Pregnancy

There are no data from the use of pemetrexed in pregnant women but pemetrexed, like other anti-metabolites, is suspected to cause serious birth defects when administered during pregnancy. Animal studies have shown reproductive toxicity (see section 5.3). Pemetrexed should not be used during pregnancy unless clearly necessary, after a careful consideration of the needs of the mother and the risk for the foetus (see section 4.4).

Breast-feeding

It is unknown whether pemetrexed is excreted in human milk and adverse reactions on the breast-feeding child cannot be excluded. Breast-feeding must be discontinued during pemetrexed therapy (see section 4.3).

Fertility

Owing to the possibility of pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, it has been reported that pemetrexed may cause fatigue. Therefore patients should be cautioned against driving or operating machines if this event occurs.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported undesirable effects related to pemetrexed, whether used as monotherapy or in combination, are bone marrow suppression manifested as anaemia, neutropenia, leukopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis. Other undesirable effects include renal toxicities, increased aminotransferases, alopecia, fatigue, dehydration, rash, infection/sepsis and neuropathy. Rarely seen events include Stevens-Johnson syndrome and toxic epidermal necrolysis.

Tabulated list of adverse reactions

The table 4 lists the adverse drug events regardless of causality associated with pemetrexed used either as a monotherapy treatment or in combination with cisplatin from the pivotal registration studies (JMCH, JMEI, JMBD, JMEN and PARAMOUNT) and from the post marketing period.

ADRs are listed by MedDRA body system organ class. The following convention has been used for classification of frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 4 Frequencies of all grades adverse drug events regardless of causality from the pivotal registration studies: JMEI (Pemetrexed vs Docetaxel), JMDB (Pemetrexed and Cisplatin versus GEMZAR and Cisplatin, JMCH (Pemetrexed plus Cisplatin versus Cisplatin), JMEN and PARAMOUNT (Pemetrexed plus Best Supportive Care versus Placebo plus Best Supportive Care) and from post-marketing period.

System Organ Class (MedDRA)	Adverse reaction and frequency	
Infections and infestations	Very common	Infection [a], Pharyngitis
	Common	Sepsis [b]
	Very rare	Dermohypodermitis
	Very common	Neutropenia, Leukopenia, Haemoglobin decreased

Blood and lymphatic system disorders	Common	Febrile neutropenia, Platelet count decreased
	Uncommon	Pancytopenia
	Rare	Autoimmune, Haemolytic anaemia
Immune system disorders	Common	Hypersensitivity
	Rare	Anaphylactic shock
Metabolism and nutrition disorders	Common	Dehydration
Nervous system disorders	Common	Taste disorder, Peripheral motor neuropathy, Peripheral sensory neuropathy, Dizziness
	Uncommon	Cerebrovascular accident, Ischaemic stroke, Haemorrhage intracranial
Eye disorders	Common	Conjunctivitis, Dry eye, Lacrimation increased, Keratoconjuctivitis sicca, Eyelid oedema, Ocular surface disease
Cardiac disorders	Common	Cardiac failure, Arrhythmia
	Uncommon	Angina, Myocardial infarction, Coronary artery disease, Arrhythmia supraventricular
Vascular disorders	Uncommon	Peripheral ischaemia [c]
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary embolism, Interstitial pneumonitis [b d]
Gastrointestinal disorders	Very common	Stomatitis, Anorexia, Vomiting, Diarrhoea, Nausea
	Common	Dyspepsia, Constipation, Abdominal pain
	Uncommon	Rectal haemorrhage, Gastrointestinal haemorrhage, Intestinal perforation, Oesophagitis, Colitis [e]
Hepatobiliary disorders	Common	Aalanine aminotransferase increased, Aspartate aminotransferase increased
	Rare	Hepatitis
Skin and subcutaneous tissue disorders	Very common	Rash, Skin exfoliation
	Common	Hyperpigmentation, Pruritus, Erythemamultiforme, Alopecia, Urticaria
	Rare	Erythema
	Very rare	Stevens-Johnson syndrome [b], Toxic epidermal necrolysis [b], Pemphigoid, Dermatitis bullous, Acquired epidermolysis bullosa, Erythematous oedema [f], Pseudocellulitis, Dermatitis, Eczema, Prurigo
Renal and urinary disorders	Very common	Creatinine clearance decreased, Blood creatinine increased [e]
	Common	Renal failure, Glomerular filtration rate decreased
	Not known	Nephrogenic diabetes insipidus, Renal tubular necrosis
General disorders and administration site conditions	Very common	Fatigue
	Common	Pyrexia, Pain, Oedema, Chest pain, Mucosal inflammation
Investigations	Common	Gamma-glutamyltransferase increased
Injury, poisoning and procedural complications	Uncommon	Radiation oesophagitis, Radiation pneumonitis
	Rare	Recall phenomenon

[a] with and without neutropenia

[b] in some cases fatal

[c] sometimes leading to extremity necrosis

[d] with respiratory insufficiency

[e] seen only in combination with cisplatin

[f] mainly of the lower limbs

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Health Product Pharmacovigilance Center at http://thaihpvc.fda.moph.go.th.

4.9 Overdose

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, sensory polyneuropathy and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia and anaemia. In addition, infection with or without fever, diarrhoea, and/or mucositis may be seen. In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of calcium folinate / folinic acid in the management of pemetrexed overdose should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA04

Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

In vitro studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the *de novo* biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

The European Medicines Agency has waived the obligation to submit the results of studies with pemetrexed in all subsets of the paediatric population in the granted indications (see Section 4.2).

Clinical efficacy

Mesothelioma

EMPHACIS, a multicentre, randomised, single-blind phase 3 study of pemetrexed plus cisplatin versus cisplatin in chemonaive patients with malignant pleural mesothelioma, has shown that patients treated with pemetrexed and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone.

During the study, low-dose folic acid and vitamin B_{12} supplementation was introduced to patients' therapy to reduce toxicity. The primary analysis of this study was performed on the population of all patients randomly assigned to a treatment arm who received study drug (randomised and treated). A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy (fully supplemented). The results of these analyses of efficacy are summarised in the table below:

Table 5 Efficacy of pemetrexed plus cisplatin vs. cisplatin in malignant pleural mesothelioma

	Randomized and treated patients		Fully supplemented patients	
Efficacy parameter	**Pemetrexed / Cisplatin (N=226)**	**Cisplatin (N=222)**	**Pemetrexed / Cisplatin (N=168)**	**Cisplatin (N=163)**
Median overall survival (months) (95 % CI)	12.1 (10.0 – 14.4)	9.3 (7.8 – 10.7)	13.3 (11.4 – 14.9)	10.0 (8.4 – 11.9)
Log Rank p-value [a]	0.020		0.051	
Median time to tumour progression (months) (95 % CI)	5.7 (4.9 – 6.5)	3.9 (2.8 – 4.4)	6.1 (5.3 – 7.0)	3.9 (2.8 – 4.5)
Log Rank *p*-value [a]	0.001		0.008	
Time to treatment failure (months) (95 % CI)	4.5 (3.9 – 4.9)	2.7 (2.1 – 2.9)	4.7 (4.3 – 5.6)	2.7 (2.2 – 3.1)
Log Rank *p*-value [a]	0.001		0.001	
Overall response rate [b] (95 % CI)	41.3% (34.8 – 48.1)	16.7% (12.0 – 22.2)	45.5% (37.8 – 53.4)	19.6% (13.8 – 26.6)
Fisher's exact *p*-value [a]	<0.001		<0.001	

Abbreviation: CI = confidence interval

[a] *p*-value refers to comparison between arms.

[b] In the pemetrexed /cisplatin arm, randomized and treated (N=225) and fully supplemented (N=167)

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the pemetrexed /cisplatin arm (212 patients) versus the cisplatin arm alone (218 patients) was demonstrated using the Lung Cancer Symptom Scale. Statistically significant differences in pulmonary function tests were also observed. The separation between the treatment arms was achieved by improvement in lung function in the pemetrexed /cisplatin arm and deterioration of lung function over time in the control arm.

There are limited data in patients with malignant pleural mesothelioma treated with pemetrexed alone. Pemetrexed at a dose of 500 mg/m^2 was studied as a single-agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1%.

NSCLC, second-line treatment

A multicentre, randomised, open label phase 3 study of pemetrexed versus docetaxel in patients with locally advanced or metastatic NSCLC after prior chemotherapy has shown median survival times of 8.3 months for patients treated with pemetrexed (Intent To Treat population n=283) and 7.9 months for patients treated with docetaxel (ITT n=288). Prior chemotherapy did not include pemetrexed. An analysis of the impact of NSCLC histology on the treatment effect on overall survival was in favour of pemetrexed versus docetaxel for other than predominantly squamous histologies (n=399, 9.3 versus 8.0 months, adjusted HR=0.78; 95% CI=0.61-1.00, *p*=0.047) and was in favour of docetaxel for squamous cell carcinoma histology (n=172, 6.2 versus 7.4 months, adjusted HR=1.56; 95% CI=1.08-2.26, *p*=0.018). There were no clinically relevant differences observed for the safety profile of pemetrexed within the histology subgroups.

Limited clinical data from a separate randomized, Phase 3, controlled trial, suggest that efficacy data (overall survival, progression free survival) for pemetrexed are similar between patients previously pretreated with docetaxel (n=41) and patients who did not receive previous docetaxel treatment (n=540).

Table 6 Efficacy of pemetrexed vs docetaxel in NSCLC - ITT population

	Pemetrexed	Docetaxel
Survival Time (months)	(n=283)	(n=288)
Median (m)	8.3	7.9
95% CI for median	(7.0 – 9.4)	(6.3 – 9.2)
HR	0.99	
95% CI for HR	(0.82 - 1.20)	
Non-inferiority *p*-value (HR)	0.226	
Progression free survival (months)	(n=283)	(n=288)
Median	2.9	2.9
HR (95% CI)	0.97 (0.82 – 1.16)	
Time to treatment failure (TTTF – months)	(n=283)	(n=288)
Median	2.3	2.1
HR (95% CI)	0.84 (0.71 – 0.997)	
Response (n: qualified for response)	(n=264)	(n=274)
Response rate (%) (95% CI)	9.1 (5.9 – 13.2)	8.8 (5.7 – 12.8)
Stable disease (%)	45.8	46.4

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = total population size.

NSCLC, first-line treatment

A multicentre, randomised, open-label, Phase 3 study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with locally advanced or metastatic (Stage IIIb or IV) non-small cell lung cancer (NSCLC) showed that pemetrexed plus cisplatin (Intent-To-Treat [ITT] population n=862) met its primary endpoint and showed similar clinical efficacy as gemcitabine plus cisplatin (ITT n=863) in overall survival (adjusted hazard ratio 0.94; 95% CI=0.84-1.05). All patients included in this study had an ECOG performance status 0 or 1.

The primary efficacy analysis was based on the ITT population. Sensitivity analyses of main efficacy endpoints were also assessed on the Protocol Qualified (PQ) population. The efficacy analyses using PQ population are consistent with the analyses for the ITT population and support the non-inferiority of AC versus GC.

Progression free survival (PFS) and overall response rate were similar between treatment arms: median PFS was 4.8 months for pemetrexed plus cisplatin versus 5.1 months for gemcitabine plus cisplatin (adjusted hazard ratio 1.04; 95% CI=0.94-1.15), and overall response rate was 30.6% (95% C=27.3-33.9) for pemetrexed plus cisplatin versus 28.2% (95% CI=25.0-31.4) for gemcitabine plus cisplatin. PFS data were partially confirmed by an independent review (400/1725 patients were randomly selected for review).

The analysis of the impact of NSCLC histology on overall survival demonstrated clinically relevant differences in survival according to histology, see table below.

Table 7 Efficacy of pemetrexed + cisplatin vs. gemcitabine + cisplatin in first-line non-small cell lung cancer – ITT population and histology subgroups.

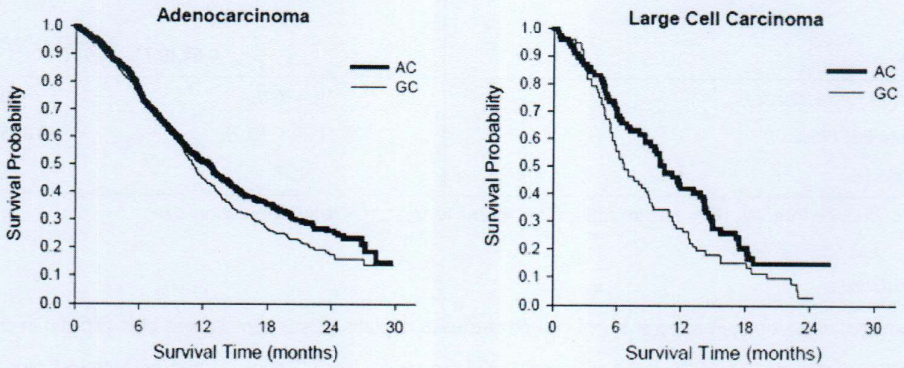
ITT population and histology subgroups	Median overall survival in months (95% CI)				Adjusted hazard ratio (HR) (95% CI)	Superiority *p*-value
	Pemetrexed + cisplatin		Gemcitabine + cisplatin			
ITT population (N = 1725)	10.3 (9.8 – 11.2)	N=862	10.3 (9.6 – 10.9)	N=863	0.94 [a] (0.84 – 1.05)	0.259

Adenocarcinoma (N = 847)	12.6 (10.7 – 13.6)	N=436	10.9 (10.2 – 11.9)	N=411	0.84 (0.71 – 0.99)	0.033
Large cell (N=153)	10.4 (8.6 – 14.1)	N=76	6.7 (5.5 – 9.0)	N=77	0.67 (0.48–0.96)	0.027
Other (N=252)	8.6 (6.8 – 10.2)	N=106	9.2 (8.1 – 10.6)	N=146	1.08 (0.81 – 1.45)	0.586
Squamous cell (N=473)	9.4 (8.4 – 10.2)	N=244	10.8 (9.5 – 12.1)	N=229	1.23 (1.00 – 1.51)	0.050

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = total population size.

[a] Statistically significant for non-inferiority, with the entire confidence interval for HR well below the 1.17645 non-inferiority margin ($p<0.001$).

Kaplan Meier plots of overall survival by histology



There were no clinically relevant differences observed for the safety profile of pemetrexed plus cisplatin within the histology subgroups.

Patients treated with pemetrexed and cisplatin required fewer transfusions (16.4% versus 28.9%, $p<0.001$), red blood cell transfusions (16.1% versus 27.3%, $p<0.001$) and platelet transfusions (1.8% versus 4.5%, $p=0.002$). Patients also required lower administration of erythropoietin/darbopoietin (10.4% versus 18.1%, $p<0.001$), G-CSF/GM-CSF (3.1% versus 6.1%, $p=0.004$), and iron preparations (4.3% versus 7.0%, $p=0.021$).

NSCLC, maintenance treatment

JMEN

A multicentre, randomised, double-blind, placebo-controlled Phase 3 study (JMEN), compared the efficacy and safety of maintenance treatment with pemetrexed plus best supportive care (BSC) (n=441) with that of placebo plus BSC (n=222) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) Non Small Cell Lung Cancer (NSCLC) who did not progress after 4 cycles of first line doublet therapy containing Cisplatin or Carboplatin in combination with Gemcitabine, Paclitaxel, or Docetaxel. First line doublet therapy containing pemetrexed was not included. All patients included in this study had an ECOG performance status 0 or 1. Patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomisation after completion of first line (induction) therapy. Patients received a median of 5 cycles of maintenance treatment with pemetrexed and 3.5 cycles of placebo. A total of 213 patients (48.3%) completed ≥6 cycles and a total of 103 patients (23.4%) completed ≥10 cycles of treatment with pemetrexed.

The study met its primary endpoint and showed a statistically significant improvement in PFS in the pemetrexed arm over the placebo arm (n = 581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (hazard ratio=0.60, 95% CI=0.49-0.73, $p<0.00001$). The independent review of patient scans confirmed the findings of the investigator assessment of