

## Regimen Monograph

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## A - Regimen Name

## CISPGEMC(W) Regimen

CISplatin-Gemcitabine

**Disease Site** Breast

**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.

**Rationale and Uses** Treatment of metastatic breast cancer, in patients who have received at least one prior treatment in the palliative setting.

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## B - Drug Regimen

<a href="#">CISplatin</a>	30 mg /m <sup>2</sup>	IV	Days 1 and 8
<a href="#">gemcitabine</a>	750 mg /m <sup>2</sup>	IV	Days 1 and 8

**Note:** Some studies used cisplatin 20 mg/m<sup>2</sup> and gemcitabine 600 mg/m<sup>2</sup> if the patient had received more than two lines of chemotherapy.

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Until disease progression or unacceptable toxicity

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**Antiemetic Regimen:** Moderate

**Other Supportive Care:**

Also refer to [CCO Antiemetic Summary](#)

All patients should receive adequate hydration and premedication for emesis, according to local guidelines.

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

**Dosage with toxicity**

Dose on Day 1 of Cycle:

Worst Toxicity in Previous Cycle		Gemcitabine	Cisplatin
<b>Non-Hematologic (related organ)</b>		<b>% Full Dose<sup>1</sup></b>	<b>% Full Dose<sup>1</sup></b>
Grade 3	or	75% <sup>2</sup>	75%
	Febrile neutropenia, thrombocytopenic bleeding, ANC < 0.5 for > 5 days or < 0.1 for > 3 days, or platelets < 25		

Grade 4			Consider discontinuing, or ↓ to 50-75% <sup>3</sup>	Consider discontinuing, or ↓ to 50-75% <sup>3</sup>
> 1 occurrence of Day 8 holds			75%	100%
Pneumonitis			Hold and investigate. If confirmed, discontinue	Hold and investigate. If confirmed, discontinue.
Hemolytic Uremic Syndrome (HUS), Capillary Leak Syndrome (CLS)			Discontinue	Consider Discontinue
Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)			Discontinue	Consider Discontinue
Posterior reversible encephalopathy syndrome (PRES)			Discontinue	
<p><sup>1</sup> Do not retreat until ANC ≥ 1.5 x 10<sup>9</sup>/L, platelets ≥ 100 x 10<sup>9</sup>/L and toxicity ≤ grade 2</p> <p><sup>2</sup> if toxicity recurs after gemcitabine dose reduction, omit day 8 gemcitabine</p> <p><sup>3</sup> If the reduced dose is tolerated well, a re-increase to 75% may be considered for the following cycle</p>				

Dose on Day 8 of Cycle:

Toxicity on Day 8 of cycle					Day 8 dose	
Non-hematologic (related organ)		Hematologic			Gemcitabine (% Full Dose)	Cisplatin (% Full Dose)
		ANC (x 10 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)		
≤ grade 2	and	≥ 1.5	and	≥ 100	100%	100%
≤ grade 2	and	1.0-1.49	and/or	75-99	↓ to 50%	↓ to 50%
grade 3 or 4	and/or	< 1.0	and/or	< 75	Omit	Omit

Pneumonitis, HUS SJS TEN CLS		-		-	Discontinue	Consider Discontinue
PRES		-		-	Discontinue	

### Cisplatin - Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of [Management of Cancer Medication-Related Infusion Reactions](#).

There is insufficient evidence that routine prophylaxis with extended cisplatin infusion reduces IR rates.

Grade	Management	Re-challenge
1 or 2	<ul style="list-style-type: none"> <li>Stop or slow the infusion rate.</li> <li>Manage the symptoms.</li> </ul> <p><b>Restart:</b></p> <ul style="list-style-type: none"> <li>After symptom resolution, restart with pre-medications ± reduced infusion rate.</li> </ul>	<ul style="list-style-type: none"> <li>Consider pre-medications* and infusing at a reduced infusion rate prior to re-challenge.</li> <li>May consider adding oral montelukast ± oral acetylsalicylic acid.</li> </ul>
3 or 4	<ul style="list-style-type: none"> <li>Stop treatment.</li> <li>Aggressively manage symptoms.</li> </ul>	<ul style="list-style-type: none"> <li>Re-challenge is discouraged, especially if vital signs have been affected.</li> <li>Consider desensitization if therapy is necessary.</li> </ul>

\* Up to 50% of patients can experience recurrent reactions during re-challenge **despite** using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist)

### Hepatic Impairment

Gemcitabine should be used with caution in patients with hepatic impairment (cirrhosis, hepatitis, alcoholism, metastases, etc.); initial dose reduction should be considered if the patient is treated, especially in hyperbilirubinemia.

<b>Bilirubin</b>	<b>Suggested Gemcitabine Starting Dose (% of usual dose)</b>	<b>Cisplatin</b>
> 1.2 x ULN	Consider dose reduction; 80%	No dosage adjustment required

### **Renal Impairment**

In some clinical trials, patients were not treated with cisplatin unless CrCl  $\geq$  45mL/min. If the benefit of continued treatment is clinically warranted, the following dose modifications could be considered at the physician's discretion:

<b>Creatinine Clearance (mL/min)</b>	<b>Cisplatin (% previous dose)</b>	<b>Gemcitabine</b>
46-60	75%	Use with caution; insufficient information for recommendation. Close monitoring for occurrence of hemolytic uremic syndrome is required.
30-45	50% or consider discontinuing	
< 30	Discontinue	

### **Dosage in the Elderly**

Geriatric patients may be at higher risk of developing nephrotoxicity, ototoxicity/neurotoxicity or hematologic adverse effects with cisplatin. Gemcitabine clearance is lower in the elderly but no dose adjustment necessary.

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**F - Adverse Effects**

Refer to [CISplatin](#), [gemcitabine](#) 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
<ul style="list-style-type: none"> <li>• Myelosuppression ± infection, bleeding (may be severe)</li> <li>• ↑ LFTs (may be severe)</li> <li>• Nausea or vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Fatigue, flu-like symptoms</li> <li>• Nephrotoxicity (may be severe)</li> <li>• Abnormal electrolytes</li> <li>• Proteinuria</li> <li>• Neurotoxicity, ototoxicity</li> <li>• Rash (may be severe)</li> </ul>	<ul style="list-style-type: none"> <li>• Edema</li> <li>• Musculoskeletal pain</li> <li>• Alopecia (generally mild)</li> <li>• Diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• Pneumonitis/ARDS</li> <li>• Capillary leak syndrome</li> <li>• Posterior reversible encephalopathy syndrome</li> <li>• Leucoencephalopathy</li> <li>• Seizures</li> <li>• Optic neuritis/other eye disorders</li> <li>• Hyperuricemia</li> <li>• Hemolytic-uremic syndrome</li> <li>• Thrombotic microangiopathy</li> <li>• SIADH</li> <li>• Arterial and venous thromboembolism</li> <li>• Arrhythmia</li> <li>• Cardiotoxicity</li> <li>• Hypersensitivity</li> <li>• Injection site reaction</li> <li>• Toxic epidermal necrolysis</li> <li>• Stevens-Johnson syndrome</li> <li>• Radiosensitization</li> <li>• Vasculitis</li> <li>• Raynaud's</li> <li>• Secondary malignancy</li> </ul>

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## G - Interactions

Refer to [CISplatin](#), [gemcitabine](#) drug monograph(s) for additional details

- Ascertain renal function prior to giving renally excreted drugs; monitor for toxicity
- Avoid nephrotoxic drugs; use with extreme caution during or shortly after cisplatin treatment (1 to 2 weeks)
- Avoid concomitant use of ototoxic drugs and cisplatin; use with extreme caution if essential
- Monitor serum levels for anticonvulsant agents (valproic acid, carbamazepine, phenytoin) when used with cisplatin, and adjust dose if necessary
- Monitor INR closely with concurrent warfarin use and adjust warfarin dose as needed, as gemcitabine may decrease metabolism and synthesis of clotting factors.
- Gemcitabine is a known radiosensitizer.

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## H - Drug Administration and Special Precautions

Refer to [CISplatin](#), [gemcitabine](#) drug monograph(s) for additional details

### Administration – Cisplatin:

- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Drug dilution and infusion durations vary according to the regimen. Some centres dilute cisplatin in 500 mL NS.
- All patients should receive adequate hydration and premedication for emesis, according to local guidelines.
- Additional hydration may be ordered for hypovolemic patients.
- Hydration and diuresis for patients with pre-existing renal, cardiac, or diabetic history at discretion of physician.
- Adequate hydration and urinary output must be maintained for 24 hours following cisplatin treatment.
- Oral hydration with 8 glasses of fluid per day is strongly encouraged on treatment day and for 1-2 days after cisplatin; if nausea and vomiting prevent oral hydration, the patient may need to return for more IV hydration.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur.

Also refer to the CCO guideline for detailed description of [Management of Cancer Medication-Related Infusion Reactions](#).

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**Administration – gemcitabine:**

- May dilute reconstituted drug in normal saline for IV infusion, resulting in a minimum final concentration of at least 0.1 mg/mL.
- Gemcitabine is for IV administration only and should be infused over 30 minutes.
- To prevent increased toxicity, avoid an infusion time of > 60 minutes or dosing more frequently than once weekly.

**Contraindications:**

- patients with known hypersensitivity to gemcitabine or platinum containing compounds
- Patients who are myelosuppressed (cisplatin)
- Patients with pre-existing renal impairment and hearing impairment, unless the possible benefits of treatment outweigh the risks (cisplatin)

**Other Warnings/Precautions:**

- Use gemcitabine with extreme caution in patients with compromised bone marrow reserve.
- Use gemcitabine with caution in patients with hepatic impairment (including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis) and patients with renal impairment.
- Acute shortness of breath with a temporal relationship to gemcitabine injection administration may occur
- Patients receiving concurrent radiation while receiving full dose gemcitabine should be closely monitored for reactions. Potentially life-threatening esophagitis and pneumonitis, particularly in patients receiving large volumes of radiotherapy have been observed.

**Pregnancy and Lactation:**

- Cisplatin and gemcitabine are not recommended for use in pregnancy. Appropriate contraception should be used by both sexes during treatment, and for at least **6 months** in females (general recommendation) and **2 years** in males after the last dose.
- Male patients should not donate semen while using cisplatin and up to 2 years after the last dose.
- Breastfeeding is not recommended (cisplatin is secreted into breast milk).
- Fertility effects: Yes

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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 treatment
- Liver function tests; baseline and before each cycle
- Renal function tests; baseline and before each cycle
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium; baseline and before each cycle
- Audiogram; baseline and as clinically indicated
- Clinical toxicity assessment (infection, bleeding, flu-like symptoms, injection site reactions, fatigue, edema, rash, nausea/vomiting and other GI effects, neurotoxicity, ototoxicity, thromboembolism, signs/symptoms of capillary leak syndrome, cardiovascular or respiratory effects); at each visit
- Grade toxicity using the current [NCI-CTCAE \(Common Terminology Criteria for Adverse Events\) version](#)

### Suggested Clinical Monitoring

- Urinalysis; baseline and as clinically indicated
- INR for patient receiving warfarin; baseline and as clinically indicated

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## J - Administrative Information

Approximate Patient Visit	3 hours
Pharmacy Workload (average time per visit)	34.104 minutes
Nursing Workload (average time per visit)	46.667 minutes

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## K - References

Chew HK, Doroshow JH, Frankel P, et al. Phase II studies of gemcitabine and cisplatin in heavily and minimally pretreated metastatic breast cancer. *J Clin Oncol*. 2009 May 1;27(13):2163-9.

Cisplatin and gemcitabine drug monographs, Cancer Care Ontario.

Heinemann V, Stemmler HJ, Wohlrab A, et al. High efficacy of gemcitabine and cisplatin in patients with predominantly anthracycline- and taxane-pretreated metastatic breast cancer. *Cancer Chemother Pharmacol*. 2006 May;57(5):640-6.

Nagourney RA, Link JS, Blitzer JB, et al. Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. *J Clin Oncol*. 2000 Jun;18(11):2245-9.

Sánchez-Escribano Morcuende R, Alés-Martínez JE, et al. Low dose gemcitabine plus cisplatin in a weekly-based regimen as salvage therapy for relapsed breast cancer after taxane-anthracycline-containing regimens. *Clin Transl Oncol*. 2007 Jul;9(7):459-64.

**June 2021** Updated Dose Modifications, Adverse effects, Interactions, Drug administration and precautions and Monitoring 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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### **Regimen Monographs**

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

*The information set out in the drug monographs, regimen monographs, appendices and symptom management*

*information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.*

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*Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.*

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