Regimen Monograph

A - Regimen Name

CAPE Regimen

Capecitabine

Disease Site Unknown Primary

Intent Palliative

Regimen Category **Evidence-Informed :**

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Supplementary Public Funding **capecitabine**
ODB - General Benefit (capecitabine) (ODB Formulary)

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B - Drug Regimen

capecitabine	1000-1250 mg /m²	PO	BID* Days 1 to 14

(*Total dose 2000-2500 mg/m^2/day, available in 150 mg and 500 mg tablets)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low – No routine prophylaxis; PRN recommended

Febrile Neutropenia Risk: Low

Other Supportive Care:

- Topical emollients (e.g. hand creams, udder balm) may ameliorate the manifestations of hand-foot syndrome in patients receiving capecitabine.
- Standard antidiarrheal agents (e.g. loperamide) should be initiated, as medically appropriate, as early as possible.

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Patients with baseline neutrophil counts of <1.5 x 10^9/L and/or thrombocyte counts of <100 x 10^9/L should not receive capecitabine therapy.

Patients should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Supportive care should be provided, including loperamide for diarrhea.

Doses should not be re-escalated if reduced for toxicity. Missed or omitted doses of capecitabine should not be replaced.

Dose modifications are mandatory for gastrointestinal, dermatological toxicity, neurotoxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

Non-hematologic Toxicity:

Toxicity	Action 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	Hold until resolved to ≤ grade 1	100%
2nd appearance	Hold until resolved to ≤ grade 1	75%
3rd appearance	Hold until resolved to ≤ grade 1	50%
4th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
1st appearance	Hold until resolved to ≤ grade 1	75%
2nd appearance	Hold until resolved to ≤ grade 1	50%

3rd appearance, OR any evidence of Stevens-Johnson syndrome or Toxic epidermal necrolysis	Discontinue treatment permanently	Not applicable
Grade 4 1st appearance, including SJS or TEN, OR cardiotoxicity OR acute renal failure	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue and no evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis, interrupt until resolved to ≤ grade 1.	Discontinue OR 50%
2nd appearance OR any occurrence of confirmed leukoencephalopathy	Discontinue permanently	Not applicable

Hematologic Toxicity:

Hold capecitabine during a treatment cycle in the presence of grade 3 or 4 hematologic toxicity.

Hepatic Impairment

Hepatic impairment	Capecitabine Dose
Mild to moderate impairment	No starting dose adjustment necessary
Severe	No data, has not been studied

Renal Impairment

Moderate renal impairment results in an increase in severe toxicity.

Creatinine Clearance (mL/min)	% of Starting Dose
51 - 80	100 % with close monitoring
30 - 50	75 % (use with caution)
<30	discontinue

Dosage in the Elderly

No dose adjustment for the starting dose is required but patients should be closely monitored. Older patients (≥ 65 years) are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3/4 adverse effects, especially when used in combination.

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F - Adverse Effects

Refer to capecitabine drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Palmar-plantar erythrodysesthesia syndrome (PPES) (may be severe)	• Diarrhea (may be severe) • Nausea, vomiting	• Mucositis • ↑ Bilirubin (may be severe) • Fatigue • Abdominal pain	• Cardiotoxicity • Arterial / Venous thromboembolism • Hypersensitivity • Myelosuppression +/- infection, bleeding • Leukoencephalopathy • GI perforation / obstruction • Nephrotoxicity • Hepatic failure • Idiopathic thrombocytopenic purpura • Eye disorders • Dehydration • Rash

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G - Interactions

Refer to capecitabine drug monograph(s) for additional details

- Concomitant use with sorivudine or analogues is contraindicated, given the increased risk of capecitabine toxicity (may be fatal). Wait at least 4 weeks after sorivudine (or chemically related analogues) treatment before starting capecitabine.
- Avoid concomitant administration with phenytoin as capecitabine may increase phenytoin levels.
- Caution and monitor with the coadministration of leucovorin as this may increase capecitabine toxicity.

- Caution and monitor PT/INR when administered with warfarin; capecitabine increases warfarin exposure.
- Caution with the use of proton pump inhibitors and monitor for reduced effectiveness of capecitabine; consider switching to a magnesium and aluminum hydroxide-containing antacid.

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H - Drug Administration and Special Precautions

Refer to capecitabine drug monograph(s) for additional details

Administration:

- Oral self-administration; drug available by outpatient prescription.
- Doses are given orally approximately 12 hours apart, within 30 minutes after the end of a meal.
- Swallow tablets whole; do not crush or cut tablets.
- If a capecitabine dose is missed, skip this and give the next dose at the usual time. Missed or omitted doses should not be replaced.
- Store tablets at 15ºC to 30ºC in the original package.

Contraindications:

- Patients who have a known hypersensitivity to capecitabine, its excipients, 5-fluorouracil or any ingredient in the formulation or component of the container.
- Patients with severe renal impairment (CrCl <30 mL/min).
- Patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Concomitant use with sorivudine or related analogues (i.e. brivudine), given potential fatal drug interaction.

Other Warnings/Precautions:

- Contains lactose and should not be used in patients with hereditary galactose/glucose/lactase disorders.

- Use with caution in patients with risk factors for dehydration, pre-existing renal dysfunction or on nephrotoxic agents.
- Use with caution in patients with a history of cardiovascular disease as well as patients taking anticoagulants such as warfarin.
- Patients with partial DPD deficiency - use with extreme caution. Refer to the DPD Deficiency Guidance for Clinicians for more information.

Pregnancy/Lactation:

- Capecitabine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.
    - Due to the potential for serious adverse reactions in the breastfed infant, breast-feeding is not recommended during treatment and for **2 weeks** after the last dose.
- Fertility effects: Probable

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; Baseline and at each visit
- Renal function tests; Baseline and as clinically indicated
- INR and/or PT; Baseline and as clinically indicated if patient is on anticoagulants
- Clinical toxicity assessment for diarrhea, dehydration, infection, stomatitis, rash or hand-foot syndrome, cardiac, hepatic and neurotoxicity; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Liver function tests; Baseline and as clinically indicated (if severe organ

failure suspected)

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Capecitabine drug monograph, Cancer Care Ontario.

Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19(21):4097-106.

Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001;19(8):2282-92.

April 2023 Updated DPD deficiency information in the Dose Modifications and Special Precautions sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

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undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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