CAPECITABINE:

Class: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog)

Indications: -Metastatic breast cancer –Metastatic colon cancer - Dukes' C colon cancer, adjuvant therapy
- Esophageal and gastric cancers - Hepatobiliary cancers, advanced
- Ovarian, fallopian tube, or peritoneal cancer, platinum-refractory
- Neuroendocrine (pancreatic/islet cell) tumors, metastatic or unresectable
- Pancreatic cancer, metastatic - Unknown primary cancer

Available dosage form in the hospital: 500 MG TAB

Trade Names: Xeloda, Apecitab (AR); Capecitabina (PE); Capibine (IN)

Dosage: **Note:** Details concerning dosing in combination regimens should also be consulted. Capecitabine toxicities, particularly hand-foot syndrome, may be higher in North American populations (for the treatment of colorectal cancer); therapy initiation at doses of 1000 mg/m^2 twice daily (for 2 weeks every 21 days) may be considered (Haller, 2008; NCCN Colon Cancer Guidelines v3.2013)

-**Breast cancer, metastatic**: Oral: 1250 mg/m^2 twice daily for 2 weeks, every 21 days (as either monotherapy or in combination with docetaxel)

-**Colorectal cancer, metastatic**: Oral: 1250 mg/m^2 twice daily for 2 weeks, every 21 days

-**Dukes' C colon cancer, adjuvant therapy**: Oral: 1250 mg/m^2 twice daily for 2 weeks, every 21 days, for a recommended total duration of 24 weeks (8 cycles of 2 weeks of drug administration and 1 week rest period).

Unlabeled uses:

-**Breast cancer, metastatic (unlabeled dosing):** Oral: 1000 mg/m^2 twice daily (in combination with ixabepilone) on days 1-14 of a 3-week cycle until disease progression or unacceptable toxicity (Thomas, 2007)

-**Breast cancer, metastatic, HER2+ (unlabeled dosing):** Oral: 1000 mg/m^2 twice daily (in combination with lapatinib) on days 1-14 of a 3-week cycle until disease progression or unacceptable toxicity (Geyer, 2006) or 1250 mg/m^2 twice daily (in combination with trastuzumab) on days 1-14 of a 3-week cycle (Bartsch, 2007)

-**Breast cancer, metastatic, HER2+ with brain metastases, first-line therapy (unlabeled dosing):** Oral: 1000 mg/m^2 twice daily (in combination with lapatinib) on days 1-14 of a 3-week cycle until disease progression or unacceptable toxicity (Bachelot, 2012)

-**Colorectal cancer (unlabeled dosing):** Oral: 1000 mg/m^2 twice daily (in combination with oxaliplatin) on days 1-14 of a 3-week cycle for 8 or 16 cycles (Cassidy, 2008; Haller, 2011; Schmoll, 2007)

-**Esophageal and gastric cancers (unlabeled uses): Oral:**

-Preoperative or definitive chemoradiation: 800 mg/m^2 twice daily (in combination with cisplatin and radiation) on days 1-5 weekly for 5 weeks (Lee, 2007; NCCN Esophageal/Esophagogastric Cancers, v2.2013; NCCN Gastric Cancer, v2.2013) or 625 mg/m^2 twice daily (in combination with oxaliplatin and radiation) on days 1-5 weekly for 5 weeks (Javle, 2009; NCCN Esophageal/Esophagogastric Cancers, v2.2013; NCCN Gastric Cancer, v2.2013)

-Perioperative chemotherapy: 625 mg/m^2 twice daily (in combination with epirubicin and cisplatin or oxaliplatin) on days 1-21 of a 3-week cycle; 3 cycles administered both before

and after surgery (NCCN Esophageal/Esophagogastric Cancers, v2.2013; NCCN Gastric Cancer, v2.2013)

-Postoperative chemoradiation: 625-825 mg/m^2 twice daily on days 1-5 or days 1-7 weekly for 5 weeks (in combination with radiation) (Lee, 2006; NCCN Esophageal/Esophagogastric Cancers, v2.2013; NCCN Gastric Cancer, v2.2013)

-Locally-advanced or metastatic (chemoradiation not indicated): 1000-1250 mg/m^2 twice daily (monotherapy or in combination with cisplatin with or without trastuzumab) on days 1-14 of a 3-week cycle (Bang, 2010; Hong, 2004; Kang, 2009) or 625 mg/m^2 twice daily (in combination with epirubicin and cisplatin or oxaliplatin) on days 1-21 of a 3-week cycle for up to 8 cycles (Cunningham, 2008; Sumpter, 2005)

-**Hepatobiliary cancers, advanced (unlabeled use):** Oral: 650 mg/m^2 twice daily (in combination with gemcitabine) on days 1-14 of a 3-week cycle (Knox, 2005) or 1000 mg/m^2 twice daily (in combination with oxaliplatin) on days 1-14 of a 3-week cycle (Nehls, 2008) or 1250 mg/m^2 twice daily (in combination with cisplatin) on days 1-14 of a 3-week cycle (Kim, 2003); all regimens continued until disease progression or unacceptable toxicity

-**Neuroendocrine (pancreatic/islet cell) tumors, metastatic or unresectable**: Oral: 750 mg/m^2 twice daily (in combination with temozolomide) on days 1-14 of a 4-week cycle (Strosberg, 2011)

-**Ovarian, fallopian tube, or peritoneal cancer, platinum-refractory**: Oral: 1000 mg/m^2 twice daily on days 1-14 of a 3-week cycle until disease progression or unacceptable toxicity (Wolf, 2006)

-**Pancreatic cancer, metastatic (unlabeled use):** Oral: 1000 mg/m^2 twice daily on days 1-14 of a 3-week cycle (NCCN Pancreatic Cancer v1.2013) or 1250 mg/m^2 twice daily on days 1-14 of a 3-week cycle (Cartwright , 2002) or 830 mg/m^2 twice daily (in combination with gemcitabine) on days 1-21 of a 4-week cycle until disease progression or unacceptable toxicity (Cunningham, 2009)

-**Unknown primary cancer (unlabeled use):** Oral: 850-1000 mg/m^2 twice daily (in combination with oxaliplatin) on days 1-14 of a 3-week cycle for up to 6 cycles or until disease progression (Hainsworth, 2010; NCCN Occult Primary v1.2013) or 800 mg/m^2 twice daily (in combination with carboplatin and gemcitabine) on days 1-14 of a 3-week cycle for up to 8 cycles or until disease progression or unacceptable toxicity (Schneider, 2007).

Geriatric

The elderly may be more sensitive to the toxic effects of fluorouracil. Insufficient data are available to provide dosage modifications.

Renal impairment:

Renal impairment at treatment initiation:

- Cl_{cr} ≥51 mL/minute: Initial: No dosage adjustment necessary.
- Cl_{cr} 30-50 mL/minute: Initial: Administer 75% of usual dose (Superfin, 2007).
- Cl_{cr} <30 mL/minute: Use is contraindicated (Superfin, 2007)

Renal toxicity during treatment: Refer to dosage adjustment for toxicity.

Hepatic impairment:

Hepatic impairment at treatment initiation:

-Mild-to-moderate impairment: No starting dose adjustment is necessary (Ecklund, 2005; Superfin, 2007); however, carefully monitor patients.

-Severe hepatic impairment: No dosage adjustment provided in manufacturer's labeling (has not been studied).

Hepatotoxicity during treatment: Hyperbilirubinemia, grade 3 or 4: Interrupt treatment until bilirubin ≤3 times ULN.

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

See table (**Note:** Capecitabine dosing recommendations apply to both monotherapy and when used in combination therapy with docetaxel).

Monitor carefully for toxicity and adjust dose as necessary. Doses reduced for toxicity should not be increased at a later time. For combination therapy, also refer to docetaxel product labeling for docetaxel dose modifications. If treatment delay is required for either capecitabine or docetaxel, withhold both agents until appropriate to resume combination treatment.

Recommended Capecitabine Dose Modifications

Toxicity Grades	During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1	100%
2nd appearance	Interrupt until resolved to grade 0-1	75%
3rd appearance	Interrupt until resolved to grade 0-1	50%
4th appearance	Discontinue treatment permanently	
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1	75%
2nd appearance	Interrupt until resolved to grade 0-1	50%
3rd appearance	Discontinue treatment permanently	
Grade 4		

Recommended Capecitabine Dose Modifications		
Toxicity Grades	**During a Course of Therapy**	**Dose Adjustment for Next Cycle (% of starting dose)**
1st appearance	Discontinue permanently	
	or	
	If in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

Dosage adjustments for hematologic toxicity in combination therapy with ixabepilone:

-Neutrophils <500/mm^3 for ≥7 days or neutropenic fever: Hold for concurrent diarrhea or stomatitis until neutrophils recover to >1000/mm^3, then continue at same dose

-Platelets <25,000/mm^3 (or <50,000/mm^3 with bleeding): Hold for concurrent diarrhea or stomatitis until platelets recover to >50,000/mm^3, then continue at same dose

Common side effect:

>10%:

Cardiovascular: Edema (9% to 15%)

Central nervous system: Fatigue (16% to 42%), fever (7% to 18%), pain (12%)

Dermatologic: Palmar-plantar erythrodysesthesia (hand-and-foot syndrome) (54% to 60%; grade 3: 11% to 17%; may be dose limiting), dermatitis (27% to 37%)

Gastrointestinal: Diarrhea (47% to 57%; may be dose limiting; grade 3: 12% to 13%; grade 4: 2% to 3%), nausea (34% to 53%), vomiting (15% to 37%), abdominal pain (7% to 35%), stomatitis (22% to 25%), appetite decreased (26%), anorexia (9% to 23%), constipation (9% to 15%)

Hematologic: Lymphopenia (94%; grade 4: 14%), anemia (72% to 80%; grade 4: <1% to 1%), neutropenia (2% to 26%; grade 4: 2%), thrombocytopenia (24%; grade 4: 1%)

Hepatic: Bilirubin increased (22% to 48%; grades 3/4: 11% to 23%)

Neuromuscular & skeletal: Paresthesia (21%)

Ocular: Eye irritation (13% to 15%)

Respiratory: Dyspnea (14%)

5% to 10%:

Cardiovascular: Venous thrombosis (8%), chest pain (6%)

Central nervous system: Headache (5% to 10%), lethargy (10%), dizziness (6% to 8%), insomnia (7% to 8%), mood alteration (5%), depression (5%)

Dermatologic: Nail disorder (7%), rash (7%), skin discoloration (7%), alopecia (6%), erythema (6%)

Endocrine & metabolic: Dehydration (7%)

Gastrointestinal: Motility disorder (10%), oral discomfort (10%), dyspepsia (6% to 8%), upper GI inflammatory disorders (colorectal cancer: 8%), hemorrhage (6%), ileus (6%), taste perversion (colorectal cancer: 6%)

Neuromuscular & skeletal: Back pain (10%), weakness (10%), neuropathy (10%), myalgia (9%), arthralgia (8%), limb pain (6%)

Ocular: Abnormal vision (colorectal cancer: 5%), conjunctivitis (5%)

Respiratory: Cough (7%)

Miscellaneous: Viral infection (colorectal cancer: 5%)

Pregnancy Risk Factor: D