# PEMEtrexed Monotherapy

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|---|---|---|---|
| Maintenance treatment of locally advanced or metastatic non-small cell lung cancer NSCLC other than predominantly squamous cell histology in patients who disease has not progressed immediately following platinum-based chemotherapy. | C34 | 00222a | Hospital |
| Second line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology. | C34 | 00222b | Hospital |

## TREATMENT:

*The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.*

PEMEtrexed is administered once every 21 days until disease progression or unacceptable toxicity develops.

| Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|
| **1** | PEMEtrexed | 500mg/m$^2$ | IV infusion | 100ml 0.9% NaCl over 10min | Every 21 days |
| | Folic Acid or multivitamin containing 350-1000 micrograms folic acid | 350-1000 micrograms[b] | PO | | |
| [b] At least five doses of folic acid must be taken during the seven days preceding the first dose of PEMEtrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of PEMEtrexed.<br>See Premedications for further treatment required. | | | | | |
| PEMEtrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection. | | | | | |

## ELIGIBILTY:

- Indications as above
- ECOG 0-2

## EXCLUSIONS:

- Hypersensitivity to PEMEtrexed, or any of the excipients
- Creatinine clearance < 45ml/min
- Breast feeding

## PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

## TESTS:

**Baseline tests**:

- FBC, renal and liver profile

**Regular tests**:

- FBC, renal and liver* profile prior to each cycle

*See Adverse Effects/Regimen Specific Complications.

**Disease monitoring:**

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

## DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

**Haematological:**

- Dose adjustments at the start of a cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy.
- Treatment may be delayed to allow sufficient time for recovery.
- Upon recovery patient should be retreated using the guidelines below.

**Table 1: Dose modification of for haematological toxicity of PEMEtrexed**

| **Based on Day 1 counts** | | | |
|---|---|---|---|
| **ANC (x$10^9$/L)** | | **Platelets (x $10^9$/L)** | **Dose of PEMEtrexed** |
| ≥ 1.5 | and | ≥ 100 | 100% |
| < 1.5 | or | <100 | Delay |
| **Based on nadir counts** | | | |
| ≥ 0.5 | and | ≥ 50 | 100% |
| <0.5 | and | ≥ 50 | 75% of previous dose |
| any | and | <50 | 75% of previous dose |
| any | and | <50 with bleeding[a] | 50% of previous dose |

[a] CTC v2.0; NCI 1998 definition of ≥CTC Grade 2 bleeding

**Renal and Hepatic Impairment:**

**Table 2: Dose modification of PEMEtrexed in renal and hepatic impairment**

| **Renal Impairment** | | **Hepatic Impairment** | | | |
|---|---|---|---|---|---|
| **CrCl (ml/min)** | **Dose** | **Bilirubin** | | **Aminotransferases** | |
| ≥45 | 100% | >1.5 x ULN | and/or<br><br>or | > 3 x ULN (hepatic metastases absent)<br>> 5 x ULN (presence of hepatic metastases | Not recommended. **Clinical decision** |
| <45 | Not recommended | | | | |

**Management of adverse events:**

**Table 3: Dose Modification of PEMEtrexed for Adverse Events**

| Adverse reactions | Recommended dose modification |
|---|---|
| **Non-haematologic toxicities** [a,b] | |
| Any grade ≥3 toxicity other than mucositis or<br>Any diarrhoea requiring hospitalisation (irrespective of grade) or grade ≥3 diarrhoea | Withhold treatment until resolution to less than or equal to patient's pre-therapy value<br>Resume at 75% of previous dose of PEMEtrexed |
| Grade ≥3 mucositis | Withhold treatment until resolution to less than or equal to patient's pre-therapy value<br>Resume at 50% of previous dose for PEMEtrexed |
| Grade ≥3 toxicity after 2 dose reductions | Discontinue |
| **Neurotoxicity** | |
| Grade 3-4 | Discontinue |
| **Haematologic Toxicity** | |
| Grade ≥3 toxicity after 2 dose reductions | Discontinue |

[a]CTC v2.0; NCI 1998; [b] Excluding neurotoxicity

## SUPPORTIVE CARE:

**EMETOGENIC POTENTIAL:** Low (**Refer to local policy).**

### PREMEDICATIONS:

- A corticosteroid should be given the day prior to, on the day of, and the day after PEMEtrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day.
- Intramuscular injection of vitamin $B_{12}$ (hydroxycobolamin) (1,000 micrograms) in the week preceding the first dose of PEMEtrexed and once every three cycles thereafter. Subsequent vitamin $B_{12}$ injections may be given on the same day as PEMEtrexed.

### OTHER SUPPORTIVE CARE:

None usually required.

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

*The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.*

- **Myelosuppression:** Usually the dose limiting toxicity with PEMEtrexed. PEMEtrexed should not be given to patients until absolute neutrophil count (ANC) returns to $1.5x10^9$/L and platelet count returns to $100x10^9$ /L. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle.
  **Skin reactions:** Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions.
- **Renal Toxicity:**
  - Serious renal events, including acute renal failure, have been reported with PEMEtrexed alone or in association with other chemotherapeutic agents.
  - Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with PEMEtrexed alone or with other chemotherapeutic agents. Most of these events resolved after PEMEtrexed withdrawal. Patients should be regularly monitored for acute tubular

necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).

- **Cardiotoxicity:** Serious cardiovascular events including MI and cerebrovascular events have been uncommonly reported usually when PEMEtrexed is given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

## DRUG INTERACTIONS:

- In patients with normal renal function (CrCl > 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and aspirin at higher dose (> 1.3 g daily) may decrease PEMEtrexed elimination and, consequently, increase the occurrence of PEMEtrexed adverse events.
- The concomitant administration of PEMEtrexed with NSAIDs or aspirin at higher dose should be avoided for 2 days before, on the day of, and 2 days following PEMEtrexed administration on patients with mild to moderate renal insufficiency (CrCl from 45 to 79 ml/min).
- In patients with mild to moderate renal insufficiency eligible for PEMEtrexed therapy, NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following PEMEtrexed administration.
- Nephrotoxic drugs (e.g. loop diuretics and aminoglycosides) may decrease the clearance of PEMEtrexed.
- Concomitant administration of substances that are also tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of PEMEtrexed.
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

PEMEtrexed - L01BA04

## REFERENCES:


1. Hanna N et al. Randomized phase III trial of PEMEtrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004;22(9):1589-97.
2. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance PEMEtrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-40.
3. Pemetrexed (ALIMTA®)Summary of Product Characteristics. Last updated: 10/04/2019.Accessed April 2020. Available at https://www.ema.europa.eu/en/documents/product-information/alimta-epar-product-information_en.pdf
4. NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf


| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 15/04/2014 | | Prof Maccon Keane |
| 2 | 9/3/2016 | Updated dosing in hepatic dysfunction and clarification of dose modifications for adverse events (table 1) | Prof Maccon Keane |
| 3 | 18/04/2018 | Updated with new NCCP regimen template, updated emetogenic status | Prof Maccon Keane |

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|---|---|---|---|
| | | and adverse effects and drug interactions | |
| 4 | 29/04/2020 | Reviewed. Updated adverse events | Prof Maccon Keane |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.