Pemetrexed Monotherapy

INDICATIONS FOR USE:

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

ELIGIBILTY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

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

TESTS:

Baseline tests: FBC, U&Es, LFTs.

Regular tests: FBC, U&Es, LFTs*
*See Adverse Effects/Regimen Specific Complications.

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

TREATMENT:

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

Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
Pemetrexed	500mg/m^2	IV infusion over 10min	100ml 0.9% NaCl	1-6
Folic Acid or multivitamin containing 350-1000micrograms folic acid	350-1000micrograms*	PO		
*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.				
See Premedications for further treatment required.				
Pemetrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection.				

DOSE MODIFICATIONS:

Any dose modification should be discussed with a Consultant

Renal impairment:

CrCl (ml/min)	Dose
≥45	100%
<45	Not recommended

Hepatic impairment:

Bilirubin	AP, AST or SGOT and ALT or SGPT	Dose
≤1.5 x ULN	≤3 x ULN	100%

Alkaline phosphatase, AST and ALT ≤ 5 xULN is acceptable if liver has tumour involvement.

Patients with hepatic impairment such as bilirubin > 1.5 ULN and/or aminotransferase > 3.0 ULN (hepatic metastases absent) or > 5.0 ULN (hepatic metastases present) have not been specifically studied.

Haematological:

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

Haematological:

Based on Day 1 counts			
ANC (x10^9/L)		**Platelets (x 10^9/L)**	**Dose**
≥ 1.5	and	≥ 100	100%
< 1.5	or	<100	Delay
Based on nadir counts			
≥ 0.5	and	≥ 50	100%
<0.5		≥ 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

Table 1: Dose modification schedule for pemetrexed based on adverse events

Adverse reactions	**Discontinue**	**Recommended dose modification**
Non-haematologic toxicities [a,b]		
Any grade ≥3 toxicity other than mucositis or 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 Resume at 75% of previous dose.
Grade ≥3 mucositis		Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at 50% of previous dose
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: Minimal **(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.

TAKE HOME MEDICATIONS:

None usually required

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. 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.
- **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).
- 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

REIMBURSEMENT CATEGORY:

Pemetrexed is funded through local hospital budgets (October 2013)

PRESCRIPTIVE AUTHORITY:

Medical oncologist.

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. ALIMTA®Summary of Product Characteristics Accessed February 2016 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000564/WC500025611.pdf

Version	Date	Amendment	Approved By
1	15/04/2014	Initial Draft	Dr Maccon Keane
2	9/3/2016	Updated dosing in hepatic dysfunction and clarification of dose modifications for adverse events (table 1)	Dr Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.