**Regimen Monograph**



## A - Regimen Name

# DAC Regimen

**DOCEtaxel-DOXOrubicin-Cyclophosphamide**

| | |
|---|---|
| **Disease Site** | Breast |
| **Intent** | Neoadjuvant<br>Adjuvant |
| **Regimen Category** | **Evidence-Informed :**<br><br>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. |
| **Rationale and Uses** | Neoadjuvant treatment for non-metastatic breast cancer (inoperable locally advanced, inflammatory or to downsize tumour pre-surgery) or adjuvant therapy for node-positive and high risk node-negative breast cancer patients. If the tumour is HER2 positive, refer to the TRAS (Breast -Adjuvant) regimen for regimen and funding details. |

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## B - Drug Regimen

| | | | |
|---|---|---|---|
| **DOXOrubicin** | 50 mg /m² | IV | Day 1 |
| **cyclophosphamide** | 500 mg /m² | IV | Day 1 |
| **DOCEtaxel** | 75 mg /m² | IV | Day 1 |

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## C - Cycle Frequency

**REPEAT EVERY 21 DAYS**

For 6 cycles in the absence of disease progression or unacceptable toxicity

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## D - Premedication and Supportive Measures

**Antiemetic Regimen:** High

**Febrile Neutropenia Risk:** High

Consider G-CSF prophylaxis for patients at high risk of febrile neutropenia. See G-CSF recommendations.

In some studies, febrile neutropenia rates of up to 25% were reported, including deaths. Antibiotic prophylaxis (e.g. ciprofloxacin 500mg PO bid x 10d, starting on day 5) was used in most clinical trials, especially when growth factors were not used.

**Other Supportive Care:**

Also refer to CCO Antiemetic Summary

- dexamethasone 8 mg bid po for 3 days starting 1 day prior to docetaxel (prevent anaphylaxis / fluid retention).

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## E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

**Dosage with toxicity**

| **Worst Toxicity / Counts x $10^9$/L in Prior Cycle** | **Doxorubicin (% previous dose)** | **Cyclophosphamide (% previous dose)** | **Docetaxel (% previous dose)** |
|---|---|---|---|
| ANC < 0.5 ≥ 7 days; Thrombocytopenic bleeding; Febrile neutropenia | 75% * (or consider GCSF – for isolated neutropenia) | | |
| Cardiotoxicity ** | Discontinue | Caution | Caution |
| Grade 3 neurotoxicity; Grade 3 skin toxicity | 100% | | 75%*; Discontinue if recurs |
| Other grade 3 related organ / non-hematologic | 75% for suspect drug(s)* | | |
| Grade 4 related organ / non-hematologic | Discontinue | | |

* Do not retreat until toxicity recovered to ≤grade 2 and platelets ≥100x$10^9$/L, and ANC ≥1.5x$10^9$/L.
** Including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the lower limit of normal, a greater than 20% decline in LVEF from any level, or LVEF ≤ 45%.

**Hypersensitivity**

Hypersensitivity reactions may occur within a few minutes following the initiation of docetaxel infusion

| **Toxicity** | **Action** |
|---|---|
| Mild hypersensitivity reaction | ↓ infusion rate (and/ or hold) and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate. Consider premedication for next infusion. |
| Moderate hypersensitivity reaction | Hold and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate; complete infusion at ↓ rate if possible. Use premedication for next infusion. |
| Severe hypersensitivity | Hold and manage symptoms aggressively with beta-agonists, antihistamines, antipyretics, and/or corticosteroids. Discontinue |

| | |
|---|---|
| reaction or Pulmonary Toxicity | permanently and do not rechallenge |

**Hepatic Impairment**

| | **AST and/or ALT** | | **Alk Phosp** | **Cyclophosphamide (% previous)** | **Doxorubicin (% previous)** | **Docetaxel (% previous)** |
|---|---|---|---|---|---|---|
| Mild-moderate | > 1.5 - 3.5 X ULN | AND | > 2.5 to 6 x ULN | 100%; caution with moderate hepatic impairment | 50-75% | Do not treat |
| Severe | > 3.5 x ULN | OR | > 6 x ULN | Caution | Discontinue | Do not treat. Discontinue* if treatment already started. |

*Discontinue if bilirubin > ULN and any AST/ALT/Alk phosp

**Renal Impairment**

Renal failure may lead to the reduced excretion of metabolites and increased toxicity of cyclophosphamide. Significant falls in creatinine clearance (25-80%) with increased exposure have been documented in patients with renal impairment. Cyclophosphamide is hemodialysable.

| **Creatinine Clearance (mL/min)** | **Cyclophosphamide (% of previous)** | **Doxorubicin (% of previous)** | **Docetaxel (% of previous)** |
|---|---|---|---|
| > 50 | 100% | 100% | 100% |
| 10 - 50 | 75% | 100% | 100% |
| <10 | Use with extreme caution or OMIT | 100% | 100% |

**Dosage in the Elderly**

No dose modification routinely required with docetaxel, cyclophosphamide and doxorubicin; caution should be exercised, especially in elderly patients with poor performance status.

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## F - Adverse Effects

Refer to DOXOrubicin, cyclophosphamide, DOCEtaxel 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 |
|---|---|---|---|
| • Alopecia<br>• Fatigue<br>• Nausea and vomiting<br>• Myelosuppression ± infection / bleeding (may be severe) | • Fluid retention (may be severe)<br>• Neuropathy (may be severe)<br>• Hypersensitivity reactions (may be severe)<br>• Mucositis, diarrhea, anorexia<br>• Skin and nail effects (may be severe)<br>• Musculoskeletal pain<br>• Constipation<br>• Irregular | • Fever<br>• Lacrimation / tear duct obstruction<br>• Dyspepsia<br>• Taste changes<br>• Hot flashes<br>• Headache<br>• Abdominal pain | • Cardiotoxicity, AMI, arrhythmia<br>• Arterial thromboembolism<br>• Venous thromboembolism<br>• DIC<br>• Hemolytic uremic syndrome<br>• Venous occlusive disease<br>• SIADH<br>• Secondary leukemia / malignancies<br>• Pneumonitis<br>• GI obstruction, |

| | | | |
|---|---|---|---|
| | menses, amenorrhea | | perforation<br>• Pancreatitis<br>• Rhabdomyolysis<br>• Extravasation (doxorubicin) |

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## G - Interactions

Refer to DOXOrubicin, cyclophosphamide, DOCEtaxel drug monograph(s) for additional details

- CYP2D6 inhibitors (doxorubicin)
- P-glycoprotein inducers and inhibitors (docetaxel, doxorubicin)
- CYP3A4 inhibitors, substrates, and inducers (docetaxel and doxorubicin)
- Barbiturates, quinolones, calcium channel blockers (cyclophosphamide)
- Cardiac gylcosides (doxorubicin, cyclophosphamide)
- CYP2B6 inhibitors (cyclophosphamide, doxorubicin), substrates (doxorubicin), and inducers (cyclophosphamide)

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## H - Drug Administration and Special Precautions

Refer to DOXOrubicin, cyclophosphamide, DOCEtaxel drug monograph(s) for additional details

**Administration:**

**Docetaxel:**

- Mix in 250mL D5W or NS to a maximum concentration of 0.3-0.74 mg/mL. For doses over 185 mg, use a larger volume of the infusion vehicle so the maximum concentration is not exceeded.
- ALWAYS premedicate with dexamethasone. Infuse through main IV line over 1 hour.
- Use non-PVC equipment to minimize patient exposure to DEHP.
- To minimize hypersensitivity reactions, docetaxel infusion should be started at a slow rate, then increased incrementally to planned rate (e.g. infuse at an 8 hourly rate for 5 minutes, then at a 4 hourly rate for 5 minutes, then at a 2 hourly rate for 5 minutes, then finally, resume at the 1 hourly infusion rate).

**Doxorubicin:**

- Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline or 2/3-1/3). Depending on the dose volume and vein condition, administer the dose between 3 to at least 10 minutes to minimize thrombosis risk or perivenous extravasation.
- Do not admix with other drugs unless data are available;
- Avoid contact with alkaline solutions as this can lead to hydrolysis of doxorubicin
- Slow down injection rate if erythematous streaking or facial flushing occurs.
- If any signs or symptoms of extravasation occur, the injection or infusion should be immediately terminated and restarted in another vein. Any known or suspected extravasation should be managed promptly

**Cyclophosphamide:**

- Oral hydration is strongly encouraged; for IV cyclophosphamide: 2-3 L of fluid/day; poorly hydrated patients may need more IV hydration. Inadequate total hydration may result in dose-related hemorrhagic cystitis. Patients should be encouraged to empty their bladder frequently to minimize dwell times

| Dose | Suggested Dilution volume and rate |
|---|---|
| < 1000 mg | 100 mL sodium chloride 0.9% over 15 minutes |
| > 1000 mg | 250 mL sodium chloride 0.9% over 30 minutes |

- sodium chloride 0.9% to reconstitute cyclophosphamide
- Do not reconstitute or dilute with benzyl alcohol-containing solutions (ie. Bacteriostatic sodium chloride), since it may catalyse the decomposition of cyclophosphamide or cause toxicity in infants
- Avoid the use of aluminium-containing preparation and administration equipment, since darkening of aluminium and gas production have been reported

**Contraindications:**

- Patients who have a hypersensitivity to cyclophosphamide, doxorubicin or any of its components, other anthracyclines or anthracenediones (i.e. epirubicin, daunorubicin, mitoxantrone or mitomycin C)
- Patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80
- Patients with persistent myelosuppression or with severe liver impairment
- Patients with urinary outflow obstruction (cyclophosphamide)
- Severe myocardial insufficiency, arrhthymias or history of cardiac disease or recent myocardial infarction

- Previous treatment with maximum cumulative doses of doxorubicin, other anthracyclines or anthracenediones
- Avoid the use of live vaccines; use may result in serious infections in immunocompromised patients

**Other warnings/precautions:**

- Use docetaxel with caution in patients with pre-existing effusions or ascites.
- Docetaxel contains ethanol and may be administered with agents such as antihistamines which may cause drowsiness. Patients should be cautioned regarding driving and the use of machinery.
- Caution use of cyclophosphamide in patients with adrenal insufficiency and in combination with neuromuscular blockers.
- All 3 medications are 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 contraindicated in patients on docetaxel and is not recommended with doxorubicin and cyclophosphamide.

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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 before each cycle
- Liver function tests; baseline and before each treatment
- Renal function tests; baseline and before each treatment
- Cardiac examination especially with risk factors (including prior therapy with epirubicin, mitoxantrone, or other cardiotoxic drug), or a cumulative doxorubicin dose of > 450 mg/m$^2$; baseline and as clinically indicated
- Clinical toxicity assessment (including GI, cardiotoxicity, local toxicity, cystitis, neurologic, skin and nails, fluid retention, ophthalmic, hypersensitivity, fatigue, infection, bleeding, musculoskeletal pain, thromboembolism, respiratory effects); at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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## J - Administrative Information

| | |
|---|---|
| Approximate Patient Visit | 2 to 2.5 hours |
| Pharmacy Workload (average time per visit) | 45.0 minutes |
| Nursing Workload (average time per visit) | 84.167 minutes |

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## K - References

Cyclophosphamide, docetaxel and doxorubicin drug monographs, Cancer Care Ontario.

Costa SD, Loibl S, Kaufmann M, et al. Neoadjuvant chemotherapy shows similar response in patients with inflammatory or locally advanced breast cancer when compared with operable breast cancer: a secondary analysis of the GeparTrio trial data. J Clin Oncol. 2010 Jan 1;28(1):83-91.

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Martín M, Seguí MA, Antón A, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. N Engl J Med 2010;363(23):2200-10.

Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302-13.

Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365(14):1273-83.

Swain SM, Jeong JH, Geyer CE Jr, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 2010;362(22):2053-65.

Swain SM, Tang G, Geyer CE, et al. NSABP B-38: Definitive analysis of a randomized adjuvant trial comparing dose-dense (DD) AC→paclitaxel (P) plus gemcitabine (G) with DD AC→P and with docetaxel, doxorubicin, and cyclophosphamide (TAC) in women with operable, node-positive breast cancer. J Clin Oncol 2012 (suppl; abstr LBA1000).

von Minckwitz G, Kummel S, Vogel P, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. Journal of the National Cancer Institute 2008;100(8):542-51.

von Minckwitz G, Kummel S, Vogel P, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. Journal of the National Cancer Institute 2008;100(8):552-62.

**PEBC Advice Documents or Guidelines**

- Optimal Systemic Therapy for Early Female Breast Cancer

**September 2016** updated dosage with hepatic impairment table for docetaxel

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## M - Disclaimer

*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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