**Drug Monograph**

**Drug Name**

**Mechanism of Action and Pharmacokinetics**

**Indications and Status**

**Adverse Effects**

**Dosing**

**Administration Guidelines**

**Special Precautions**

**Interactions**

**Recommended Clinical Monitoring**

**Supplementary Public Funding**

**References**

**Disclaimer**

---

**A - Drug Name**

pemetrexed

COMMON TRADE NAME(S): Alimta®

back to top

**B - Mechanism of Action and Pharmacokinetics**

Pemetrexed is a pyrrolopyrimidine antifolate that exerts its antineoplastic activity by inhibiting thymidylate synthase (TS), glycaminide ribonucleotide formyltransferase (GARFT) and dihydrofolate reductase (DHFR), which are involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide synthesis.

**Distribution**

Pemetrexed plasma concentration-time functions followed a two-compartment model. PK are dose proportional and no accumulation occurs over multiple cycles. Pemetrexed is primarily confined to the plasma and interstitial compartments. Accumulation in 3rd spaces may occur.

<table>
<thead>
<tr>
<th>Cross blood brain barrier?</th>
<th>No information found</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPB</td>
<td>81 %</td>
</tr>
</tbody>
</table>

**Metabolism**

Pemetrexed is not metabolized to an appreciable extent.

<table>
<thead>
<tr>
<th>Active metabolites</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive metabolites</td>
<td>No information found</td>
</tr>
</tbody>
</table>

**Elimination**

70 to 90% excreted as unchanged drug

<table>
<thead>
<tr>
<th>Urine</th>
<th>70 to 90% excreted as unchanged drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>3.5 hours</td>
</tr>
</tbody>
</table>

back to top

**C - Indications and Status**

---

Any use of the information is subject, at all times, to CCO’s Terms and Conditions.

CCO Formulary - December 2019
Health Canada Approvals:

- In combination with cisplatin for the first-line treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery
- In combination with cisplatin for initial treatment of good performance status patients with locally advanced or metastatic nonsquamous non-small cell lung cancer
- Monotherapy as a treatment option for patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy*
- Monotherapy as maintenance treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer, in good performance status patients without disease progression, immediately following 4 cycles of first-line platinum doublet chemotherapy

* Approval is based on similarity of the response rate, median survival rate and 1-year survival rate, for the overall study population, between pemetrexed and docetaxel.

D - Adverse Effects

Emetogenic Potential: Low
Extravasation Potential: Minimal

The following table lists adverse effects that occurred in >1% of patients in phase III trials with pemetrexed monotherapy. Severe adverse events from other studies or post-marketing, may also be included.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT* (%)</th>
<th>ONSET**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Arrhythmia (&lt;1%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Arterial thromboembolism (rare)</td>
<td>E D</td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolism (rare)</td>
<td>E D</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Alopecia (6%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Radiation recall reaction (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Rash (14%) (may be severe)</td>
<td>E</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain (3%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Anorexia (22%)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Constipation (6%)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Diarrhea (13%) (may be severe)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Gl perforation (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Gl ulcer (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Mucositis (15%) (including esophagitis, may be severe)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting (31%)</td>
<td>I</td>
</tr>
</tbody>
</table>
### General
- Edema (8%) E
- Fatigue (34%) I E

### Hematological
- Hemolysis (rare) E
- Myelosuppression ± infection, bleeding (15%) (3% severe) E

### Hepatobiliary
- ↑ LFTs (10%) (may be severe) E

### Hypersensitivity
- Hypersensitivity (1%) I

### Nervous System
- Neuropathy (9%) D

### Ophthalmic
- Eye disorders (≤5%) (including conjunctivitis and increased lacrimation) E

### Renal
- Creatinine increased (2%) (may be severe) E D

### Respiratory
- Pneumonitis (rare) E

### Vascular
- Peripheral ischemia (rare) E

---

* *Incidence* may refer to an absolute value or the higher value from a reported range.

"Rare" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = immediate (onset in hours to days)   E = early (days to weeks)
  D = delayed (weeks to months)   L = late (months to years)

The most common side effects for pemetrexed include fatigue, nausea, vomiting, anorexia, mucositis, myelosuppression ± infection, bleeding, rash, diarrhea and ↑ LFTs.

Severe myelosuppression is often dose-limiting for pemetrexed. Sepsis, in some cases fatal, have occurred in approximately 1% of patients in clinical trials. Prophylactic folic acid and intramuscular vitamin B12 supplements are necessary to reduce hematologic or non-hematologic toxicities.

Pemetrexed may cause serious and in some cases fatal dermatologic toxicities. Rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Severe (and potentially fatal) renal toxicity has been reported with pemetrexed. Renal toxicity may occur with single-agent pemetrexed or when used in combination with other chemotherapy agents.

Pneumonitis has been reported and may occur more frequently in association with radiation.

Radiation recall may occur in patients administered pemetrexed who received radiation previously (weeks to years).

---

### E - Dosing

Refer to protocol by which patient is being treated.

NSAIDs should be held for at least 2-5 days prior to, and at least 2 days after pemetrexed infusion (see Interactions section).

**Premedications:**
Vitamin supplementation starting ≥ 1 week prior to first pemetrexed dose; continue until 3 weeks after last dose to reduce treatment-related toxicities:

- Folic acid 0.4 mg - 1mg PO daily
- Vitamin B₁₂ 1000 mcg IM q9 weeks

Dexamethasone (e.g. 4mg PO BID) beginning on the day before chemotherapy for a total of 3 days to reduce the incidence and severity of cutaneous reactions.

Patients should not begin a new treatment cycle unless:

- ANC ≥ 1.5 x 10⁹/L
- Platelets ≥ 100 x 10⁹/L
- Creatinine clearance is ≥ 45 mL/min

**Adults:**

Single agent or in combination with cisplatin:

500mg/m² IV on Day 1 q 3 weeks

**Dosage with Toxicity:**

**Single-agent:**

**Hematologic:**

<table>
<thead>
<tr>
<th>Worst toxicity in previous cycle</th>
<th>Grade</th>
<th>Pemetrexed (% previous dose)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenic bleeding</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>ANC</td>
<td>Grade 4</td>
<td>75%</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ Grade 3</td>
<td></td>
</tr>
<tr>
<td>Recurrent myelosuppression after 2 dose reductions</td>
<td>≥ Grade 3</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

*Start next cycle only when ANC ≥ 1.5 x 10⁹/L, platelets ≥ 100 x 10⁹/L and related organ/non-hematologic toxicity ≤ grade 2 (or recovery to baseline).

**Non-hematologic:**

<table>
<thead>
<tr>
<th>Worst toxicity in previous cycle</th>
<th>Grade</th>
<th>Pemetrexed (% previous dose)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity</td>
<td>Grade 2</td>
<td>100%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Grade</td>
<td>Action</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Mucositis</td>
<td>≥ Grade 3</td>
<td>Discontinue</td>
</tr>
<tr>
<td></td>
<td>≥ Grade 3</td>
<td>50%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>≥ Grade 3 or requiring hospitalization</td>
<td>75%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Any</td>
<td>Hold and investigate; discontinue if confirmed</td>
</tr>
<tr>
<td>All other related organ / non-hematologic toxicity</td>
<td>Grade 3</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Any</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>Any</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Recurrent non-hematologic toxicity after 2 dose reductions</td>
<td>≥ Grade 3</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

*Start next cycle only when ANC ≥ 1.5 x 10⁹/L, platelets ≥ 100 x 10⁹/L and related organ/non-hematologic toxicity ≤ grade 2 (or recovery to baseline).

**Combination:** Refer to specific regimen monograph(s)

**Dosage with 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.

**Dosage with Renal Impairment:**

Use with caution as pemetrexed exposure is increased in renal impairment.

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Pemetrexed (% of previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 45</td>
<td>100%*</td>
</tr>
<tr>
<td>&lt; 45</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

* Exercise caution with co-administration of NSAIDs for patients with CrCl 45-79mL/min

**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. In maintenance therapy, more frequent myelosuppression, renal and severe GI adverse events were noted in patients ≥ 65 years of age. There was no observed effect of age on pemetrexed pharmacokinetics over the range of 26 to 80 years.

**Children:**

The safety and effectiveness of pemetrexed in children have not been established.

---

**F - Administration Guidelines**

- Reconstitute as directed with Normal Saline (preservative free).
- Dilute drug to a total volume of 100mL with normal saline only and infuse intravenously over 10 minutes.
- Reconstituted solution maybe colourless to yellow or green-yellow.
- 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.

---

**G - Special Precautions**

**Contraindications:**

- Patients with a known hypersensitivity to the drug/excipients.
- Concomitant use of yellow fever vaccine.

**Other Warnings/Precautions:**

- Exercise caution in patients with pre-existing cardiovascular risk factors.
- Patients with moderate-severe renal dysfunction (CrCl < 45 mL/min).
- Avoid the use of live or live-attenuated vaccines.
Pregnancy and Lactation:

- Clastogenicity: Yes
- Mutagenicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes

Pemetrexed 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.

- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Yes
  Pemetrexed may cause irreversible infertility. Sperm preservation should be considered prior to starting treatment in males.

H - Interactions

In vitro results suggest that pemetrexed is unlikely to inhibit cytochrome P-450 isoenzymes (3A, 2D6, 2C9, 1A2). It is not expected to cause significant enzyme induction. Low to moderate ASA doses (e.g. 325 mg PO q6h) do not affect the pharmacokinetics of pemetrexed. Pemetrexed is a substrate of OAT3.

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxic drugs</td>
<td>↑ toxicity</td>
<td>↓ Clearance of pemetrexed</td>
<td>Caution</td>
</tr>
<tr>
<td>Tubular secreted drugs (e.g.,</td>
<td>↑ toxicity</td>
<td>Delayed clearance of pemetrexed</td>
<td>Caution</td>
</tr>
<tr>
<td>probenecid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs with short half-lives</td>
<td>↑ toxicity</td>
<td>↓ Clearance of pemetrexed</td>
<td>Hold NSAIDs with short half-lives at</td>
</tr>
<tr>
<td>(i.e., ibuprofen) in patients</td>
<td></td>
<td></td>
<td>least 2 days before to at least</td>
</tr>
<tr>
<td>with CrCl 45-79 ml/min</td>
<td></td>
<td></td>
<td>2 days after pemetrexed</td>
</tr>
<tr>
<td>NSAIDs with long half-lives</td>
<td>Potential ↑ in toxicity</td>
<td>Potentially ↓ clearance of pemetrexed</td>
<td>Hold NSAIDs with long half-lives at at least 5 days before to at least 2 days after pemetrexed</td>
</tr>
<tr>
<td>(i.e., piroxicam)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Baseline, before each cycle, on days 8 and 15 of each cycle (for nadir or recovery), and as clinically</td>
</tr>
<tr>
<td>Renal function tests</td>
<td>Baseline and at each visit</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Baseline and at each visit</td>
</tr>
<tr>
<td>Clinical toxicity assessment for fatigue, pneumonitis, thromboembolism, diarrhea, mucositis, neurotoxicity, infection, bleeding and rash</td>
<td>At each visit</td>
</tr>
</tbody>
</table>


### J - Supplementary Public Funding

**New Drug Funding Program ([NDFP Website](#))**
- Pemetrexed - Non-Small Cell Lung Cancer (Second or Subsequent Line)
- Pemetrexed - Combination with Platinum for Non-Small Cell Lung Cancer
- Pemetrexed - Non-Small Cell Lung Cancer (following Crizotinib)
- Pemetrexed - Advanced Malignant Pleural Mesothelioma (MPM)
- Pemetrexed - Maintenance Treatment of Nonsquamous Non-Small Cell Lung Cancer (NSCLC)
- Pemetrexed - Adjuvant Treatment of Completely Resected Stage II or IIIA Non-Small Cell Lung Cancer

### K - References


**December 2019** updated NDFP form titles

### L - Disclaimer

Any use of the information is subject, at all times, to CCO’s Terms and Conditions.
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.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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.

While care has been taken in the preparation of the information contained in the Formulary, 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.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

Any use of the information is subject, at all times, to CCO’s Terms and Conditions.