Regimen Monograph

A - Regimen Name

CISPPEME Regimen

CISplatin-Pemetrexed

Disease Site

Lung
Mesothelioma (Pleural)

Intent

Curative
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

First-line treatment of patients with advanced symptomatic malignant pleural mesothelioma

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B - Drug Regimen

pemetrexed	500 mg /m²	IV in 100 mL NS over 10 minutes	Day 1
CISplatin	75 mg /m²	IV over 2 hours; 30 minutes after the end of Pemetrexed	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity, usually up to 6 cycles due to cumulative cisplatin toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: High

Other Supportive Care:

Also refer to CCO Antiemetic Summary

- Standard regimens for Cisplatin premedication and hydration should be followed when used in combination with pemetrexed. Refer to local guidelines.
- Vitamin B12 1000mcg IM every 9 weeks, Folic acid 0.4 - 1 mg PO daily (both starting ≥ 1 week prior to pemetrexed administration; continue throughout and 3 weeks after last dose of Pemetrexed).
- Dexamethasone 4mg PO BID for 3 days starting day before chemotherapy suggested for rash prophylaxis.
- Note: NSAIDs should be held for 2-5 days prior and 2 days after pemetrexed.

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E - Dose Modifications

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

Dosage with toxicity

Worst toxicity in previous cycle	Pemetrexed (% previous dose)*	Cisplatin (% previous dose, if applicable)*
Thrombocytopenic bleeding	50%	50%
Grade 4 ANC or ≥ Grade 3 platelets	75%	75%
Grade 2 neurotoxicity	100%	50%
Grade 3 or 4 mucositis	50%	100%
Diarrhea requiring hospitalization, or grade 3 or 4	75%	75%
Grade 3 or 4 neurotoxicity	Discontinue	
Symptoms suggesting pneumonitis	Hold and investigate; discontinue if confirmed	
Other Grade 3 related organ / non-hematologic toxicity	75%	75%
Other Grade 4 related organ / non-hematologic toxicity	Discontinue	
Grade 3 or 4 toxicity after 2 prior dose reductions, any occurrence of Stevens-Johnson syndrome, Toxic epidermal necrolysis	Discontinue	
*Start next cycle only when ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and related organ/non-hematologic toxicity ≤ grade 2 (or recovery to baseline).		

Hepatic Impairment

Pemetrexed is not extensively metabolized in the liver. No specific studies have been performed in patients with moderate or severe hepatic impairment. Pemetrexed should be used with caution in patients with hepatic impairment. Refer to the dose modification table above.
CISplatin: No adjustment required.

Renal Impairment

Creatinine clearance (mL/min)	Cisplatin (% previous dose)	Pemetrexed (% previous dose)
61-79	100%	100%; but use NSAIDs with extreme caution
45-60	75%	
30-<45	50%	Discontinue
<30	Discontinue	Discontinue

Dosage in the Elderly

No dose adjustments are needed but patients should be monitored closely. Myelosuppression, infection, nausea and renal effects are more common in the elderly in combination with cisplatin for NSCLC.

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F - Adverse Effects

Refer to pemetrexed, CISplatin 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
• Nausea, vomiting (may be severe)	• Nephrotoxicity (may be severe) • Fatigue • Hearing impairment • Myelosuppression +/- infection, bleeding (may be severe)	• Anorexia • Mucositis (may be severe) • Rash (may be severe) • Diarrhea (may be severe) • Abnormal electrolytes	• Neuropathy • Radiation recall reaction • Arterial/venous thromboembolism • Arrhythmia • GI perforation, ulcer • Hemolysis • Hemolytic uremic syndrome

			• Hypersensivity • Pneumonitis • Vasculitis • Secondary malignancy

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G - Interactions

Refer to pemetrexed, CISplatin drug monograph(s) for additional details

- Nephrotoxic drugs (e.g. aminoglycosides) may increase the toxicity of pemetrexed and exacerbate nephro and ototoxicity with cisplatin; avoid if possible, or caution during or shortly after cisplatin therapy (for 1-2 weeks)
- NSAIDs may increase the toxicity of pemetrexed. Hold NSAIDs with shorter half-lives (e.g. ibuprofen) at least 2 days before to 2 days after pemetrexed. Hold NSAIDs with long half-lives (e.g. piroxicam) 5 days before to 2 days after pemetrexed.
- Phenytoin levels may be altered by cisplatin. Monitor and adjust phenytoin dose as required.

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H - Drug Administration and Special Precautions

Refer to pemetrexed, CISplatin drug monograph(s) for additional details

Administration

Cisplatin:

- Ensure good urinary output during chemotherapy visit. Patient should void at least once during chemotherapy visit. Use locally approved hydration regimens.
- Blood pressure should be taken before and after chemotherapy.
- 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.
- 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.
- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur.

Pemetrexed:

- Reconstitute as directed with Normal Saline.
- Dilute drug in 100mL (Normal Saline only); Infuse IV over 10 minutes.
- Incompatible with calcium-containing solutions.
- Do not co-administer with other drugs and diluents.
- Keep unopened vials at room temperature. Pemetrexed is not light sensitive.

Contraindications

- Patients who have a hypersensitivity to these drugs or other platinum-containing compounds
- Patients who are myelosuppressed
- Patients with moderate-severe renal impairment (CrCl < 45 ml/min)
- Patients with hearing impairment, unless the possible benefits outweigh the risk
- Avoid the use of live vaccines

Other warnings/precautions

- Patients with pre-existing cardiovascular risk factors

Pregnancy & lactation

- This regimen is **not recommended** for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is **not recommended** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

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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 regular
- Renal function tests; baseline and regular, including electrolytes

- Audiogram; baseline and as clinically indicated
- Clinical toxicity assessment for neurotoxicity, ototoxicity, hypersensitivity, bleeding, infection, GI, and pulmonary 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	4-6 hours
Pharmacy Workload (average time per visit)	41.935 minutes
Nursing Workload (average time per visit)	46.667 minutes

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K - References

Cisplatin and pemetrexed drug monographs, Cancer Care Ontario.

Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol 2008;3(7):756-63.

Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21(14):2636-44.

PEBC Advice Documents or Guidelines

- Endorsement of the 2018 ASCO Treatment of Malignant Pleural Mesothelioma Guideline

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M - Disclaimer

Regimen Abstracts

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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.

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