2004, Koizumi 2003, Sakamoto 2006).Based on favorable findings from CRC, the North Central Cancer Treatment Group (NCCTG) conducted a phase 2 study investigating the utility of oxaliplatin plus capecitabine as first-line therapy in patients with metastatic adenocarcinoma of the esophagus, GEJ, and gastric cardia (Jatoi 2006). Patients	REAL-2, a large phase 3 randomized trial that isolated the effect of capecitabine compared to a backbone of triplet chemotherapy, met its primary endpoint demonstrating that switching capecitabine for fluorouracil in a triplet chemotherapy backbone results in non-inferior OS. Although adenocarcinoma was the major tumor histology, there was a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	were treated with oxaliplatin 130 mg/m^2 IV on day 1 and capecitabine 1000 mg/m^2 orally twice a daily on days 1–14, of a 21-day cycle. However, due to treatment-related deaths, the capecitabine starting dose was modified to 850 mg/m^2. Of the 43 patients evaluable for tumor response, ORR was 35% (95% CI 23% to 50%), all assessed to be partial responses. Median duration of response was 3.9 months (range 2.3–11.1). • In REAL-2, 1,002 patients with previously untreated metastatic or unresectable esophageal cancer, GEJ or gastric adenocarcinoma were randomized to epirubicin, cisplatin, fluorouracil (ECF) or variations of it, substituting fluorouracil for capecitabine or cisplatin for oxaliplatin (i.e., epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + 5FU [EOF], and epirubicin + oxaliplatin + 5FU [EOX]) (Cunningham 2008). All three tumor sites were represented equally with the majority having adenocarcinoma histologic subtype; however, there were between 7 – 12% of patients with SCC in each treatment. • REAL-2 was designed as a non-inferiority (NI) study with a predefined margin of 1.23 for a 2x2 comparison of the triplet combinations containing capecitabine vs. fluorouracil and oxaliplatin vs. cisplatin; the primary endpoint was OS (Cunningham 2008). In the 964 per protocol population, results showed that capecitabine containing triplet regimen were non-inferior to those containing fluorouracil. The HR for death in the capecitabine groups was 0.86 (95% CI, 0.80 to 0.99) with the upper limit of the	fair representation of SCC among patients with esophageal cancer. Furthermore, in REAL-2, although conducted outside of the US (i.e., UK and Australia), characteristics of the patients enrolled appeared to be similar to US patients diagnosed with these malignancies. The evidence of efficacy for use of capecitabine in this setting comes from this non-inferiority trial evaluating triplet regimens. However, there are concerns regarding the safety of these regimens in many patients. Limited data on capecitabine-containing doublet chemotherapy demonstrates durable response rate, and when considering the significant added toxicity of triplet therapy, it is reasonable to include the option of doublet capecitabine-containing chemotherapy as one that provides benefit to patients with a more tolerable toxicity profile. Patients with metastatic adenocarcinoma of the gastroesophageal junction or stomach may derive clinical benefit from a response to chemotherapy, as responses in critical anatomic regions such as the stomach and GE junction may improve key functional

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	95% CI well below the non-inferiority margin. The median survival and 1-year survival rate for capecitabine as compared with fluorouracil were 10.9 months versus 9.6 months and 44.6% (95% CI, 40.1 to 49.0) versus 39.4% (95% CI, 35.0 to 44.0), respectively. • The capecitabine dose in REAL-2 was initially 500 mg/m2 BID (1000 mg/m^2 daily) and was escalated to 625 mg/m2 BID (1250 mg/m2 daily) after 80 patients had been recruited, with safety of the dose escalation confirmed after 204 patients (Cunningham 2008). There were no formal stopping rules or formal review of the primary end point after each review. • An alternative dose of 850 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle is supported by phase 2 trials which combine capecitabine with oxaliplatin as a doublet chemotherapy (e.g., CapeOx), with delivered doses of capecitabine ranging from 850 – 1000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle(Jatoi 2006, Kim 2012, Bang 2010).	abilities (e.g. swallowing, oral intake, etc.). The NCCTG study, which was a single arm trial of a doublet regimen, is viewed as lower level of evidence but generally supportive. A limitation of this study is that it did not isolate the effect of capecitabine and had limited number of patients, however multiple trials of single agent capecitabine have demonstrated its anti-tumor activity. Multiple dosing regimens are supported for capecitabine depending on the combination regimen used. Taking the available evidence into consideration, the conclusion of the review team is that capecitabine, either as a doublet with oxaliplatin or as part of a triplet cytotoxic regimen, has an acceptable benefit/risk profile for first-line treatment of advanced/metastatic esophageal carcinoma, or GEJ and gastric adenocarcinoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	HER2-positive disease • Capecitabine use in patients with HER2-overexpressing metastatic adenocarcinoma of the gastroesophageal junction or stomach in combination with cisplatin and trastuzumab is supported by the ToGA trial (Bang 2010). In this randomized, Phase III trial, the addition of trastuzumab to combination chemotherapy (cisplatin plus either fluorouracil [FP] or capecitabine [XP]) improved OS compared to chemotherapy doublet (HR 0.74; 95% CI 0.60 – 0·91, p=0.0046). • The dose of capecitabine in the ToGA trial was 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity (Bang 2010). • This indication and dosage regimen is currently included in the trastuzumab label.	**HER2-positive disease** In patients with metastatic adenocarcinoma of the stomach or GE junction whose tumors overexpress HER2, the addition of trastuzumab to capecitabine (or 5FU) plus cisplatin is recommended. It represents standard of care as first-line treatment for this patient subset as this strategy has been shown to improve OS.
Risk and Risk Management	• Of the 46 patients who received chemotherapy in the NCCTG trial, common (>10%) grade 3/4 non-hematologic AEs included nausea, diarrhea, vomiting, abdominal pain, anorexia, fatigue, dyspnea, dehydration, and hypokalemia (Jatoi 2006). • In REAL-2, as compared to the ECF group more frequent grade 3/4 toxicities noted were neutropenia (~52%) and hand–foot syndrome (~10%) in the ECX group, stomatitis (4.4%) in the EOF group and lethargy in the EOX (~25%) group (Cunningham 2008). Grade 1/2 elevations in creatinine occurred in each group ranging from 7.9% in the EOX group to 16.5% in the ECX group, as compared to 19.2% in the ECF group. The overall rate of thromboembolic events was 11.4% (95%	The safety profile of capecitabine in combination with other cytotoxic agents, either as a platinum doublet or triplet regimen, with or without trastuzumab is acceptable for the intended population, and is manageable with current labeling. Myelosuppression, diarrhea and hand-foot syndrome are included under Warnings and Precautions. No REMS is indicated at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	CI, 9.4 to 13.4), but did not differ significantly between the groups receiving capecitabine and those receiving fluorouracil (10.4% vs. 12.4%, P = 0.33). • In ToGA, the addition of trastuzumab did not significantly alter the toxicity profile of chemotherapy, including for capecitabine (Bang 2010). The most common adverse events in the trastuzumab plus chemotherapy vs. chemotherapy alone, respectively were nausea (67% vs 63%), vomiting (50% vs 46%), and neutropenia (53% vs 57%). Rates of overall grade 3 or 4 adverse events and cardiac adverse events did not differ between groups at 68% and 6%, respectively.	

The Applicant's Position

The Applicant agrees with all FDA proposed updates outlined in the subsection 2.3 Esophageal, Gastroesophageal Junction, and Gastric Cancer.

The FDA's Assessment

The FDA agrees with the Applicant's position. The indication and dosage and administration language that specifies the indication has been updated to reflect the disease entity rather than the anatomic location of the disease.

REAL-2 was an adequate and well-controlled randomized, non-inferiority, 2x2 factorial trial, based on a critical evaluation of the stated methods from the published literature. The clinical meaningfulness and objectivity of objective response rate as the major efficacy outcome measure and the observed results provides confidence in the effect demonstrated. This trial is supported by a well-established safety profile and mechanism of action, with confirmatory evidence of anti-tumor effects of capecitabine demonstrated in clinical trials across other cancer types. Within this context, the review team's determination is that there is substantial evidence of effectiveness of capecitabine for treatment of adults with unresectable or metastatic cancer of the esophagus, gastroesophageal junction, and stomach as a component of a combination chemotherapy regimen.

ToGA was an adequate and well-controlled multicenter, randomized, open-label trial, based on a critical evaluation of the stated methods from the published literature. The clinical meaningfulness and objectivity of overall survival as the major efficacy outcome measure and the observed results provides confidence in the effect demonstrated. This trial is supported by a well-established safety profile and mechanism of action, with confirmatory evidence of anti-tumor effects of capecitabine demonstrated in clinical trials across other cancer types. Within this context, the review team's determination is that there is substantial evidence of effectiveness of capecitabine for the treatment of adults with HER2-overexpressing metastatic adenocarcinoma of the gastroesophageal junction or stomach who have not received prior treatment for metastatic disease as a component of a combination regimen.

2.4 Pancreatic Cancer

XELODA is indicated for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.

Recommended Dosage for Pancreatic Cancer

The recommended dosage of XELODA is 830 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle until disease progression, unacceptable toxicity, or for a maximum 6 cycles in combination with gemcitabine 1,000 mg/m^2 administered intravenously on days 1, 8, and 15 of each cycle.

Refer to Prescribing Information for gemcitabine for additional dosing information as appropriate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pancreatic cancer accounts for about 3% of all cancers in the United States and about 7% of all cancer deaths (Siegal 2020b). It is slightly more common in men than in women. The most common histologic subtype is adenocarcinoma, accounting for approximately 90% of all pancreatic malignancies. • Since 2000, the incident rate for pancreatic cancer has been slowly increasing from 0.6 to 1.7 per 100,000 (Siegal 2020b, Cancer.org). The lifetime risk of developing pancreatic	Adenocarcinoma of the pancreas is a serious and life-threatening condition. Diagnosis is often made at a late stage, but even patients diagnosed at an early stage and are candidates for curative surgical resection are at high risk for recurrence with high probability of dying from their disease within the next 5 years after diagnosis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cancer is approximately 1.6%. In 2020, new cases and deaths from pancreatic cancer in the US are estimated at 57,600 (3.2%) and 47,050 (7.8%), respectively (Siegal Jan 2020b, Cancer.org). • The vast majority of pancreatic cancer are diagnosed at an advanced stage; only an approximate 11% of all pancreatic cancer are localized at diagnosis (Siegal 2020b, Cancer.org). • Survival from pancreatic cancer is partly dependent on stage at diagnosis. The 5-year relative survival of pancreatic cancer diagnosed at a localized stage is approximately 39.4% (Cancer.org).	
Current Treatment Options	• Surgical resection is the only potentially curative modality for pancreatic cancer; however, the vast majority of patients (>80%) present with unresectable disease (Li 2004). • Even with the most optimal surgical resection (R0), additional therapy is required for all patients with pancreatic adenocarcinoma because recurrent rates are very high in this disease. • There is no specific systemic treatment regimen for the adjuvant treatment of pancreatic cancer. Meta-analysis supports the use of chemotherapy with fluorouracil or gemcitabine (Liao 2013). Use of post-operative gemcitabine demonstrated significant improvements in disease free survival (DFS, median 13.4 vs 6.7 months) and overall survival (OS, 5-year OS 20.7% vs 10.4%) compared to observation (Oettle 2013). When comparing	There is an unmet medical need to improve the outcomes of patients with pancreatic adenocarcinoma, even for those diagnosed at an early (resectable) stage. No definite standard has been established as the adjuvant treatment for pancreatic cancer but several treatment option exist. These provide improved outcomes in terms of DFS and/or OS. For patients of good performance status, combination chemotherapy is preferred over monotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients who received fluorouracil + leucovorin versus gemcitabine following surgery, no significant difference in OS was observed (median OS ~23 months), although gemcitabine tended to be better tolerated (Neoptolemos 2010). • Combination chemotherapy have demonstrated overall survival benefit over single-agent chemotherapy (Conroy 2011, Neoptolemos 2017). However, combination chemotherapy is often limited to patients with good performance status. • Preferred combination regimens in the adjuvant setting include 5FU + leucovorin + oxaliplatin + irinotecan (FOLFIRINOX) (Conroy 2011) or gemcitabine plus capecitabine (Neoptolemos 2010). Other contemporary chemotherapy options include gemcitabine, fluorouracil with leucovorin or continuous fluorouracil infusion.	
Benefit	• Monotherapy with capecitabine has been shown in a phase 2 study that included 42 patients with metastatic or unresectable locally advanced pancreatic cancer to provided important benefit in tumor-related symptoms and notable objective response activity in a subset of patients (ORR 9.5%; 90% CI, 3.3% to 20.5%) (Cartwright 2002), providing a rationale to further explore the role of capecitabine in pancreatic cancer. • ESPAC-4 (Neoptolemos 2017) enrolled 732 patients who had undergone	ESPAC-4 met its primary endpoint and isolated the effect of capecitabine in patients following complete resection for adenocarcinoma of the pancreas. The recommended dose of capecitabine is also supported by this trial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	complete macroscopic resection for adenocarcinoma of the pancreas (R0 or R1 resection) and were randomly assigned (1:1) to receive adjuvant gemcitabine monotherapy or gemcitabine plus capecitabine. Respectively, 366 and 364 patients (n=730) were included in the final efficacy analysis. • The dose of capecitabine used in the combination arm was 830 mg/m2 orally twice daily (=1660 mg/m^2/day) for the first 21 days of each 28-day cycle for maximum of 6 cycles (Neoptolemos 2017). • The hazard ratio (HR) for median OS is 0.82 (95% CI 0.68-0.98, p=.032). Median OS for the combination of gemcitabine + capecitabine was 28 months (95% CI 23.5-31.5) compared with 25.5 months (95% CI 22.7-27.9) in the monotherapy arm (Neoptolemos 2017). • In patients with R1 status, median OS for patients in the combination arm was 23.7 months (95% CI 20.7-27.1); median OS in patients with R0 status was 39.5 months (95% CI 32.0–58.0) (Neoptolemos 2017).	
Risk and Risk Management	• Of the 725 patients included in the ESPAC-4 safety analysis set, 608 (83.9%) experienced grade 3/4 adverse events (AEs); a higher proportion of patients reported grade 3/4 AEs (~63%) in the gemcitabine plus capecitabine arm compared to gemcitabine arm (~54%) (Neoptolemos 2017). Grade 3 or 4 neutropenia was more	The safety profile of capecitabine in combination with gemcitabine is acceptable for the intended population, and is manageable with current labeling. Myelosuppression, diarrhea and hand-foot syndrome are included under Warnings and Precautions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	common in the combination arm (38%) than in the monotherapy arm (24%). However, the rate of febrile neutropenia was low in both groups and there were fewer other infective manifestations in the combination arm (3%) compared to monotherapy arm (7%). • As expected with known toxicity profile of capecitabine, more grade 3/4 diarrhea events occurred with the addition of capecitabine (5% vs. 2%). Additionally, grade 3/4 hand-foot syndrome events occurred only with the combination arm (7%); this was generally manageable with appropriate capecitabine dose modification (Neoptolemos 2017). • Quality of life (QOL) assessments showed no significant effect in the longitudinal estimate of QOL by treatment arm (HR -0.10, 95% CI -0.29 to 0.09, p=0.3).	Physicians are well versed in the management AEs in patients treated with capecitabine-containing chemotherapy regimens.

The Applicant's Position

The Applicant agrees with all FDA proposed updates outlined in the subsection 2.4 Pancreatic Cancer.

The FDA's Assessment

The FDA agrees with the Applicant's position.

ESPAC-4 was an adequate and well-controlled multicenter, randomized, open-label, two-group trial, based on a critical evaluation of the stated methods from the published literature. The clinical meaningfulness and objectivity of overall survival as the major efficacy outcome measure and the observed results provides confidence in the effect demonstrated. This trial is supported by a well-established safety profile and mechanism of action, with confirmatory evidence of anti-tumor effects of capecitabine demonstrated in clinical trials across other cancer types. Within this context, there is substantial evidence of effectiveness of capecitabine for

treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.

3. NONCLINICAL PHARMACOLOGY/TOXICOLOGY PERTINENT TO PROPOSED LABELING

Capecitabine is a fluoropyrimidine that works as a nucleoside metabolic inhibitor.

Non-clinical pharmacology and toxicology information was revised; refer to sections 8, 12.1, 13, and subsections of 5 and 17 of the annotated product label for rationale and references, where applicable.

The Applicant's Position

The Applicant agrees with all FDA proposed updates outlined in the section 3 Nonclinical Pharmacology/Toxicology Pertinent To Proposed Labeling.

The FDA's Assessment

Refer to sections 8, 12.1, 13, and subsections of 5 and 17 for non-clinical pharmacology and toxicology updates to the labeling. The recommendation to not breastfeed was changed to 1 week after the last dose based on current OCE policy for drugs with short half-lives.

4. CLINICAL PHARMACOLOGY PERTINENT TO PROPOSED LABELING

Clinical pharmacology information in the proposed annotated labeling Sections 2, 5, 7, 8.6, 8.7 12.2, 12.3, and 12.5 were revised to conform with the Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance. Proposed clinical pharmacology-related changes and supporting published literature are provided in the proposed annotated labeling (Souglakos 2012, Guo 2014, Jackson 2009, Rosati 2010, Ramirez 2019, Diasio 1989, Diasio 1988, Thorn 2011, Morel 2006, Caudle 2013, Mattison 2006, Etienne 1994, Lu 1998, Amstutz 2018).

The Applicant's Position

The Applicant partially agrees and partially disagrees with FDA's proposed updates regarding clinical pharmacology outlined in this Section 4 CLINICAL PHARMACOLOGY PERTIENT TO PROPOSED LABELING. The clinical pharmacology information in Sections 2, 5, 7, 8.6, 8.7 12.2, 12.3, and 12.5 of the proposed annotated labeling is discussed below by section:

- Section 2 DOSAGE AND ADMINISTRATION

The Applicant agrees with all FDA proposed updates regarding clinical pharmacology outlined in Section 2 DOSAGE AND ADMINISTRATION, and provides additional information as FDA requested in subsections 2.6 and 2.7 discussed below:

Subsection 2.6 Dosage Modification for Renal Impairment

As per FDA's request for subsection 2.6 Dosage Modification for Renal Impairment, the Applicant provides the following statement for dosing in patients with severe renal impairment (refer to the tracked changes in the proposed annotated labeling).

"A dosage has not been established in patients with severe renal impairment."

Additionally, the Applicant provides a summary of information of patients with severe renal impairment in the report "Applicant's Position on XELODA - Severe Renal Impairment".

Subsection 2.7 Administration

As per FDA's recommendation for subsection 2.7 Administration, the Applicant includes the following instructions for the desired dosing interval and agrees with FDA proposed instructions for how to use the drug after a missed or vomited dose (refer to the tracked changes in the proposed annotated labeling),

"Take XELODA at the same time each day approximately 12 hours apart."

The detailed rationale to support the above instructions is provided in the report "Applicant's Position and Rationale for Proposed Text in XELODA USPI Section 2.7 Administration". In summary, the recommended instructions were made based on the rationale that patients deviating

from a 12-hour dosing interval, or from drug intake not close to a meal, have experienced gastrointestinal side effects, which led to discontinuation of treatment due to toxicity. Patients missing a dose (intentional/unintentional, vomiting) tend to compensate for the omitted dose by increasing the dose the next day or by prolonging a treatment cycle. This "over-adherence" was associated with a trend to high-grade toxicity and increased levels of the capecitabine metabolite FBAL (α-fluoro-β-alanine).

- Section 5 WARNINGS AND PRECAUTIONS

The Applicant agrees with all FDA proposed updates regarding clinical pharmacology outlined in Section 5 WARNINGS AND PRECAUTIONS.

- Section 7 DRUG INTERACTIONS

The Applicant agrees with all FDA proposed updates regarding clinical pharmacology outlined in Section 7 DRUG INTERACTIONS, except as to subsections 7.2 and 7.3 discussed below:

Subsection 7.2 Effect of XELODA on Other Drugs

The Applicant disagrees with FDA's omission of co-administration with CYP2C9 substrates, based on the rationale that clinically relevant drug interactions with CYP2C9 substrates have to be anticipated for drugs with a narrow therapeutic index in general. The Applicant therefore recommends to retain the following statement (refer to the tracked changes in the proposed annotated labeling),

(b) (4)

Subsection 7.3 Use with Nephrotoxic Products

FDA requested the Applicant to discuss in more details about interactions that are described in the “Contraindications” or “Warnings and Precautions” in subsection 7.3 Use with Nephrotoxic Products. However, as the use of nephrotoxic compounds involves an organ function change, the Applicant cannot describe "interactions". A majority of patients in the target indication groups have various degrees of pre-existing renal impairment (Launay-Vacher 2010, Janus 2010, Launay-Vacher 2009a , Launay-Vacher 2009b, Launay-Vacher 2007) and there are approved therapies commonly used in combination with XELODA that are known to be associated with nephrotoxicity (e.g. platinum salts, irinotecan, methotrexate, intravenous bisphosphonates). Therefore, physicians using such combination therapies in patients with renal impairment need to administer the combinations cautiously taking into account several factors such as the degree of underlying renal impairment, cause of renal impairment, XELODA dosage, type and dosage of the co-administered drugs, and patient's overall condition. The Applicant therefore recommends the following statement (refer to the tracked changes in the proposed annotated labeling),

(b) (4)

- Section 8 USE IN SPECIFIC POPULATIONS

The Applicant agrees with all FDA proposed updates regarding clinical pharmacology outlined in Section 8 USE IN SPECIFIC POPULATIONS, and provides additional information as FDA requested in subsections 8.6 and 8.7 discussed below:

Subsection 8.6 Renal Impairment

As per FDA’s request, the Applicant includes the following statement that there is limited experience with XELODA in patients with severe renal impairment and a dosage has not been established (refer to the tracked changes in the proposed annotated labeling). A summary of information of patients with severe renal impairment is provided in the report “Applicant’s Position on XELODA - Severe Renal Impairment”.

“There is limited experience with XELODA in patients with CLCr <30 mL/min, and a dosage has not been established in those patients. If no treatment alternative exists, XELODA could be administered to such patients on an individual basis applying a reduced starting dose, close monitoring of a patient's clinical and biochemical data and dose modifications guided by observed AEs.”

Subsection 8.7 Hepatic Impairment

As per FDA’s request, the Applicant provides a review of information on the effects of hepatic impairment on pharmacokinetics or safety, refer to the report “Applicant’s Position and Rationale for Proposed Text in XELODA USPI Section 8.7 Hepatic Impairment”. (b) (4),

(b) (4)

The Applicant therefore includes the following statement (refer to the tracked changes in the proposed annotated labeling),

(b) (4)

- Section 12 CLINCIAL PHARMACOLOGY

The Applicant agrees with all FDA proposed updates regarding clinical pharmacology outlined in Section 12 CLINICAL PHARMACOLOGY subject to other minor editorial revisions (refer to the tracked changes in the proposed annotated labeling), except as to subsection 12.3 discussed below. The Applicant also provides additional information as FDA requested in subsection 12.2, discussed below:

Subsection 12.2 Pharmacodynamics

As per FDA's request for subsection 12.2 Pharmacodynamics, the Applicant provides a summary of the analyses of capecitabine exposure-response relationships, refer to the report "Applicant's Position and Rationale for Proposed Text in XELODA USPI Section 12.2 Pharmacodynamics".

(b) (4)

(b) (4)

The Applicant therefore recommends the following statement for the subsection (refer to the tracked changes in the proposed annotated labeling),

(b) (4)

Subsection 12.3 Pharmacokinetics

- Patients with Hepatic Impairment

The Applicant disagrees with FDA's comment to include AST and bilirubin values or Child-Pugh class to define mild or moderate hepatic impairment in the subsection "Patients with Hepatic Impairment". The Child-Pugh classification was not used in Roche Study BK14822 and it was rationalized in line with literature that this classification is not appropriate in case of hepatic carcinoma/metastases. The Child-Pugh classification, based on serum albumin, BILI, prothrombin time, the degree of ascites and encephalopathy, is widely used in patients with cirrhosis. However, it has been found unsuited to patients with liver metastases and has not been shown to be reflective of the altered metabolism of cytotoxic drugs. A classification based on laboratory parameters bilirubin, SGOT/SGPT and alkaline phosphatase, was used to define the degree of hepatic dysfunction, based on the WHO grading system. Refer to detailed rationale provided in the report "Applicant's Position and Rationale for Proposed Text in XELODA USPI Section 8.7 Hepatic Impairment".

- Effect of Capecitabine on Celecoxib

The Applicant disagrees (b) (4)

The FDA's Assessment

The Applicant's proposed changes and rationales for Subsection 2.7 Administration, Section 5 Warnings and Precautions, Subsection 7.3 Use with Nephrotoxic Products are acceptable. For the rest of proposed changes and rationales regarding drug interaction for CYP2C9 substrates, renal impairment, hepatic impairment, and pharmacodynamics, FDA has the following assessments.

Additionally, editorial changes were made for all clinical pharmacology sections of the labeling, consistent with current labeling practice.

1. **Drug Interactions with CYP2C9 substrates** (Subsection 7.2 Effect of XELODA on Other Drugs and 12.3 Pharmacokinetics):

   i) Subsection 7.2 Effect of XELODA on Other Drugs:

The Applicant's proposal of keeping the paragraph with regard to CYP2C9 substrate with required editorial changes, given the safety concern due to increased drug exposure by Xeloda as CYP2C9 inhibitor is acceptable.

   ii) Subsection 12.3 Pharmacokinetics

(b) (4) celecoxib from Section 12.3 DDI clinical studies. Given that the CYP2C9 substrates are included in Section 7 DDI, a DDI clinical study should be summarized and included in Section 12.3 Pharmacokinetics.

2. **Renal Impairment** (Subsection 2.6 Dosage Modification for Renal Impairment, Subsection 8.6 Renal Impairment)

The Applicant's proposal of no dosing recommendation for severe renal impairment is acceptable given the concerning toxicities.

In the submitted report "Applicant's Position on XELODA - Severe Renal Impairment", the Applicant summarized that the original rationale of not using Xeloda in patients with severe renal impairment was due to the reported drug-related AEs, grade 3/4 AEs, and serious AEs in the following two reports:

> Poole C, Gardiner J, Twelves C, et al.: Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. Cancer Chemother Pharmacol 49(3), 225-234, 2002.
>
> Research Report No.1002932 - Final Clinical Study Report – Protocol WP15811: Effect of Renal Impairment on the Pharmacokinetics of Capecitabine in Cancer Patients. 09-October-2000.

In a recent publication regarding a retrospective study (Jhaveri 2012) in 12 patients with severe renal impairment receiving capecitabine starting dose 250 to 1000 mg/m^2 BID and closed monitoring for AEs, responses were documented in 4/12 patients:

months, respectively. Most patients reported grade 1 and 2 AEs, two patients reported grade 3 diarrhea and one patient died while on treatment with capecitabine. The capecitabine starting dose ranged from 250 to 1000 mg/m^2, given twice daily at variable intervals. Dose modifications, with reductions of up to 50% of the starting dose, were made following reports of AEs. Serum tumor marker levels and/or follow-up imaging studies were available on nine patients. Response to capecitabine was documented in four patients, stable disease in two, and disease progression in three. The study authors concluded that, with a reduced starting dose, with close monitoring of their clinical and chemical data, and with dose modification based on reported AEs, capecitabine can be safely administered to patients with severe renal impairment (CL_{Cr} <30 mL/min), including patients on hemodialysis.

In this article, the author also listed the detailed starting dose and dose modification, duration of treatment, AEs, and clinical outcomes:

Table 2. Capecitabine starting dose, dose change, adverse events, and outcomes

Patient	Initial dose (mg/m^2) 2 × day (weeks on, weeks off)	Change in dose (mg/m^2) 2 × day (weeks on, weeks off)	Total duration (months)	NCI AE (worst score)	Outcome while on capecitabine
1	1100(2,1)	825(1,2)	8	Nausea/vomiting (2) HFS (2) Fatigue (2) Diarrhea (2) Constipation (2) Cough (1)	Disease progression
2*	300(2,2)	600(2,1)	20	HFS (1) Fatigue (1) Diarrhea (2) Cough (1)	Disease progression
3	650(2,2)	No change	1	Fatigue (1) Diarrhea (1)	Disease progression
4*	1000(1,1)	700(1,1)	16	Vomiting (2) HFS (1) Diarrhea (1) Fatigue(1) SOB (1) Cough (1)	Disease progression
5	600(2,2)	300(2,2)	26	HFS (1) Fatigue (1) Diarrhea (1) Constipation (1) SOB (1)	Disease progression

6	625(2,1)	625(1,1)	5	Fatigue (2) Diarrhea (3)	Disease progression
7	660(2,1)	No change	1	Nausea (2) Herpes zoster (2) Diarrhea (3) Fatigue (1)	palliative care
8	1000(2,1)[a]	No change	1.5	Fatigue (1) Constipation (1)	Disease progression
9	750(2,1)	No change	1.5	Death (5) HFS (2) Diarrhea (2)	Death
10	850(3,1)	No change	1	Fatigue (1) Diarrhea (1) SOB (1)	Disease progression
11	250(1.4,1.6)	No change	2.5	Diarrhea (1) Fatigue (2)	Disease progression
12	600(2,1)	No change	2	HFS (1) Fatigue (1)	Disease progression

Initial dose is in mg/m^2, given twice daily (weeks on capecitabine, weeks off capecitabine).
[a]Only absolute dose given.
HFS: Hand and Foot Syndrome.
[b]Hemodialysis patient.

It is noted that in these 12 patients with severe renal impairment, a total of 9 patients had reduced starting dose, with 5/12 patients had doses reduced by ~50% (~600 mg/m^2), and 2/12 patients had doses reduced by >75% (200-300 mg/m^2). One patient at 750 mg/m^2 starting dose died and another patient at 660 mg/m^2 starting dose had grade 3 diarrhea.

Based on the Applicant provided information, no formal renal impairment study was conducted in severe renal impairment, and only a retrospective study report with limited sample size and varying starting dose was available to recommend the usage of capecitabine in patients with severe renal impairment with a reduced starting dose. FDA therefore agrees with the Applicant that the administration of capecitabine in patients with severe renal impairment is not recommended.

3. **Hepatic Impairment** (Subsection 8.7 Hepatic Impairment, Subsection 12.3 Pharmacokinetics):

Based on the information provided, the following is recommended by FDA for the labeling regarding hepatic impairment:

a. Agree NOT to use standard criteria to describe the hepatic functions in the labeling.
b. No dose adjustment is required for patients with mild to moderate HI, however, those patients should be closely monitored for toxicity due to increased drug exposure.
c. The effect of severe hepatic impairment on the safety and PK of capecitabine is not known and not provided in the labeling, with inclusion of the hepatic function criteria.

The following is the detailed consideration from FDA perspective:

a. Hepatic function criteria

The Applicant stated that the criteria of hepatic impairment could not be defined. Based on the information provided by the Applicant, the NCI criteria is applicable for the HI studies the

Applicant referenced, and potentially re-evaluation may be needed for the impact of hepatic impairment on the PK of capecitabine and metabolites. However, the Applicant provided the following additional rationale in response to FDA recommendation of using NCI criteria:

"The Xeloda studies for which this hepatic impairment recommendation is based on were conducted prior to the creation of the NCI criteria. The study authors stress that the applied criteria were defined after consultation with experts in the field. Reclassification of the patients according to a new set of criteria could lead to extensive reanalysis of the study data and then no longer reflect the opinion of the study authors. Therefore the Applicant strongly proposes not to apply retrospectively the new classification criteria."

Based on the above rationale, FDA agrees NOT to use a standard criterion to describe the hepatic function in the updated labeling.

In the Applicant submitted report "Applicant's Position and Rationale for Proposed Text in XELODA USPI Section 8.7 Hepatic Impairment", the Roche Study BK14822 (subsequently published article: Twelves et al. 1999) was re-iterated as the main justification for the PK and safety regarding mild to moderate hepatic impairment, and some additional articles The Applicant searched online for the information of severe hepatic impairment. Of note, Study BK14822 was the main evidence for capecitabine and metabolites PK investigation in patients with HI, at the time of original NDA approval.

b. Mild to Moderate HI:

The following is the currently approved labeling on drugs@FDA regarding hepatic impairment, where the general study information for BK14822 was included for "mild to moderate hepatic dysfunction":

> XELODA has been evaluated in 13 patients with mild to moderate hepatic dysfunction due to liver metastases defined by a composite score including bilirubin, AST/ALT and alkaline phosphatase following a single 1255 mg/m^2 dose of XELODA. Both $AUC_{0-\infty}$ and C_{max} of capecitabine increased by 60% in patients with hepatic dysfunction compared to patients with normal hepatic function (n=14). The $AUC_{0-\infty}$ and C_{max} of 5-FU were not affected. In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when XELODA is administered. The effect of severe hepatic dysfunction on XELODA is not known *[see Warnings and Precautions (5.11) and Use in Special Populations (8.6)]*.

In Study BK14822, patients were compared as Group 1: normal liver function, and Group 2: liver dysfunction, where all PK-evaluable patients in Group 2 had bilirubin, AST, ALT, ALP available:

Table 1 Demographic parameters of patients with normal liver function (Group 1) and patients with mild to moderate hepatic dysfunction (Group 2)

Values are given as arithmetic means (± SD) and range.

	Group 1 Patients with normal liver function (n = 17)[a]	Group 2 Patients with liver dysfunction (n = 16)[b]
Demographic data		
Age (years)	59 ± 13.9 (34–84)	62 ± 10.9 (44–84)
Weight (kg)	66.9 ± 16.8 (45–94)	67.4 ± 10.4 (44–84)
Body surface area (m^2)	1.76 ± 0.23 (1.49–2.22)	1.79 ± 0.15 (1.41–2.00)
Sex (males/females)	10/7	12/4
Race (Caucasian)	17	16
Karnofsky status (%)	85.3 ± 11.2 (60–100)	76.7 ± 11.1 (60–90)
Liver function[c]		
Hepatic dysfunction score (points)	0–2	5–9
Total BILI (μmol/liter)	12 ± 5.9 (4–27)	112 ± 153 (16–485)
AST (IU/liter)	39.5 ± 41.9 (6–171)	107 ± 34.1 (46–174)
ALT (IU/liter)	27.1 ± 15.4 (7–58)	112 ± 94.0 (19–341)
AP (IU/liter)	231 ± 150 (76–511)	1816 ± 1096 (370–3233)

[a] Evaluated for pharmacokinetics n = 14.
[b] Evaluated for pharmacokinetics n = 13.
[c] Patients evaluated for pharmacokinetics.

Table 2 Individual values of the liver function tests and corresponding score in the 13 patients included in the hepatic dysfunction group

Patient no.	BILI (μmol/liter)	AP (units/liter)	ALT (units/liter)	AST (units/liter)	Albumin g/liter	Prothrombin time (s)	Score
(b) (6)	29	1449	37	135	40	16	6
	487	1269	140	63	40	33	8
	33	2271	38	50	38	16	5
	22	1680	111	99	43	14	5
	11	1995	123	97	34	16	5
	45	3360	52	78	40	16	6
	19	658	53	153	39	16	5
	28	688	189	84	30	17	5
	349	963	53	90	29	14	9
	270	307	27	167	6	14	8
	36	761	52	101	32	13	6
	19	2106	116	90	41	13	5
	120	3433	206	157	37	16	9

PK of mild to moderate HI: The AUC and Cmax of 13 PK-evaluable patients with hepatic impairment was compared to 14 PK-evaluable patients with normal hepatic function:

Table 4 Statistical analysis of the effect of hepatic dysfunction on the primary and secondary kinetic parameters of capecitabine and its metabolites after a single oral administration of 1255 mg/m^2 capecitabine using the log transformation

Parameter and analytes	Backtransformed least squares means		Change (%)		Test for group difference, P
	Normal hepatic function	Hepatic dysfunction	Estimate	95% CI	
$AUC_{0-\infty}$					
Capecitabine	7.25	10.7	48.2	−3.95–128.6	0.073
5′-DFCR	14.1	9.16	−35.2	−52.6–−11.3	0.009
5′-DFUR	11.7	14.0	19.5	−4.08–48.9	0.108
5-FU	0.53	0.61	15.1	−12.95–52.2	0.310
FBAL	51.1	63.2	23.6	−22.9–98.2	0.353
C_{max}					
Capecitabine	3.95	5.91	49.5	−15.6–164.7	0.160
5′-DFCR	5.02	3.53	−29.8	−52.6–4.07	0.076
5′-DFUR	4.64	6.19	33.4	−8.95–95.4	0.133
5-FU	0.22	0.28	28.3	−18.8–102.9	0.272
FBAL	6.22	6.74	8.28	−17.8–42.6	0.557

Results showed that in patients with hepatic impairment, capecitabine, 5-DFUR, 5-FU, and FBAL exposures all increased, while 5-DFCR exposure decreased where relevant PK information for capecitabine and metabolites have been included in the labeling.

Safety of mild to moderate HI: In Study BK14822, no clinically relevant differences of TEAEs were noted between the two patient groups with and without hepatic dysfunction. In group 1 (normal hepatic function), 11 (65%) patients reported 6 mild, 19 moderate, and 5 severe TEAEs. Three of these adverse events were possibly, and 2 were probably, related to trial medication. In group 2 (hepatic impairment), 6 (43%) patients experienced 9 mild, 3 moderate, and 2 severe events. Five of these events were probably related to trial medication. No life-threatening adverse reactions were observed. In both of the treatment groups, the most frequently reported adverse events were vomiting, followed by nausea, abdominal pain, and fatigue. No patient was withdrawn from the study because of laboratory abnormalities.

However, the Applicant concluded the study sample was too small to draw definite conclusions or to assess the independent effect of liver dysfunction on AEs.

The Applicant also cited some later published articles where all recommended that patients with hepatic impairment do NOT need a priori dosage adjustment. However, the Applicant also clarified that these articles all tend to cite the original study BK14822.

Based on the information provided by the Applicant, FDA agrees that no dose adjustment is required for patients with mild to moderate HI, however those patients should be closely monitored for toxicity due to increased drug exposure.

c. Severe HI:

In the currently published labeling on drugs@FDA regarding hepatic impairment, the following language was included for "severe hepatic dysfunction":

The effect of severe hepatic dysfunction on XELODA is not known.

In the current submission, the Applicant cited several published articles where capecitabine was administered in patients with cancer. The limited data showed that capecitabine has been used on an individual basis in patients with severe HI (<5 patients in total), appears to be tolerable.

Given the limited data for severe HI, FDA agrees with the Applicant to include the statement that the effect of severe hepatic impairment on the safety and PK of capecitabine is not known in the labeling, with inclusion of the hepatic function criteria.

4. **Pharmacodynamics** (Section 12.2 Pharmacodynamics)

FDA agrees with including the positive relationship for AUC(5-FU) and G3/4 hyperbilirubinemia. FDA disagrees (b) (4)

In the submitted report "Applicant's Position and Rationale for Proposed Text in XELODA USPI Section 12.2 Pharmacodynamics", the Applicant's main justification was based on Roche conducted population PK/PD analysis of capecitabine and major metabolites, which was considered "most comprehensive":

Gieschke et al., 1998: Relationships between metrics of exposure to Xeloda and occurrence of adverse effects.

Gieschke et al., 2002: Population pharmacokinetic analysis of the major metabolites of capecitabine.

Gieschke et al., 2003: Population pharmacokinetic analysis of the major metabolites of capecitabine.

Among the above 3 articles, the Gieschke et al., 2003 publication utilized clinical data from a total of 481 patients with advanced or metastatic colorectal cancer from 2 Phase III studies. In the article, exposure-response analysis for both efficacy and safety were reported.

(b) (4)

Based on the above consideration, FDA recommended NOT to include the (b) (4)

b. E-R for Safety:

Regarding the positive relationship for AUC(5-FU) and G3/4 hyperbilirubinemia, the following discussion was noted in the article:

"Since 5-FU is the active metabolite and hyperbilirubinemia has been reported after administration of other fluoropyrimidines, such a relationship with AUC of 5-FU may be expected.

With less 5-FU there is less chance of toxicity, which would result in a lower probability of hyperbilirubinemia. The findings from the combined data were consistent with the results seen for each study independently."

The results and discussions are acceptable. FDA agrees with the statement of positive relationship for AUC(5-FU) and G3/4 hyperbilirubinemia.

iii) Subsection 12.5 Pharmacogenomics

Patients treated with 5-FU and its oral prodrug capecitabine may experience early-onset toxicity, which may include serious, life-threatening GI symptoms and neutropenia. Pharmacokinetic studies have linked the risk of 5-FU-related toxicity to a reduction in 5-FU clearance (Innocenti, 2020). The enzyme dihydropyrimidine dehydrogenase (DPD) catalyzes the first, rate-limiting step of 5-FU catabolism, converting approximately 80% of 5-FU to its inactive metabolite (Falvella, 2015). Genetic variation in *DPYD*, the gene encoding DPD, can lead to partial to complete absence of DPD activity (partial to complete DPD deficiency, respectively), resulting in increased 5-FU exposures, and consequently increasing the risk of treatment-related toxicities.

In White populations, complete and partial DPD deficiency have been estimated to be approximately 0.2%, and 3-5%, respectively (Morel, 2006). DPD deficiency is estimated to be approximately 8% in Black or African American populations (Mattison, 2006). Of note, these frequencies can vary with the method used to determine DPD status and may be underestimated. Insufficient information is available to estimate the prevalence of DPD deficiency in other populations.

DPYD variants can exhibit racial/ethnic diversity, although variation is not well defined (White, 2021). Four *DPYD* variants have been consistently associated with impaired DPD activity in White individuals with European ancestry, especially when present as homozygous or compound heterozygous variants: *DPYD**2A (c.1905+1G>A), *DPYD**13 (c.1679T>G, p.I560S), c.2846A>T (p.D949V) and c.1129–5923C>G (Haplotype B3). The variant c.557A>G (p.Y186C) was associated with a reduction in DPD activity in African American individuals (Amstutz, 2017; Saif, 2014; Offer 2013). It is important to note that the listing is not complete. Also, the absence of known *DPYD* variants does not exclude the risk for toxicity, as other factors, such as additional uncharacterized *DPYD* variants, variants in genes encoding other drug metabolizing enzymes, and clinicodemographic characteristics, may also contribute to 5-FU-related toxicity.

5. SAFETY PERTINENT TO PROPOSED LABELING

Existing safety data was reviewed and any proposed safety-related changes and supporting published literature are provided in the proposed annotated labeling.

Substantive changes to the safety sections of the XELODA labeling include the following.

- The following changes were made to the Warnings and Precautions (W&P) section:
  - This section was reordered to reflect the relative clinical significance of the adverse reactions.
  - Titles of some W&P were renamed for clarity.
  - A W&P was added to describe risks associated with crushing the tablets.
- Adverse Reactions listed the most clinically significant ARs and indicated where (i.e., specific section) more detailed information about these ARs are found in labeling.

The Applicant's Position

The Applicant agrees with all FDA proposed updates regarding safety subject to other minor editorial revisions (refer to the tracked changes in the proposed annotated labeling), except as to subsections 2.5 and 4.2 discussed below. The Applicant recommends replacement of the word (b) (4) with "serious" in subsection 5.2 and provides the rationale below. The Applicant also provided FDA requested information in subsections 5.10, 8.1, 8.2, 8.5 and 8.6, discussed below:

- Section 2 DOSAGE AND ADMINISTRATION

Subsection 2.5 Dosage Modifications for Adverse Reactions

The Applicant disagrees with FDA's proposed removal of "General" statement in subsection 2.5 Dosage Modifications for Adverse Reactions. The information currently provided in the "General" statement might not be universally available as it provides important information to not increase a dose, once it has been reduced. XELODA dosage may need to be individualized to optimize patient management. Toxicity due to XELODA administration may be managed by symptomatic treatment, dose interruptions and adjustment of XELODA dose. Therefore, the Applicant recommends retaining the following statement,

(b) (4)

The Applicant agrees with FDA's proposed recommendations for dosage modifications in subsection 2.5 Dosage Modifications for Adverse Reactions, Table 1, that also applies to specific

adverse reactions in Section 5 WARNINGS AND PRECAUTIONS, with the following additional considerations:

- Hyperbilirubinemia: the approved label text in Section 5 WARNINGS AND PRECAUTIONS recommends that patients who experience Grade 3-4 hyperbilirubinemia may resume treatment when bilirubin level is <3 x ULN (corresponding to Common Terminology Criteria for Adverse Events [CTCAE] Grade 2 Blood bilirubin increased), whereas the new instructions in Table 1 recommend withholding treatment until the ADR is Grade 0-1 (corresponding to bilirubin <1.5 x ULN). The Applicant therefore recommends adding the following statement in subsection 2.5, below Table 1:

  "*Patients with Grade 3-4 hyperbilirubinemia may resume treatment once the event is Grade 2 or less (<3 x ULN), using the percent of current dose as shown in column 3 of Table 1*".

- Increased risk of serious adverse reactions with partial or absent dihydropyrimidine dehydrogenase (DPD) activity: The Applicant recommends adding the following statement in subsection 2.5, below Table 1:

(b) (4)

- Section 4 CONTRAINDICATIONS

Subsection 4.1 Severe Renal Impairment

The Applicant agrees with FDA's proposed removal of severe renal impairment in subsection 4.1. In addition, as per FDA's request, the Applicant provides an additional statement in subsections 8.6 Renal Impairment that there is limited experience with XELODA in patients with severe renal impairment and a dosage has not been established in patients with severe renal impairment (refer to the Applicant's Position in Section 4).

Subsection 4.2 Hypersensitivity

The Applicant disagrees [redacted] (b) (4)

[redacted] (b) (4)

Therefore, the Applicant recommends [redacted] (b) (4) (refer to the tracked changes in the proposed annotated labeling). The recommended statement is as follows:

[redacted] (b) (4)

- Section 5 WARNINGS AND PRECAUTIONS

Subsection 5.2 Increased Risk of Serious Adverse Reactions with Partial or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity

The Applicant recommends to replace "severe" with "serious", which is the term used in the heading of this section 5.2 Increased Risk of Serious Adverse Reactions with Partial or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity and earlier in the same paragraph, as well as for the purpose of consistency with the other sections in the USPI. Although similar, the term "severe" is defined specifically by CTCAE to indicate adverse events that are Grade 3 or higher with the grading scale specific to each individual event, and is most often applied in clinical trials, whereas "serious" is a more general designation that can be applied to any adverse events associated with high risk to patient (e.g. events with fatal outcome, life-threatening events, events resulting in hospitalization, events that require intervention to prevent permanent impairment, congenital abnormalities, etc.).

Subsection 5.10 Hyperbilirubinemia

The Applicant provides additional consideration regarding dosage modification in the subsection 5.10 Hyperbilirubinemia. The rationale and recommendation are presented in the previous discussion of subsection 2.5 Dosage Modifications for Adverse Reactions. The Applicant therefore recommends adding the following statement in subsection 5.10 Hyperbilirubinemia:

> *"Patients with Grade 3-4 hyperbilirubinemia may resume treatment once the event is Grade 2 or less (<3 x ULN), using the percent of current dose as shown in Table 1 [see Dosage and Administration (2.5)]."*

- Section 6 Adverse Reactions

Subsection 6.1 Clinical Trial Experience

As per FDA's request, the Applicant removed less common adverse reactions (ARs) that are unlikely to have been caused by XELODA, revised the less common AR list in the Pooled Safety Population, and revised the categories in alphabetical order in this subsection 6.1 Clinical Trial Experience.

The Applicant removed the less common ARs that are unlikely to have been caused by XELODA per FDA's comment [W102] in the subsection 6.1. The Applicant removed terms for less common ARs that meet one or more of the following criteria:

1. Adverse drug reaction (ADR) terms reported only in patients receiving combination therapy (i.e. not reported in patients receiving monotherapy), either verbatim or with a medically similar term, at the data cut-off (30 April 2001) for the original list of terms.
2. Causal role of therapy is highly implausible (although all events were classified originally by study investigators to be at least remotely/ possibly related to treatment).

3. Redundant terms (i.e. covered with high specificity by other terms in the list).

The Applicant analyzed the clinical trial data from the pooled company clinical database of 14 capecitabine pivotal trials in gastrointestinal and breast cancer, both for XELODA monotherapy and XELODA combination regimens as well as controlled with 5-FU.

- ADR terms that meet criterion #1

The following ADR terms were reported only in patients receiving combination therapy (i.e. not reported as related in patients receiving monotherapy), and can be removed:

Idiopathic thrombocytopenia purpura, ventricular extrasystoles, extrasystoles, pericardial effusion, ascites, toxic dilation of intestine, hoarseness, irritability, difficult in walking, chest mass, collapse, sedation, laryngitis, bronchopneumonia, bone pain, abnormal coordination, loss of consciousness, asthma, hemoptysis, cerebrovascular accident.

- ADR terms that meet criterion #2

The Applicant concluded that a causal role of therapy was unlikely for several ADR terms in the original list of terms (e.g. chest mass). However, those terms were already excluded according to criterion #1.

- ADR terms that meet criterion #3

Several terms are covered by other synonymous or medically similar terms in the list (e.g. bronchopneumonia vs bronchitis and pneumonia, abnormal coordination vs ataxia) and therefore could be excluded according to criterion #3. However, these terms were already excluded according to criterion #1.

The remaining terms represent symptoms/signs/diagnoses for which a causal role of treatment is at least plausible. In particular, many are possible manifestations of risks described elsewhere in the label (e.g. Section 5 WARNING AND PRECAUTIONS, or in tables of adverse reactions for specific indications and treatment combinations in this subsection 6.1). The Applicant proposes to retain those terms.

Lymphedema and fibrosis were reported as related events in patients receiving monotherapy. These may be effects of underlying malignancy or damage to lymphatic drainage by surgery or radiotherapy. However, several publications provide information indicating a possible causal role of chemotherapy (Hopkins 2017, Kataru 2019, Kim 2013, Kim 2015, Norman 2010). The Applicant proposes to retain those terms.

The following terms were not reported verbatim but were reported using terms that have a similar or overlapping meaning. The Applicant proposes to retain those terms:

Original term as shown in approved USPI	Corresponding/medically similar term
coagulation disorder	Coagulopathy
bone marrow depression	bone marrow toxicity
drug hypersensitivity	Hypersensitivity
keratoconjunctivitis	Keratitis
Arthritis	gouty arthritis
impaired balanced	balance disorder
Confusion	confusional state
renal impairment	renal failure
respiratory distress	respiratory failure
sweating increased	Hyperhidrosis
skin ulceration	skin ulcer
radiation recall phenomenon	recall phenomenon

The FDA has requested to remove the sentence, "Occurrences of each grade 3 and 4 adverse event are provided in parentheses", in the subsection of Pooled Safety Population. (b) (4)

(b) (4)

As FDA requested in comment [W103], adverse events are presented in alphabetical order by system organ class (SOC).

FDA recommended in comment [W86], [W93], and [W101] to combine the incidence of Grades 3 and 4 adverse reactions in Tables 4, 5 and 7 in the proposed annotated USPI. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Subsection 6.2 Postmarketing Experience

The Applicant added in the subsection 6.2 Postmarketing Experience the adverse reaction of angioedema, which was approved by the FDA in sNDA S-043 on 19 May 2021. Refer to the tracked changes in the proposed annotated labeling for all revisions made.

- Section 8 USE IN SPECIFIC POPULATIONS

Subsection 8.1 Pregnancy

As per FDA's request for the subsection 8.1 Pregnancy, the Applicant performed a cumulative review and summarized case reports and relevant published literatures concerning risks associated with capecitabine exposure during pregnancy as requested (see DSR No: 1113501). The available information presented in the report confirms the limited and partially incomplete evidence of human data with XELODA use in pregnant women but emphasizes its potential and risk to cause major birth defects and miscarriage upon exposure prior to conception or during pregnancy. Therefore, the Applicant is of the opinion that the current USPI label text of subsection 8.1 adequately describes the risks and precautions that are needed and no change is required.

Subsection 8.2 Lactation

As per FDA's request for subsection 8.2 Lactation, the Applicant provides the following statement on presence of drug in human milk, effect of drug on breastfed infant, effect of drug on milk production, and recommendation for breastfeeding. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Subsection 8.5 Geriatric Use

As per FDA's request for the subsection 8.5 Geriatric Use, the Applicant provided the percentage and numbers of patients 65 years or older with various indications who were treated with XELODA (refer to the tracked changes in the proposed annotated labeling). The geriatric use of XELODA has been summarized in this subsection based on both Global and Local Clinical trials where information was available. For recently added indication of pancreatic cancer, the information was taken directly from the publication.

In addition, the Applicant provides the following statements on geriatric use of the drug,

> "*No overall differences in efficacy were observed comparing older versus younger patients across the different indication groups and treatment regimens.*
>
> (b) (4)

The rationale for the above proposed statement is based on the analysis of efficacy and safety results from 7 Clinical Study Reports (CSRs) for the original pivotal and supportive Phase III studies in breast, gastric, esophageal, and colorectal cancer included prespecified analyses of comparative efficacy and/or safety by age group (Study NO16966, Study NO16967, Study NO16968, Study M66001, Study ML17032, Study REAL-2, and Study SO14999). Elderly patients comprised a substantial proportion of patients in all those studies. Refer to the report

"Applicant's Position and Rationale for Proposed Text in Xeloda USPI Section 8.5 Geriatric Use".

In conclusion, the comparative efficacy of capecitabine-containing regimens vs control treatment was apparent in both younger and older patients across a range of indications and treatment combinations, with no evidence of age × treatment interaction. Based on a comparison of AE contingency tables, several studies found that Grade 3/4 AEs and certain specific AEs occurred in a greater proportion of older versus younger patients among those receiving capecitabine, whereas the age effect was not as apparent in patients receiving control treatments. In particular, older patients appeared to be more prone to gastrointestinal side effects of capecitabine-containing regimens than younger patients. Although inconclusive, the available data are sufficient to justify the proposed statement to the product label, explaining that older patients may be more susceptible to gastrointestinal side effects of capecitabine. The data are not sufficient to draw definitive conclusions about differences in AE profile by age between indication and combination treatment. Therefore, the statement should be a general statement that covers all indications and treatment combinations.

The FDA's Assessment

The Applicant's proposed changes to Subsection 8.2 Lactation were deleted because they were based on limited data following fluorouracil infusion. The recommendation to not breastfeed was changed to 1 week after the last dose based on current OCE policy for drugs with short half-lives.

6. PEDIATRIC INFORMATION PERTINENT TO PROPOSED LABELING

Pediatric information was reviewed; changes related to pediatric information and supporting published literature are discussed in the pediatric sections in the proposed annotated labeling, including section 8.4 and other sections, where applicable.

The Applicant's Position

The Applicant agrees with all FDA proposed updates outlined in this Section 6 PEDIATRIC INFORMATION PERTINENT TO PROPOSED LABELING.

The FDA's Assessment

Refer to the label for updates pertinent to pediatric information.

7. ADDITIONAL PROPOSED LABELING CONSIDERATIONS

Full Prescribing Information: Following review of the existing product labeling, and independent FDA review of available evidence, the FDA included additional proposed modifications in the proposed annotated product labeling attached to the Supplement Request Letter to more closely adhere to current guidance and regulations.

Where applicable, format and content of the labeling were updated to conform to the Physician Labeling Rule (PLR) and current labeling guidances.

HIGHLIGHTS

- The Applicant should update the highlights to reflect final labeling proposal.

TABLE OF CONTENTS

- The Applicant should update the table of contents to reflect final labeling proposal.

Section 3

- Revised to clearly identify dosage form and strengths.

Section 4

- The contraindication on Severe Renal Impairment was removed, as the FDA does not agree with retaining this contraindication based on current labeling practices. Other drugs that can cause serious adverse reactions in patients with renal impairment do not include a contraindication.

Section 5

- Revisions made throughout – refer to the product labeling.

Section 6

- Revisions made throughout – refer to the product labeling.

Section 8

- Revisions made throughout – refer to the product labeling.

Section 10

- Information on uridine triacetate should be added by the Applicant. Refer to drugs@fda.

Section 11

- Updated to include the chemical formula for capecitabine.

Section 14

- Revisions made throughout – refer to the product labeling.

Section 17

- Revisions made throughout – refer to the product labeling.

Patient Labeling: The FDA will propose updates to the existing PPI as part of labeling negotiations.

Package and Container Labeling: The Applicant should submit copies of all container/carton labeling with any necessary updates to ensure adherence to current regulations and guidance.

The Applicant's Position

The Applicant agrees with all FDA proposed updates outlined in this Section 7 ADDITIONAL PROPOSED LABELING CONSIDERATIONS subject to other minor editorial revisions (refer to the tracked changes in the proposed annotated labeling), except as to Section 17 discussed below. The Applicant also provided FDA requested information in Section 10, discussion below:

- Section 4 CONTRAINDICATIONS

The Applicant agrees with FDA proposed removal of the severe renal impairment contraindication, with additional statement added in the subsection 8.6 Renal Impairment in the proposed annotated labeling (rationale provided in the Applicant's Position in Section 4 Clinical Pharmacology Pertinent to Proposed Labeling). Refer to the tracked changes in the proposed annotated labeling.

- Section 5 WARNINGS AND PRECAUTIONS

The Applicant agrees with FDA proposed modifications, with minor editorial revisions made in the subsection 5.2 Increased Risk of Serious Adverse Reactions with Partial or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity, and additional considerations added for the subsubsection 5.10 Hyperbilirubinemia (rationale provided in the Applicant's Position in Section 5 Safety Pertinent to Proposed Labeling). Refer to the tracked changes in the proposed annotated labeling.

- Section 6 ADVERSE REACTIONS

The Applicant removed less common adverse reactions in the subsection 6.1 Clinical Trial Experience, as FDA requested (rationale provided in the Applicant's Position in Section 5 Safety Pertinent to Proposed Labeling). Refer to the tracked changes in the proposed annotated labeling.

In response to FDA's request [W76], the Applicant has elected not to update the "<1%" as "0.X%" nor include one decimal place as this does not provide additional useful information to Healthcare professionals or patients.

- Section 8 USE IN SPECIFIC POPULATIONS

The Applicant agrees with FDA's proposed modifications, with minor editorial revisions throughout Section 8 and additional summaries of information provided (details in the Applicant's Position in Section 4 Clinical Pharmacology Pertinent to Proposed Labeling and

Section 5 Safety Pertinent to Proposed Labeling). Refer to the tracked changes in the proposed annotated labeling.

- Section 10 OVERDOSAGE

The Applicant agrees with FDA proposed modifications. In addition, as per FDA's request in Section 10 OVERDOSAGE, the Applicant provides the following brief statement on the use of uridine triacetate (Ma 2017) (refer to the tracked changes in the proposed annotated labeling),

"*Administer uridine triacetate within 96 hours for management of XELODA overdose*".

- Section 14 CLINICAL STUDIES

In response to FDA's requests [W144] to [W147], the Applicant did not have acronyms for Studies 1-4. Therefore the Applicant includes the study numbers and NCT numbers instead. Refer to the tracked changes in the proposed annotated labeling.

- Section 17 PATIENT COUNSELING INFORMATION

(b) (4)

The Applicant recommends adding a subsection of "Hypersensitivity and Angioedema" and pertinent advice to the patient in Section 17. The adverse reaction of angioedema was approved by the FDA in sNDA S-043 on 19 May 2021. Refer to the tracked changes in the proposed annotated labeling.

The Applicant disagrees with FDA's references to grapefruit juice and St. John's Wort in subsection "Drug interactions". Metabolism of capecitabine does not depend on CYP enzymes. There are no literature reports on an interaction of capecitabine or 5-FU with grapefruit juice or with St. John's Wort. The Applicant therefore recommends deletion of drug interactions with grapefruit, grapefruit juice or St. John's Wort. The Applicant recommends the following statement instead (refer to the tracked changes in the proposed annotated labeling),

(b) (4)

In addition, the Applicant agrees with FDA proposed revisions of storage temperature range in Section 16 HOW SUPPLIED/STORAGE AND HANDLING. As per FDA request, copies of all cartons, containers, and labels with corresponding updates (four total: 150mg carton and label, and 500mg carton and label) are submitted in Module 1.14.1.1 within this sNDA for review.

The FDA's Assessment

Additional labeling changes that were included after receipt of the supplemental NDA from the Applicant include the following:

- Dosage and Administration, Section 2.2, Recommended Dosage for Breast Cancer was revised to include the dose of 1,000 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle until disease progression or unacceptable toxicity as a single agent and also for use in combination with docetaxel.
- Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency, Section 5.2 was revised based on a citizen's petition submitted to the FDA.

8. FDA RECOMMENDATIONS

8.1 Clinical

The FDA review team recommends approval.

8.2 Non-Clinical

The FDA review team recommends approval.

8.3 Clinical Pharmacology

The FDA review team recommends approval.

8.4 Quality

The FDA review team recommends approval.

9. FDA REVIEW TEAM SIGNATURE PAGE

X	X
Haw-Jyh (Brian) Chiu, PhD Primary Pharm/Tox Reviewer	Tiffany Ricks, PhD Pharm/Tox Team Lead
X	X
Lili Pan, PharmD Primary Clinical Pharmacology Reviewer	Jeanne Fourie-Zirkelbach, PharmD Clinical Pharmacology Team Lead

X

Sundeep Agrawal, MD
Clinical Reviewer and Team Lead

X

William Pierce, PharmD

Associate Director for Labeling

10. OFFICE DIRECTOR (OR DESIGNEE)

X _____

Jennifer Gao, MD
Associate Director
Oncology Center of Excellence

11. APPENDICES

See annotated package insert containing FDA's recommended updates**.**

11.1 Sources of Clinical Data and Review Strategy

The Project Renewal Support team reviewed information regarding potential unapproved uses in the post-marketing setting as described in multiple drug compendia.[3] Following identification of potential labeling changes regarding new/updated indications and dosage regimens, the Project Renewal Support team obtained agreement from the new drug application holder for participation in this process. The Project Renewal Support team then identified Research Team Members (RTMs), defined as subject matter experts and key opinion leaders with expertise in these disease areas based on recommendations by relevant professional organizations.[4] Medical hematology/oncology fellows were also included as part of the educational component of this project; both RTMs and hematology/oncology fellows evaluated scientific literature identified through a python-based tool of PubMed describing such unapproved uses, including both positive and negative studies.

Research teams were formed with relevant disease-specific expertise; the teams discussed the available data in a series of meetings to reach consensus regarding proposals for labeling modifications. Specifically, the teams considered existing labeling including dose, safety, pharmacology, and special populations, and whether there were adequate data to establish the effectiveness of the drug for any new uses. For new uses, the Research Team provided recommendations for the proposed indication(s) and recommended dosage regimen.

[3] Center for Medicare and Medicaid Services-designated compendia; Lexicomp Online (Walters Kluwer Lexi-Drugs); Micromedex (Truvent Analytics Micromedex Drug DEX), and the National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium.
[4] Professional organizations include, but are not limited to, the American Society for Clinical Oncology (ASCO); American Society for Hematology (ASH); American Association for Cancer Research (AACR).

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Haw-Jyh (Brian) Chiu, PhD	OOD/DHOT	Sections: 3 and subsection 8.2	**Select one:** ☒ Authored ☒ Approved
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Nonclinical Team Leader	Tiffany Ricks, PhD	OOD/DHOT	Sections: 3 and subsection 8.2	**Select one:** ☐ Authored ☒ Approved
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Clinical Pharmacology Reviewer	Lili Pan, PhD	OCP/DCPII	Sections: 4, 5, 6, 7 and subsection 8.3	**Select one:** ☒ Authored ☒ Approved
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Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	OCP/DCPII	Sections: 4, 5, 6, 7 and subsection 8.3	**Select one:** ☐ Authored ☒ Approved
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Genomics Team Leader	Rosane Charlab Orbach, PhD	OCP/DTPM	Sections: 4, 5 (subsection 5.2), 7 and subsection 8.3	**Select one:** ☒ Authored ☒ Approved
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Associate Director for Labeling (ADL)	William Pierce, PharmD, MPH	OCE	Sections: All	**Select one:** ☒ Authored ☒ Approved
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Clinical Reviewer and Cross-Disciplinary Team Leader (CDTL)	Sundeep Agrawal, MD	OOD/DO1 OCE	Sections: All	**Select one:** ☒ Authored ☒ Approved
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Office Director (Clinical)	Jennifer Gao, MD	OCE	Sections: All	**Select one:** ☒ Authored ☒ Approved
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12/13/2022 04:36:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020896Orig1s044,045,046,047,048,049,050,051

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 21, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 020896/S-044 through S-051
Product Name and Strength:	Xeloda (capecitabine) tablets, 150 mg and 500 mg
Applicant/Sponsor Name:	Genentech, Inc.
OSE RCM #:	2022-590-1
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 16, 2022 for Xeloda. The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Xeloda (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Thomas, S. Label and Labeling Review for Xeloda (NDA 020896/S-044 through S-051). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUN 24. RCM No.: 2022-590.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 24, 2022
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 020896/S-044 through S-051
Product Name, Dosage Form, and Strength:	Xeloda (capecitabine) tablets, 150 mg and 500 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	February 15, 2022
OSE RCM #:	2022-590
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

Genentech, Inc. submitted supplements for Xeloda (capecitabine) tablets in connection with Project Renewal, which is a voluntary public health initiative that aims to update relevant scientific information in labeling for oncology products. This is one labeling update that covers all supplements S-044 to S-051. Subsequently, the Division of Oncology 1 (DO1) requested in their March 17, 2022 consult that we review the proposed Xeloda prescribing information (PI), patient information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Xeloda PI and patient information and note significant edits to the Dosage and Administration sections of the PI, including edits to the administration instructions, added and revised dosing regimen and dosing modification information, removal of the dose calculation table, and removal of the creatinine clearance calculation equations under the section titled "Adjustment of Starting Dose in Special Populations." We also note edits to Sections 16 and 17, the How Supplied/Storage and Handling and Patient Counseling Information sections. Upon review of the container labels and carton labeling, we note edits to the storage temperature information and capitalization of the "KEEP TIGHTLY CLOSED." warning, in order to align with the PI.

We understand that FDA already reviewed and provided edits to the PI in the earlier Project Renewal process, for which DMEPA was not involved. These edits included removal of the table

outlining the rounding and number of tablets to achieve a BSA-based dose using the available tablet strengths. We are not aware of postmarket medication errors related to the table, but we will align with the previous FDA recommendation. However, we do recommend adding a statement to round to the nearest dose that can be achieved with a whole tablet to avoid cutting or splitting of tablets.

We find the edits to the PI, container labels and carton labeling acceptable from a medication safety perspective but note the labels and labeling can be further improved to promote the safe use of the product. Therefore, we provide recommendations to improve the labels and labeling in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI, container labels and carton labeling may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information (PI)

1. Dosage and Administration Sections, Highlights and Full PI

    a. In order to improve legibility of the proposed larger numerical dose and prevent the reader from misinterpreting numbers in the thousands ("1000") as hundreds ("100") or ten-thousands ("10000"), consider stating the doses in thousands with a comma (e.g., 1250 mg/m^2 and 1000 mg/m^2 doses with a comma, as follows: 1,250 mg/m^2 and 1,000 mg/m^2).[a]

2. Dosage and Administration Section, Highlights

    a. We recommend revising the last bullet of the Highlights Dosage and Administration section to specify that section 2.5 provides dosage modifications for adverse reactions, as well as include section 2.6 since section 2.6 of the full PI also provides dose modification information, as follows: "Refer to Sections 2.5 and 2.6 for information related to dosage modifications for adverse reactions and renal impairment (2.5 and 2.6)."

3. Dosage and Administration Section, Full PI

    a. We recommend adding the statement "Round to the nearest dose that gives a whole tablet rather than cutting tablets in half." for clarity when healthcare providers determine how to achieve the BSA-based dose with the available tablet strengths.

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[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2022 JUNE 2]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

b. We note a "*" provided after "Severity" in Table 1 but do not note a corresponding footnote reference. We recommend adding the appropriate reference for the "*".

4. Dosage Forms and Strengths, Full PI

   a. We recommend adding the additional tablets imprint descriptor provided in Section 16 to the Section 3 tablet description (e.g., with "XELODA" on one side and ["150" or "500"] on the other).

4.2 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of the NDA Supplements:

A. General Comments (Container labels & Carton Labeling)

1. We recommend adding the following warning to the principal display panel of the container labels and carton labeling: "Warning: Hazardous Drug" for consistency with the PI.
2. We note the format of the expiration date is not specified on the container labels or carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a slash be used to separate the portions of the expiration date.[b]
3. Consider revising the usual dose statements from:

   (b) (4)

   to "Recommended Dosage: see prescribing information.", in order to ensure consistency with the PI.

[b] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

B. Carton Labeling

1. We note the absence of a lot number and expiration date on the proposed carton labeling. Add the lot number and expiration date in accordance with 21 CFR 201.10(i)(1) and 21 CFR 211.137, respectively.

    a. Ensure the lot number and expiration date are clearly differentiated from one another.[c]

    b. Also, ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[d]

2. We note the 2D data matrix barcode, serial number, lot number, and expiration date are missing from the carton labeling. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.
   The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier.
   The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following:

   NDC: [insert NDC]
   SERIAL: [insert serial number]
   LOT: [insert lot number]
   EXP: [insert expiration date]

   We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.[e]

[c] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[d] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

[e] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xeloda received on February 15, 2022 from Genentech, Inc.

Table 2. Relevant Product Information for Xeloda	
Initial Approval Date	April 30, 1998
Active Ingredient	capecitabine
Indication	Xeloda (capecitabine) is a nucleoside metabolic inhibitor indicated for: *(Proposed)* *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 failure of prior anthracycline-containing chemotherapy.* *Esophageal, Gastroesophageal Junction and Gastric Cancer* • *treatment of adults with unresectable or metastatic cancer of the esophagus, gastroesophageal junction, and stomach as a component of a combination chemotherapy regimen.* • *treatment of adults with HER2-overexpressing metastatic adenocarcinoma of the gastroesophageal junction or stomach 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.*
Route of Administration	oral
Dosage Form	tablets
Strength	150 mg and 500 mg
Dose and Frequency	*(Proposed)* *Adjuvant Treatment of Colon Cancer* • *Single agent: 1,250 mg/m^2 twice daily orally for the first 14 days of each 21 day cycle for a maximum of 8 cycles.* • *In combination with Oxaliplatin-Containing Regimens: 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle for a maximum of 8 cycles in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.* *Perioperative Treatment of Rectal Cancer* • *With Concomitant Radiation Therapy: 825 mg/m^2 orally twice* • *Without Radiation Therapy: 1250 mg/m^2 orally twice daily* *Unresectable or Metastatic Colorectal Cancer:* • *Single agent: 1250 mg/m^2 twice daily orally for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity.* • *In Combination with Oxaliplatin: 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.* *Advanced or Metastatic Breast Cancer:* • *Single agent: 1,250 mg/m^2 twice daily orally for the first 14 days of each 21 day cycle until disease progression or unacceptable toxicity.* • *In combination with docetaxel: 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle, until disease progression or unacceptable toxicity in combination with docetaxel at 75 mg/m^2 administered intravenously on day 1 of each cycle* *Unresectable or Metastatic Cancer of the Esophagus, Gastroesophageal Junction or Stomach* • *625 mg/m^2 orally twice daily on days 1 to 21 of each 21-day cycle for a maximum of 8 cycles in combination with platinum-containing chemotherapy.*

	OR • *850 mg/m^2 or 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.* *HER2-overexpressing metastatic adenocarcinoma of the gastroesophageal junction or stomach* • *1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with cisplatin and trastuzumab.* *Pancreatic cancer* • *830 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle for maximum of 6 cycles in combination with gemcitabine 1,000 mg/m^2 administered intravenously on days 1, 8, and 15 of each cycle.* (b) (4)
How Supplied	• 150 mg, biconvex, oblong, film-coated, light peach tablets with "XELODA" on one side and "150" on the other; available in bottles of 60 (NDC 0004-1100-20), individually packaged in a carton. • 500 mg, biconvex, oblong, film-coated, peach tablets with "XELODA" on one side and "500" on the other; available in bottles of 120 (NDC 0004-1101-50), individually packaged in a carton.
Storage	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*. KEEP TIGHTLY CLOSED.
Container Closure	Bottle 90 mL high density polyethylene (HDPE), (b) (4) closure

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 31, 2022, we searched for previous DMEPA label and labeling reviews relevant to this current review using the terms, Xeloda, capecitabine, and NDA# 20896. Our search identified 3 previous reviews[f,g,h], and we considered our previous recommendations to see if they are applicable for this current review.

[f] Gao, T. Label and Labeling Review for Xeloda (NDA 020896/S-040). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 May 11. RCM No.: 2017-550.

[g] Gao, T. Label and Labeling Review for Xeloda (NDA 020896/S-042). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Oct 11. RCM No.: 2018-1981.

[h] Gao, T. Label and Labeling Review for Xeloda (NDA 020896/S-042). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 4. RCM No.: 2018-1981-2.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Xeloda labels and labeling submitted by Genentech, Inc.

- Container labels received on February 15, 2022
- Carton labeling received on February 15, 2022
- Prescribing Information (Image not shown) received on February 15, 2022, available from \\CDSESUB1\evsprod\nda020896\0108\m1\us\redlined-label-text.docx
- Patient Information received on February 15, 2022, available from \\CDSESUB1\evsprod\nda020896\0108\m1\us\clean-label-text-pi.docx

G.2 Label and Labeling Images

Container Labels

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SARAH E THOMAS
06/24/2022 02:43:57 PM

ASHLEIGH V LOWERY
06/24/2022 03:02:01 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 23, 2022

To: Clara Lee, PhD, Health Scientist, Oncology Center of Excellence (OCE)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for XELODA® (capecitabine) tablets, for oral use

NDA: 020896/Supplements-044 through S-051

In response to OCE's consult request dated March 17, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for XELODA® (capecitabine) tablets, for oral use (Xeloda). These supplements (S-044 through S-051) propose labeling revisions as part of OCE's Project Renewal.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from OCE (Clara Lee) on March 23, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on May 12, 2022.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 15, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
05/23/2022 09:38:49 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 12, 2022
To:	Clara Lee, PhD Health Scientist **Oncology Center of Excellence**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	XELODA (capecitabine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 020896
Supplement Number:	S-044 through S-051
Applicant:	Genentech, Inc.

1 INTRODUCTION

On February 15, 2022, Genentech, Inc. submitted for the Agency's review eight Prior Approval Supplements (PAS)- Efficacy to their approved New Drug Application (NDA) 020896 for XELODA (capecitabine) tablets. These supplements were submitted in response to the Agency's Correspondence to the Applicant dated August 20, 2019 requesting their participation in Project Renewal, and a Prior Approval Supplement Request Letter dated September 30, 2021 related to Project Renewal, proposing the following labeling revisions to the Prescribing Information (PI):

- Updates to the current indications for XELODA (capecitabine) tablets and their current recommended dosage regimens to contain additional relevant information to enhance the safe use of this drug;
- Revisions to the Indication section to include proposed new indications, and their associated recommended dosage regimens, for which there appears to be substantial evidence of effectiveness;
- Revisions to the Warnings and Precautions and Clinical Pharmacology sections regarding description of the risks of capecitabine in patient with *DPYD* genetic aberrations.
- Revisions to the Clinical Studies section to include summaries of the clinical studies that facilitate an understanding of how to use the drug safely and effectively for the proposed indications, consistent with 21 CFR 201.51(c)(15);
- Revisions to the Adverse Reactions section to incorporate relevant safety information for the proposed indications;
- Edits to other sections to conform to current labeling guidances, as applicable.

The new indications submitted in the proposed supplements are as follows:

Supplement Number	Proposed Indication:
S-044	for the adjuvant treatment of patients with Stage III colon cancer as a single agent or as a component of a combination chemotherapy regimen.
S-045	for the treatment of patients with advanced or metastatic breast cancer in combination with docetaxel after failure of prior anthracycline-containing chemotherapy.
S-046	for the treatment of adults with unresectable or metastatic cancer of the esophagus, gastroesophageal junction, and stomach as a component of a combination chemotherapy regimen
S-047	for the treatment of patient with advanced or metastatic breast cancer as a single agent if an anthracycline or taxane-containing chemotherapy is not indicated.

S-048	for the treatment of patients with unresectable or metastatic colorectal cancer as a single agent or as a component of a combination chemotherapy regimen.
S-049	for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.
S-050	for perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy.
S-051	for the treatment of adults with HER-2 overexpressing metastatic adenocarcinoma of the gastroesophageal junction or stomach who have not received prior treatment for metastatic disease as a component of a combination regimen.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Oncology Center of Excellence (OCE) on March 17, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for XELODA (capecitabine) tablets.

2 MATERIAL REVIEWED

- Draft XELODA (capecitabine) tablets PPI received on February 15, 2022, and received by DMPP on March 17, 2022.
- Draft XELODA (capecitabine) tablets PPI received on February 15, 2022, and received by OPDP on March 23, 2022.
- Draft XELODA (capecitabine) tablets Prescribing Information (PI) received on March 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on March 17, 2022.
- Draft XELODA (capecitabine) Prescribing Information (PI) received on February 15, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on March 23, 2022.
- Approved XELODA (capecitabine) tablets labeling dated May 19, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
05/12/2022 03:20:49 PM

REBECCA A FALTER
05/12/2022 03:31:48 PM

LASHAWN M GRIFFITHS
05/12/2022 03:33:08 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020896Orig1s044,045,046,047,048,049,050,051

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 020896 SUPPL # 044-051 HFD # 150

Trade Name Xeloda

Generic Name Capecitabine

Applicant Name Genentech, Inc.

Approval Date, If Known December 14, 2022

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2) and SE1

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020896 Xeloda (capecitabine) tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

The applications relied on published literature to support the indications.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

The supplements 044 to 051 are based on published literature.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Clara Lee, PharmD
Title: Health Scientist/Oncology Center of Excellence
Date: October 21, 2022

Name of Director signing form: Jennifer Gao, MD
Title: Associate Director for Education/Oncology Center of Excellence

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

CLARA J LEE
12/14/2022 09:26:01 AM

JENNIFER J GAO
12/14/2022 04:45:23 PM

NDA 020896

PRIOR APPROVAL SUPPLEMENT REQUEST

Genentech, Inc.
Attention: Gigi Lee
Program Manager, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Lee:

Please refer to your new drug application (NDA) for Xeloda (capecitabine) tablets.

We refer to our August 20, 2019, correspondence requesting your participation in Project Renewal, a voluntary public health initiative that aims to update relevant scientific information in FDA-approved labeling for oncology products, and to your August 29, 2019, submission, stating your agreement to participate in this initiative.

In connection with Project Renewal, the FDA has reviewed your labeling dated February 22, 2019, concerning the use of Xeloda.

We are proposing the following labeling revisions for your PI:[1]

- Updates to the current indications for Xeloda (capecitabine) tablets and their current recommended dosage regimens to contain additional relevant information to enhance the safe use of this drug;

- Revisions to the Indication section to include proposed new indications, and their associated recommended dosage regimens, for which there appears to be substantial evidence of effectiveness;

- Revisions to the Warnings and Precautions and Clinical Pharmacology sections regarding description of the risks of capecitabine in patients with *DPYD* genetic aberrations;

[1] A citizen petition was submitted by Kenneth E. Surprenant dated November 16, 2020 (Docket No. FDA-2020-P-2213), requesting, in part, that FDA revise "the package inserts" for Xeloda. The issues raised by that petition are under review by the Agency, and FDA has not made a final decision on the issues raised in that citizen petition. The comments included in this communication do not represent a final decision by the Agency on the issues raised in the pending citizen petition.

- Revisions to the Clinical Studies section to include summaries of the clinical studies that facilitate an understanding of how to use the drug safely and effectively for the proposed indications, consistent with 21 CFR 201.51(c)(15);

- Revisions to the Adverse Reactions section to incorporate relevant safety information for the proposed indications;

- Edits to other sections to conform to current labeling guidances, as applicable.

Enclosed in this supplement request letter, refer to 1) proposed labeling with FDA's recommended changes, 2) FDA's Project Renewal Assessment Aid summarizing data and information supporting the recommended changes to the proposed labeling, and 3) Instructions for the Applicant on completing the Project Renewal Assessment Aid, as well as additional information you will need to provide to comply with PREA requirements. FDA's proposed recommendations are based, in part, on FDA's finding of safety and effectiveness for listed drug(s), published literature, and/or studies for which you would need a right of reference.

A separate efficacy supplement should be submitted for each addition or modification of an indication or claim that requires separate sets of clinical data or information [see 21 CFR 314.3(b); FDA's Guidance for Industry, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, available at http://www.fda.gov/media/72397/download.[2] We request that you submit separate prior approval supplements to this NDA at the same time, addressing the identified issues and FDA's proposed revisions to the labeling. During the review of the supplements, changes to the proposed labeling may be negotiated between you and the Agency. Any indications not currently included in the FDA's proposed labeling accompanying this letter fall outside the scope of Project Renewal and should be separately discussed with the appropriate FDA oncology division(s).

The first of these supplements should include all information (e.g., Project Renewal Assessment Aid, proposed labeling, cover letter, additional information) necessary to support the proposed new indication and/or dosage regimen under that supplement as well as to support all other new indications/dosage regimens being sought under other supplements under Project Renewal.

Your Prescribing Information (PI), approved in Physician Labeling Rule (PLR), must conform to the content and format regulations found at 21 CFR 201.56(d) and 201.57. Your PI must contain a summary of the essential scientific information needed for the safe and effective use of your product and must be informative and accurate and neither promotional in tone nor false or misleading. You must update your PI when new information becomes available that causes the labeling to become inaccurate, false, or

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

misleading [see 21 CFR 201.56(a)]. We encourage you to review the labeling review resources on the *Prescription Drug Labeling Resources* website.[3]

505(b)(2) LEGAL AND REGULATORY REQUIREMENTS

For each supplement, if you rely on the Agency's finding of safety or effectiveness for a listed drug(s) and/or on published literature (studies that you do not own or for which you do not have a right of reference), the supplement will be considered a 505(b)(2) supplement (see section 505(b)(2) of the FD&C Act; see also 21 CFR 314.54).

For each of your supplements, you must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate for each proposed indication or dosage regimen. A copy of such published literature must be included in each 505(b)(2) supplement or you should indicate in your cover letter that you are cross-referencing this information in the first supplement submitted under Project Renewal (i.e., identify the appropriate supplement number and location of the relevant information in the supplement). If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) as reflected in the drug's labeling or published literature describing an investigation conducted with a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. For each supplement, you should review the studies described in the published literature and identify any listed drug(s) (e.g., by trade name(s)) described in the literature that you are relying on for approval of the supplement (i.e., product-specific literature). We note that there are published studies listed in the References section of the Project Renewal Assessment Aid that are considered product-specific literature.

It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an application under section 505(c) of the FD&C Act. If your original application was a 505(b)(2) application and if one or more pharmaceutically equivalent product(s) was approved in one or more NDA(s) before the date of submission of your original 505(b)(2) application, your supplement must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19)).

If you intend to rely on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" between your proposed drug product and each listed

[3] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. (If you are citing reliance on a pharmaceutically equivalent listed drug for the sole purpose of complying with the regulatory requirement discussed in the paragraph above, you are not required to establish a scientific bridge to that product if it is not otherwise necessary for approval.) The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which an applicant relies.

For purposes of the legal and regulatory requirements described below, if you are submitting a supplement to a 505(b)(2) application, reliance on a listed drug(s) includes (1) continued reliance on a listed drug previously relied upon in the 505(b)(2) application; (2) as applicable, identification of a pharmaceutically equivalent product as a listed drug (or an additional listed drug) implicitly relied upon to comply with the regulatory requirement described in 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); and (3) any other reliance on a listed drug(s) to support approval of the supplement.

If you rely on one or more listed drugs for which there are no unexpired patents listed in the Orange Book, you may cite one of the following patent certifications in your supplements, as applicable:

☐ 21 CFR 314.50(i)(1)(i)(A)(*1*): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(*2*): The patent has expired. (Paragraph II certification)

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

If you rely on one or more listed drugs for which there are unexpired patents listed in the Orange Book, you would need to provide an appropriate patent certification(s) or statement(s) in your supplements from among the following:

☐ 21 CFR 314.50(i)(1)(i)(A)(*3*): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(*4*): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application is submitted. (Paragraph IV certification).

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit a Paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(*4*)).

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method-of-use patent and the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method-of-use patent does not claim a proposed indication or other condition of use (also referred to as a "method of use" statement or a "section viii statement" for ANDAs).

If your supplement does not rely on a listed drug(s), as explained in further detail above, and the sole source of reliance on studies that you do not own or for which you do not have a right of reference is published literature that does not describe a listed drug (e.g., by trade name) , you may include the following statement in your supplement:

☐ No patent certification or statement is required – the supplement does not rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and the published literature relied upon for approval does not describe a listed drug(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable (see e.g., section 505B(a)(1)(A) of the FD&C Act).

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. Refer to the Project Renewal Applicant Instructions in the supplement package. The iPSP must contain an outline of the pediatric assessment(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*, available at https://www.fda.gov/media/86340/download.

The supplements should be submitted within 90 days.

If you have any questions, contact Clara Lee, Health Scientist, at Clara.Lee@fda.hhs.gov or (240) 402-4809.

Sincerely,

{See appended electronic signature page}

Jennifer Gao, MD
Associate Director for Education
Oncology Center of Excellence

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER J GAO
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