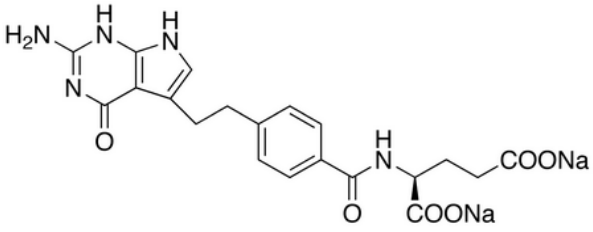
PEMETREXED APOTEX

NAME OF THE MEDICINE

Pemetrexed disodium hemipentahydrate.

Chemical Name: L-glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*] pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, hemipentahydrate.

Structural Formula:



.2½ H_2O

Molecular Formula: $C_{20}H_{24}N_5Na_2O_{8½}$

Molecular Weight: 516.412

CAS Registry Number: 357166-30-4

DESCRIPTION

Pemetrexed disodium is a white to almost white solid.

This medicine is supplied as a sterile lyophilized powder for intravenous infusion in single dose vials; the product is a white to either light yellow or green-yellow lyophilized solid in 100 mg and 500 mg vials. Each 100 mg vial contains pemetrexed disodium, equivalent to 100 mg pemetrexed, and 106 mg mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH. Each 500 mg vial contains pemetrexed disodium, equivalent to 500 mg pemetrexed, and 500 mg mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

PHARMACOLOGY

Pharmacological Actions

Pemetrexed is an antifolate antineoplastic agent. *In vitro* studies have shown that pemetrexed behaves as a multi-targeted 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 that are essential for cell replication. Both the reduced folate carrier and membrane folate binding protein transport systems appear to be involved in transport of pemetrexed into cells. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folyl polyglutamate synthetase. The polyglutamate forms are even more potent inhibitors of TS and GARFT than pemetrexed. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have a longer intracellular half-life than the parent drug, resulting in prolonged drug action in malignant cells. Data indicates that overexpression of TS correlates with reduced sensitivity to pemetrexed in antifolate-resistant cell lines. Results in a study with specimens from chemonaive patients with non-small cell lung cancer (NSCLC) demonstrated lower levels of TS expression in adenocarcinoma as compared to squamous cell carcinoma tumours. This data suggests that pemetrexed may offer greater efficacy for patients with adenocarcinoma as compared to squamous carcinoma histology.

An *in vitro* study with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined with cisplatin.

Pharmacokinetics

Absorption

Pemetrexed is for intravenous administration only.

Distribution

Pemetrexed has a steady-state volume of distribution of 16.1 litres. *In vitro* studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Metabolism

Pemetrexed undergoes limited hepatic metabolism.

Excretion

Pemetrexed is primarily eliminated in the urine with up to 70%–90% of the dose recovered unchanged within the first 24 hours following administration. Total plasma clearance of pemetrexed is 92 mL/min and the elimination half-life from plasma is 3½ hours in patients with normal renal function.

Special Populations

Analyses to evaluate the pharmacokinetics of pemetrexed in special populations included 287 patients with a variety of advanced tumour types from 10 single-agent Phase II studies, 70 patients from the Phase III malignant pleural mesothelioma (MPM) EMPHACIS trial and 47 patients from a Phase I renal study.

Elderly

No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26–80 years.

Renal Impairment

Pharmacokinetic analyses included 127 patients with reduced renal function. Total plasma clearance and renal clearance of pemetrexed decrease as renal function decreases. On average, patients with creatinine clearance of 45 mL/min will have a 56% increase in pemetrexed total systemic exposure (AUC) relative to patients with creatinine clearance of 90 mL/min (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment

No effect of aspartate transaminase [(AST), (SGOT)], alanine transaminase [(ALT), (SGPT)], or total bilirubin on the pharmacokinetics of pemetrexed was observed. However, specific studies in hepatically-impaired patients have not been conducted (see **PRECAUTIONS**).

CLINICAL TRIALS

Malignant Pleural Mesothelioma

The safety and efficacy of pemetrexed have been evaluated in chemonaive patients with malignant pleural mesothelioma (MPM) as a single agent and in combination with platinum-based regimens.

EMPHACIS, a multicentre, randomised, single-blind, phase III study of pemetrexed plus cisplatin *versus* cisplatin in chemonaïve patients with MPM, has shown that patients treated with pemetrexed and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone. Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m^2 and cisplatin was administered intravenously over 2 hours at a dose of 75 mg/m^2 beginning approximately 30 minutes after the end of administration of pemetrexed. Both drugs were given on Day 1 of each 21-day cycle. In this study, treatment was administered up to 6 cycles. Additional cycles were permitted for patients who were receiving benefit from therapy.

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).

Table 1 summarises the efficacy results for all patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrolment in the trial.

Table 1: Efficacy of Pemetrexed and Cisplatin *versus* Cisplatin in Malignant Pleural Mesothelioma

Efficacy Parameter	Randomized and Treated Patients		Fully Supplemented Patients	
	Pemetrexed andCisplatin (n = 226)	Cisplatin (n = 222)	Pemetrexed and Cisplatin (n = 168)	Cisplatin (n = 163)
Median Overall Survival (95% CI)	12.1 months (10.0–14.4)	9.3 months (7.8–10.7)	13.3 months (11.4–14.9)	10.0 months (8.4–11.9)
Hazard Ratio	0.77		0.75	
Log Rank p-value*	0.020		0.051	
Censored	35.8%	28.4%	43.5%	36.8%
Median Time to Tumour Progression (95% CI)	5.7 months (4.9–6.5)	3.9 months (2.8–4.4)	6.1 months (5.3–7.0)	3.9 months (2.8–4.5)
Hazard Ratio	0.68		0.64	
Log Rank p-value*	0.001		0.008	
Time to Treatment Failure** (95% CI)	4.5 months (3.9–4.9)	2.7 months (2.1–2.9)	4.7 months (4.3–5.6)	2.7 months (2.2–3.1)
Hazard Ratio	0.61		0.57	
Log Rank p-value*	0.001		0.001	
Overall Response Rate*** (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*	< 0.001		< 0.001	

* p-value refers to comparison between arms.
** Time to Treatment Failure was defined as the time from study enrolment to the first observation of disease progression, death due to any cause or discontinuation due to any other reason.
*** In the pemetrexed arm, Randomized and Treated (n = 225) and Fully Supplemented (n = 167)

Table 2 summarizes the number of cycles of treatment completed by randomized and treated patients and fully supplemented patients. Patients who never received folic acid and vitamin B_{12} during study therapy received a median of 2 cycles in both treatment arms.

Table 2: Summary of Cycles Given

Cycle Statistics	Randomized and Treated Patients		Fully Supplemented Patients	
	Pemetrexed and Cisplatin (n = 226)	Cisplatin (n = 222)	Pemetrexed and Cisplatin (n = 168)	Cisplatin (n = 163)
Median Cycles completed (Range)	6.0 (1–12)	4.0 (1–9)	6.0 (1–12)	4.0 (1–9)
Total Cycles completed	1066	877	825	650
Cycles given at full dosage (%)	1030 (96.6)	874 (99.7)	802 (97.2)	648 (99.7)

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with MPM in the pemetrexed andcisplatin arm (n = 212 patients) *versus* the cisplatin arm alone (n = 218 patients) was demonstrated using the Lung Cancer Symptom Scale (LCCS). By the end of treatment (after 6 cycles), there was a statistically significant difference in favour of pemetrexed and cisplatin for the symptoms of dyspnoea, pain, fatigue, symptom distress, interference with activity and total LCSS. Statistically significant differences in pulmonary function tests were also observed. Differences favouring the pemetrexed plus cisplatin arm were seen in all pulmonary function tests

early in therapy; these differences were occasionally significant in early cycles but uniformly became significant in later cycles. The separation between the treatment arms was achieved by improvement in lung function in the pemetrexed and cisplatin arm and deterioration of lung function over time in the control arm.

Non-Small Cell Lung Cancer

The safety and efficacy of pemetrexed have been evaluated in combination with cisplatin as initial treatment for Non-Small Cell Lung Cancer (NSCLC) and as a single-agent in patients who have previously received chemotherapy treatment.

A multicentre, randomised, open-label Phase III study of pemetrexed plus cisplatin *versus* gemcitabine plus cisplatin (for up to 6 cycles) in chemonaive patients with locally advanced or metastatic (Stage IIIb or IV) 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): Refer to Figure 1 and Table 3.

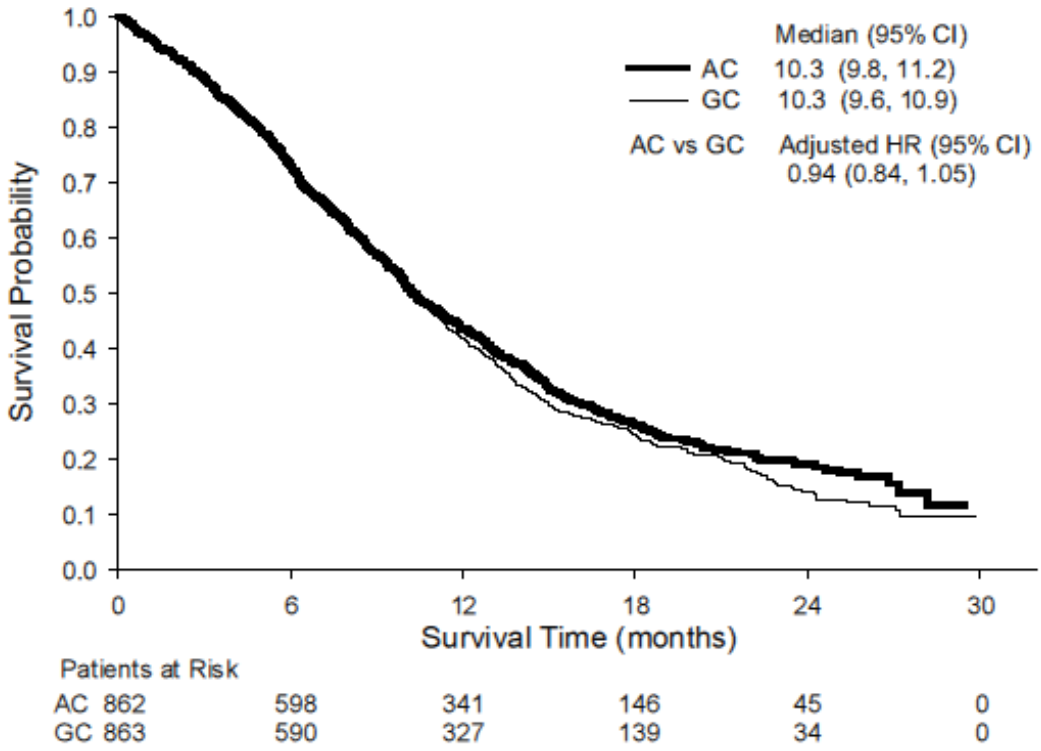


Figure 1: Kaplan-Meier Curve for Overall Survival – Pemetrexed plus Cisplatin (AC) *versus* Gemcitabine plus Cisplatin (GC) in First-line Non-Small Cell Lung Cancer – ITT Population

Table 3: Efficacy of Pemetrexed and Cisplatin *versus* Gemcitabine and Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population

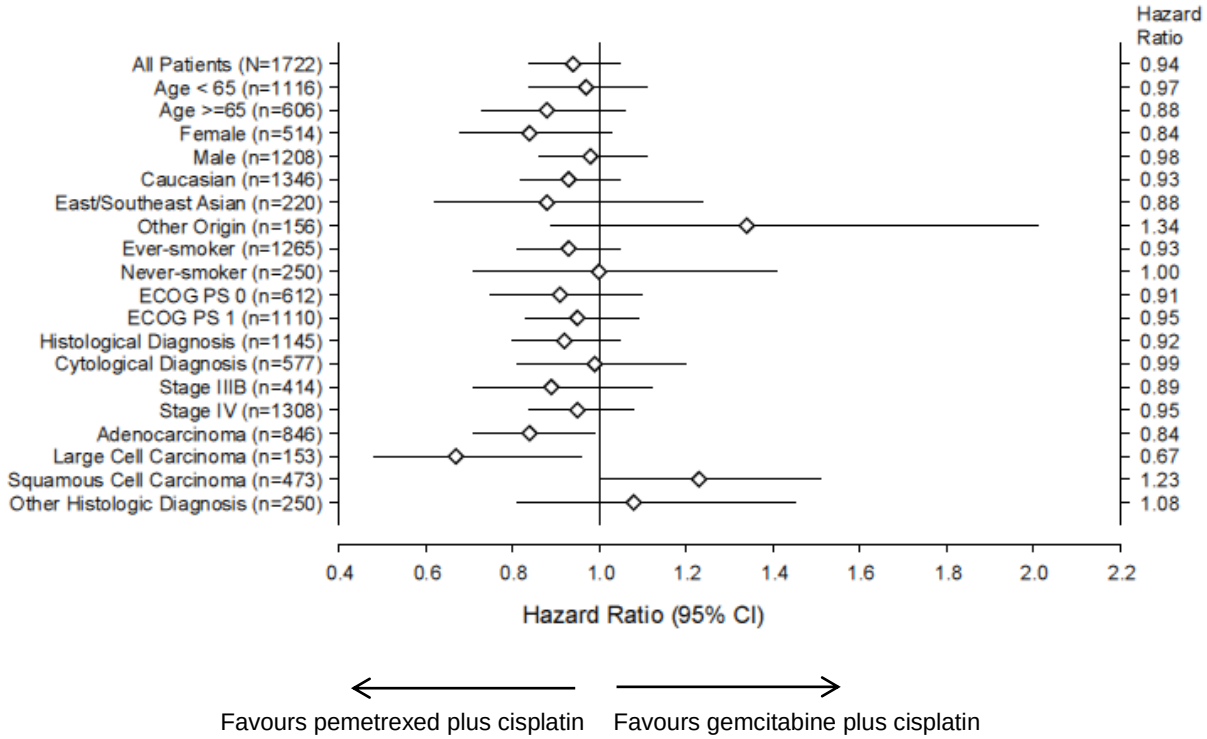
	Pemetrexed plus Cisplatin (n = 862)	Gemcitabine plus Cisplatin (n = 863)
Median Overall Survival (95% CI)	10.3 months (9.8–11.2)	10.3 months (9.6–10.9)
Adjusted Hazard Ratio (95% CI)	0.94[a] (0.84–1.05)	
12-month survival probability (95% CI)	43.5% (40.1–46.9)	41.9% (38.5–45.5)
24-month survival probability (95% CI)	18.9% (15.7–22.2)	14.0% (10.9–17.1)

	Pemetrexed plus Cisplatin (n = 862)	Gemcitabine plus Cisplatin (n = 863)
Median Progression-Free Survival (95% CI)	4.8 months (4.6–5.3)	5.1 months (4.6–5.5)
Adjusted Hazard Ratio (95% CI)	1.04[a] (0.94–1.15)	
Overall Response rate[b] (95% CI)	30.6% (27.3–33.9)	28.2% (25.0–31.4)

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

a Statistically significant for non-inferiority
b Number of tumour-qualified patients on the pemetrexed plus cisplatin arm (n = 762) and the gemcitabine plus cisplatin arm (n = 755). Investigator assessed.

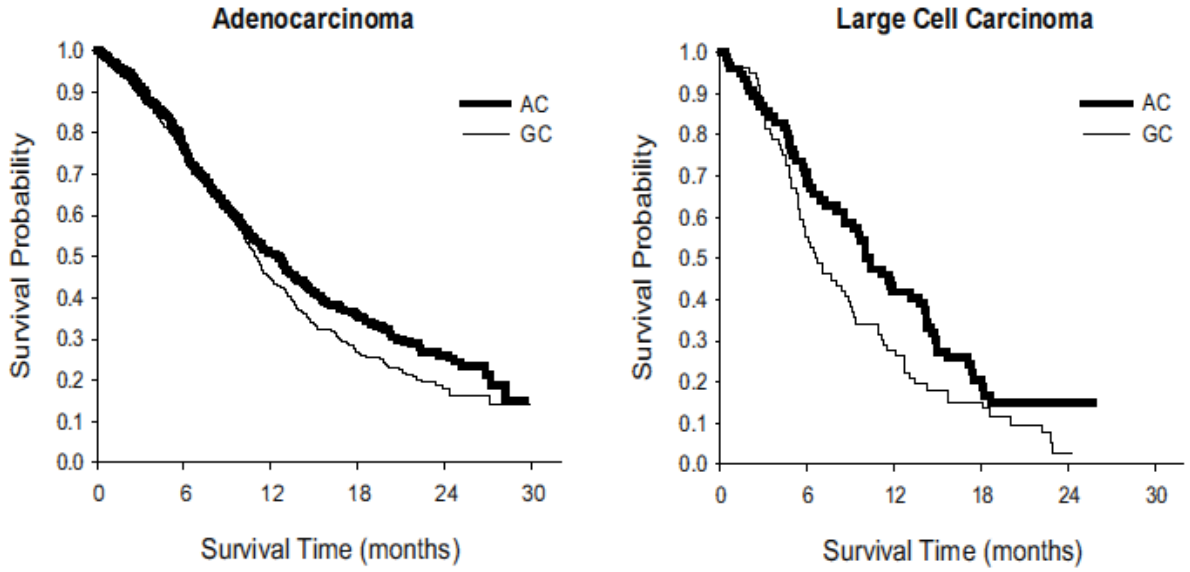
A series of subsets of patients were examined in pre-specified adjusted analyses – refer Figure 2.



Results based on Cox adjusted analyses for Eastern Cooperative Oncology Group Performance Status (ECOG PS), disease stage, gender and basis for diagnosis (histological *versus* cytological). In the analysis by group, pertaining to each of these four covariates, the variable depicting the group was excluded from the model. Three patients were missing ECOG PS and are excluded from the Cox adjusted analyses; 209 patients were missing smoking status.

Figure 2: Forest Plot for Overall Survival Adjusted Hazard Ratios of Subgroups – Pemetrexed plus Cisplatin *versus* Gemcitabine plus Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population

The analysis of the impact of NSCLC histology on overall survival demonstrated statistically significant superiority for pemetrexed plus cisplatin in the adenocarcinoma (n = 846, 12.6 *versus* 10.9 months, adjusted Hazard Ratio = 0.84; 95% CI = 0.71–0.99, p = 0.033) and large cell carcinoma subgroups (n = 153, 10.4 *versus* 6.7, adjusted Hazard Ratio = 0.67; 95% CI = 0.48–0.96, p = 0.027) but not in patients with squamous cell carcinoma (n = 473, 9.4 *versus* 10.8 months, adjusted Hazard Ratio = 1.23; 95% CI = 1.00–1.51, p = 0.050) or patients with other histologies (n = 250, 8.6 *versus* 9.2, adjusted Hazard Ratio = 1.08; 95% CI =0.81–1.45, p = 0.586). The results of the analysis of overall survival in patients with adenocarcinoma and large cell carcinoma are shown in Figure 3.



<u>Figure 3</u>: Kaplan-Meier Curve for Overall Survival –
Pemetrexed plus Cisplatin (AC) *versus* Gemcitabine plus Cisplatin (GC)
in First-line Non-Small Cell Lung Cancer – Adenocarcinoma and Large Cell Carcinoma

In this study, treatment was administered up to 6 cycles.

There were no clinically relevant differences observed

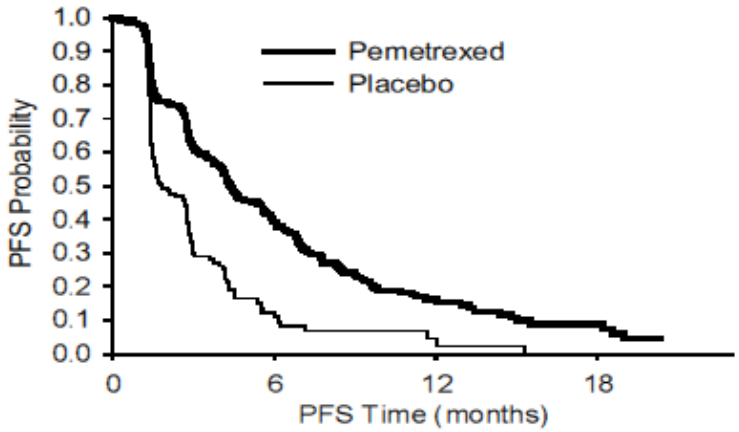
A multicentre, randomized, double-blind, placebo-controlled Phase III study (JMEN), compared the efficacy and safety of maintenance treatment with pemetrexed plus best supportive care (n = 441) with that of placebo plus best supportive care (n = 222) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC who did not progress after 4 cycles of first-line doublet therapy. All patients included in this study had an ECOG PS 0 or 1. Patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomization after completion of first line (induction) therapy. Patients received a median of 5 cycles of maintenance treatment with pemetrexed and 3½ 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.

In the overall study population, pemetrexed was statistically superior to placebo in terms of overall survival (median 13.4 months *versus* 10.6 months, Hazard Ratio = 0.79 (95% CI: 0.65–0.95), p-value = 0.012) and progression-free survival (median 4.0 months *versus* 2.0 months, Hazard Ratio = 0.60 (95% CI: 0.49–0.73), p-value < 0.00001). Consistent with previous pemetrexed studies, a difference in treatment outcomes was observed according to histological classification. For the indicated population *i.e.* patients with NSCLC other than predominantly squamous cell histology, pemetrexed was superior to placebo for overall survival (median 15.5 months *versus* 10.3 months, Hazard Ratio = 0.70 (95% CI: 0.56–0.88)) and pprogression-free survival (median 4.4 months versus 1.8 months, Hazrad Ratio = 0.47 (95% CI: 0.37–0.60)).

The progression-free survival and overall survival results in patients with squamous cell histology suggested no advantage for pemetrexed over placebo.

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

Progression-Free Survival



Overall Survival

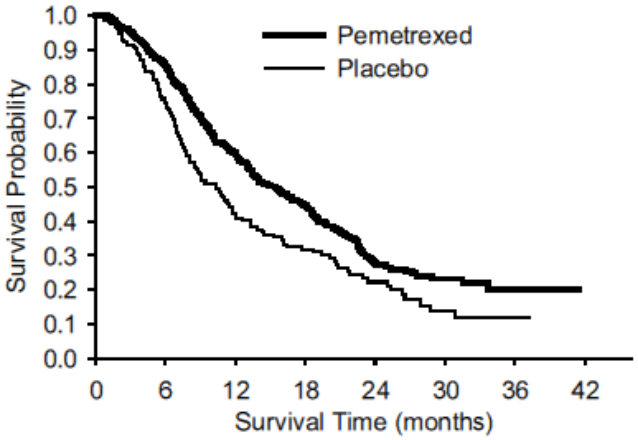


Figure 4: Kaplan-Meier Plots of Progression-Free Survival (PFS) and Overall Survival – Pemetrexed *versus* Placebo in Patients with NSCLC other than Predominantly Squamous Cell Histology

A multicentre, randomized, open-label Phase III study of pemetrexed *versus* docetaxel (with treatment until progression) 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 (ITT population n = 283) and 7.9 months for patients treated with docetaxel (ITT population n = 288) which is not statistically significantly different. These data, as outlined in Table 4, indicate comparable efficacy between pemetrexed and docetaxel.

Table 4: Efficacy of Pemetrexed *versus* Docetaxel in NSCLC – ITT Population

	Pemetrexed	**Docetaxel**
Survival Time	(n = 283)	(n = 288)
Median (95 % CI)	8.3 months (7.0–9.4)	7.9 months (6.3–9.2)
Hazard Ratio (95 % CI) Non-inferiority p-value (Hazard Ratio)	0.99 (0.82–1.20) 0.226	

	Pemetrexed	Docetaxel
% of docetaxel's survival benefit retained* (95 % CI) Non-inferiority p-value (% retention)	102% (52–157) 0.047	
Progression-Free Survival	(n = 283)	(n = 288)
Median	2.9 months	2.9 months
Hazard Ratio (95 % CI)	0.97 (0.82–1.16)	
Time to Treatment Failure	(n = 283)	(n = 288)
Median	2.3 months	2.1 months
Hazard Ratio (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; ITT = intent to treat; n = total population size.

* Based on Rothmann analysis

In this study, treatment was administered until disease progression.

An analysis of the impact of NSCLC histology on overall survival was in favour of pemetrexed *versus* docetaxel for other than predominantly squamous histology (n = 399, 9.3 *versus* 8.0 months, adjusted Hazard Ratio = 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 Hazard Ratio = 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.

INDICATIONS

Malignant Pleural Mesothelioma

Pemetrexed, in combination with cisplatin, is indicated for the treatment of patients with malignant pleural mesothelioma.

Non-Small Cell Lung Cancer

Pemetrexed, in combination with cisplatin, is indicated for initial treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology.

Pemetrexed, as monotherapy, is indicated for the treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology after prior platinum-based chemotherapy.

CONTRAINDICATIONS

Pemetrexed is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any excipients in this product.

PRECAUTIONS

Pemetrexed can suppress bone marrow function as manifested by anaemia, neutropenia, thrombocytopenia, or pancytopenia. (see **ADVERSE EFFECTS**). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and pemetrexed should not be given to patients until their absolute neutrophil count (ANC) returns to ≥ 1500 cells/mm^3 and platelet count returns to ≥ 100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematological toxicity seen in the previous cycle (see **DOSAGE AND ADMINISTRATION,** Dose Reduction Recommendations).

Patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} with pemetrexed as a prophylactic measure to reduce treatment-related toxicity (see **DOSAGE AND ADMINISTRATION**). In the Phase III mesothelioma EMPHACIS trial, less overall toxicity and reductions in Grade 3/4 haematologic and non-haematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin B_{12} was administered.

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes.

Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended.

Cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising agents. Cases of radiation recall have been reported in patients who received radiotherapy weeks or years previously.

Effects on Fertility

Administration of pemetrexed to male mice at intraperitoneal doses of ≥ 0.3 mg/m^2/day resulted in reproductive toxicity characterized by reduced fertility, hypospermia and testicular atrophy.

Use in Pregnancy (Category D)

The use of pemetrexed should be avoided in pregnant women because of the potential hazard to the foetus. Pemetrexed was teratogenic (causing cleft palate) in mice at intravenous doses of ≥ 15 mg/m^2/day. Other embryofoetal toxic effects (embryofoetal deaths, reduced foetal weights and incomplete ossification) were also observed. Embryofoetal toxicity was observed at the lowest dose tested (0.6 mg/m^2/day).

Use in Lactation

It is not known whether pemetrexed is excreted in human milk. Therefore, breast-feeding should be discontinued during pemetrexed therapy.

Paediatric Use

Pemetrexed is not recommended for use in patients less than 18 years of age, as safety and efficacy have not been established in this group of patients.

Use in the Elderly

In clinical studies, there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions other than those recommended for all patients are necessary.

Use in Renal Impairment

Pemetrexed is primarily eliminated unchanged by renal excretion. Insufficient numbers of patients have been studied with creatinine clearance below 45 mL/min. Therefore, pemetrexed should not be administered to patients whose creatinine clearance is < 45 mL/min (see **DOSAGE AND ADMINISTRATION**).

Use in Hepatic Impairment

Pemetrexed is not extensively metabolised by the liver. However, patients with hepatic impairment such as bilirubin > 1.5× the upper limit of normal (ULN) or aminotransferase > 3 times the ULN (hepatic metastases absent) or > 5 times the ULN (hepatic metastases present) have not been specifically studied.

Pemetrexed should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Treatment-related adverse events of pemetrexed seen in clinical trials have been reversible. Skin rash has been reported in patients not pre-treated with a corticosteroid in clinical trials. Pre-treatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction (see **DOSAGE AND ADMINISTRATION**).

The effect of third space fluid, such as pleural effusion and ascites, on pemetrexed is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to pemetrexed administration.

Genotoxicity

Pemetrexed has been shown to be clastogenic in the *in vivo* micronucleus assay in the mouse, but was negative in the *in vitro* chromosome aberration test in Chinese hamster ovary cells. Pemetrexed was negative in assays for gene mutation (bacteria and mammalian cells *in vitro*).

Carcinogenicity

Studies to assess the carcinogenic potential of pemetrexed have not been conducted.

Effects on Ability to Drive and Use Machinery

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 machinery if this event occurs.

INTERACTIONS WITH OTHER MEDICINES

Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. *In vitro* studies indicate that pemetrexed is actively secreted by the organic anion transporter 3 (OAT3) in the kidney. *In vitro* work also indicates that pemetrexed has affinity for OAT4 but the role of OAT4 in the renal elimination of molecules in not fully understood. Concomitant administration of nephrotoxic drugs and/or substances that are tubularly secreted could result in delayed clearance of pemetrexed.

Results from *in vitro* studies with human liver microsomes suggest that pemetrexed would not cause clinically significant interactions with drugs metabolised by CYP3A, CYP2D6, CYP2C9 and CYP1A2

The pharmacokinetics of pemetrexed are not influenced by oral folic acid and intramuscular vitamin B_{12} supplementation or by concurrently administered cisplatin**.** Total platinum clearance is not affected by pemetrexed administration.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Although NSAIDs in moderate doses can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥ 80 mL/min), renal clearance was reduced by 16% when ibuprofen was concurrently administered with pemetrexed in patients with normal renal function. Caution should be used when administering NSAIDs concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance of 45–79 mL/min). It is recommended that patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of and 2 days following administration of pemetrexed.

In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives in patients with mild to moderate renal insufficiency, patients with mild to moderate renal insufficiency taking these NSAIDs should interrupt dosing for at least 5 days before, the day of and 2 days following pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity**.**

ADVERSE EFFECTS

Single Agent Pemetrexed (NSCLC)

Table 5 provides the frequency and severity of undesirable effects that have been reported in > 5% of 265 patients randomly assigned to receive single agent pemetrexed with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single agent docetaxel. All patients were diagnosed with locally advanced or metastatic NSCLC and received prior chemotherapy.

Table 5

			Pemetrexed (n = 265)		Docetaxel (n = 276)	
System Organ Class	**Frequency**	**Adverse Event ***	**All Grades Toxicity (%)**	**Grade 3–4 Toxicity (%)**	**All Grades Toxicity (%)**	**Grade 3–4 Toxicity (%)**
Blood and Lymphatic System Disorders	Very Common	Haemoglobin	19.2	4.2	22.1	4.3
		Leukocytes	12.1	4.2	34.1	27.2
		Neutrophils/ Granulocytes	10.9	5.3	45.3	40.2
	Common	Platelets	8.3	1.9	1.1	0.4
Gastrointestinal Disorders	Very Common	Nausea	30.9	2.6	16.7	1.8
		Anorexia	21.9	1.9	23.9	2.5
		Vomiting	16.2	1.5	12.0	1.1
		Stomatitis/ Pharyngitis	14.7	1.1	17.4	1.1
		Diarrhoea	12.8	0.4	24.3	2.5
	Common	Constipation	5.7	0.0	4.0	0.0
General Disorders	Very Common	Fatigue	34.0	5.3	35.9	5.4
	Common	Fever	8.3	0.0	7.6	0.0
Hepatobiliary Disorders	Common	ALT (SGPT)	7.9	1.9	1.4	0.0
		AST (SGOT)	6.8	1.1	0.7	0.0
Skin and Subcutaneous Tissue Disorders	Very Common	Rash/ Desquamation	14.0	0.0	6.2	0.0
	Common	Pruritis	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4**	37.7	2.2**

* Refer to National Cancer Institute Common Toxicity Criteria (NCI CTC, version 2.0, NCI 1998) for lab values for each Grade of toxicity.

** According to NCI CTC (version 2.0), *alopecia* should only be reported as Grade 1 or 2.

Very Common (≥ 10%); Common (> 5% and < 10%). For the purpose of this table, a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

Clinically relevant CTC toxicity that was reported in ≥ 1% and ≤ 5% (common) of the patients that were randomly assigned to pemetrexed include sensory neuropathy, motor neuropathy, abdominal pain, increased creatinine, febrile neutropenia, infection without neutropenia, allergic reaction/ hypersensitivity and erythema multiforme.

Clinically relevant CTC toxicity that was reported in < 1% (uncommon) of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase II results from three single agent pemetrexed studies (n = 164) and the Phase III single agent pemetrexed study described above, with the exception of neutropenia (12.8% *versus* 5.3%, respectively) and alanine aminotransferase elevation (15.2% *versus* 1.9%, respectively). These differences were likely due to differences in the patient population, since the Phase II studies included

chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

Combination with Cisplatin (MPM)

Table 6 provides the frequency and severity of undesirable effects that have been reported in > 5% of 168 patients with mesothelioma who were randomly assigned to receive pemetrexed and cisplatin and 163 patients with mesothelioma randomly assigned to receive single agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B_{12}.

Table 6

			Pemetrexed plus Cisplatin (n = 168)		Cisplatin (n = 163)	
System Organ Class	**Frequency**	**Adverse Event ***	**All Grades Toxicity (%)**	**Grade 3–4 Toxicity (%)**	**All Grades Toxicity (%)**	**Grade 3–4 Toxicity (%)**
Blood and Lymphatic System Disorders	Very Common	Neutrophils	56.0	23.2	13.5	3.1
		Leukocytes	53.0	14.9	16.6	0.6
		Haemoglobin	26.2	4.2	10.4	0.0
		Platelets	23.2	5.4	8.6	0.0
Eye Disorders	Common	Conjunctivitis	5.4	0.0	0.6	0.0
Gastrointestinal Disorders	Very Common	Nausea	82.1	11.9	76.7	5.5
		Vomiting	56.5	10.7	49.7	4.3
		Stomatitis/ Pharyngitis	23.2	3.0	6.1	0.0
		Anorexia	20.2	1.2	14.1	0.6
		Diarrhoea	16.7	3.6	8.0	0.0
		Constipation	11.9	0.6	7.4	0.6
	Common	Dyspepsia	5.4	0.6	0.6	0.0
General Disorders	Very Common	Fatigue	47.6	10.1	42.3	9.2
Metabolism and Nutrition Disorders	Common	Dehydration	6.5	4.2	0.6	0.6
Nervous System Disorders	Very Common	Neuropathy – sensory	10.1	0.0	9.8	0.6
	Common	Taste disturbance	7.7	0.0***	6.1	0.0***
Renal and Urinary Disorders	Very Common	Creatinine clearance decreased**	10.7	0.6	9.8	1.2
		Genitourinary - other	16.7	1.6	18.4	2.5
Skin and Subcutaneous Tissue Disorders	Very Common	Rash	16.1	1.6	4.9	0.0
		Alopecia	11.3	0.0***	5.5	0.0***

* Refer to NCI CTC (version 2.0) for each Grade of toxicity, except the term "Creatinine clearance decreased" **, which is derived from the CTC term "renal/genitourinary-other".

*** According to NCI CTC (version 2.0), *alopecia* and *taste disturbance* should only be reported as Grade 1 or 2.

Very Common (≥ 10%); Common (> 5% and < 10%). For the purpose of this table, a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

Clinically relevant toxicity that was reported in ≥ 1% and ≤ 5% (common) of the patients that were randomly assigned to receive pemetrexed and cisplatin include increased AST (SGOT), ALT (SGPT) and GGT, infection, febrile neutropenia, renal failure, chest pain, pyrexia and urticaria.

Clinically relevant CTC toxicity that was reported in < 1% (uncommon) of the patients that were randomly assigned to receive pemetrexed and cisplatin include arrhythmia and motor neuropathy.

Combination with Cisplatin (NSCLC)

Table 7 provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of 839 patients with NSCLC who were randomised to study and received pemetrexed and cisplatin and 830 patients with NSCLC who were randomised to study and received gemcitabine and cisplatin. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B_{12}.

Table 7

			Pemetrexed plus Cisplatin (n = 839)		Gemcitabine plus Cisplatin (n = 830)	
System Organ Class	**Frequency**	**Adverse Event ***	**All Grades Toxicity (%)**	**Grade 3–4 Toxicity (%)**	**All Grades Toxicity (%)**	**Grade 3–4 Toxicity (%)**
Blood and Lymphatic System Disorders	Very Common	Haemoglobin	33.0*	5.6*	45.7*	9.9*
		Neutrophils/ Granulocytes	29.0*	15.1*	38.4*	26.7*
		Leukocytes	17.8	4.8*	20.6	7.6*
		Platelets	10.1*	4.1*	26.6*	12.7*
Gastrointestinal Disorders	Very Common	Nausea	56.1	7.2*	53.4	3.9*
		Vomiting	39.7	6.1	35.5	6.1
		Anorexia	26.6	2.4*	24.2	0.7*
		Constipation	21.0	0.8	19.5	0.4
		Stomatitis/ Pharyngitis	13.5	0.8	12.4	0.1
		Diarrhoea without colostomy	12.4	1.3	12.8	1.6
	Common	Dyspepsia/ Heartburn	5.2	0.1	5.9	0.0
General Disorders	Very Common	Fatigue	42.7	6.7	44.9	4.9
Nervous System Disorders	Common	Neuropathy – sensory	8.5*	0*	12.4*	0.6*
		Taste disturbance	8.1	0***	8.9	0***
Renal and Urinary Disorders	Very Common	Creatinine increased	10.1*	0.8	6.9*	0.5
Skin and Subcutaneous Tissue Disorders	Very Common	Alopecia	11.9*	0***	21.4*	0.5***
	Common	Rash/ Desquamation	6.6	0.1	8.0	0.5

P-values < 0.05 comparing pemetrexed and cisplatin to gemcitabine plus cisplatin, using Fisher Exact test.

** Refer to NCI CTC (version 2.0) for each Grade of toxicity.

*** According to NCI CTC (version 2.0), *alopecia* and *taste disturbance* should only be reported as Grade 1 or 2.

Very Common (≥ 10%); Common (> 5% and < 10%). For the purpose of this table, a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin

Clinically relevant CTC toxicity that was reported in ≥ 1% and ≤ 5% (common) of the patients that were randomly assigned to pemetrexed plus cisplatin include AST increase, ALT increase, infection, febrile neutropenia, renal failure, pyrexia, dehydration, conjunctivitis and creatinine clearance decrease.

Clinically relevant CTC toxicity that was reported in <1% (uncommon) of the patients that were randomly assigned to receive pemetrexed and cisplatin include: GGT increase, chest pain, arrhythmia and motor neuropathy. Acute renal failure was observed more commonly in the pemetrexed and cisplatin arm (6 cases, 0.7%) than in the gemcitabine plus cisplatin arm (0 cases).

Single Agent Pemetrexed (NSCLC Maintenance)

Table 8 provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of 800 patients randomly assigned to receive single agent pemetrexed and 402 patients randomly assigned to receive placebo in the single-agent maintenance pemetrexed study (JMEN:N=663) and continuation pemetrexed maintenance study (PARAMOUNT: N=539). All patients were diagnosed with Stage IIIB or IV NSCLC and had received prior platinum-based chemotherapy. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.

Table 8

			Pemetrexed (n =800)		Placebo (n = 402)	
System Organ Class	**Frequency [a]**	**Adverse Event [b]**	**All Grades Toxicity (%)**	**Grade 3–4 Toxicity (%)**	**All Grades Toxicity (%)**	**Grade 3–4 Toxicity (%)**
Blood and Lymphatic System Disorders	Very Common	Haemoglobin decreased	18.0	4.5	5.2	0.5
	Common	Leukocytes decreased	5.8	1.9	0.7	0.2
		Neutrophils decreased	8.4	4.4	0.2	0.0
Gastrointestinal Disorders	Very Common	Nausea	17.3	0.8	4.0	0.2
		Anorexia	12.8	1.1	3.2	0.0
	Common	Vomiting	8.4	0.3	1.5	0.0
		Mucositis/ Stomatitis	6.8	0.8	1.7	0.0
		Diarrhoea	5.2	0.5	2.7	0.0
General Disorders and Administration Site Disorders	Very Common	Fatigue	24.1	5.3	10.9	0.7
	Common	Pain	7.6	0.9	4.5	0.0
		Oedema	5.6	0	1.5	0.0
Hepatobiliary Disorders	Common	ALT (SGPT)	6.5	0.1	2.2	0.0
		AST (SGOT)	5.9	0.0	1.7	0.0
Infections and Infestations	Common	Infection	5.2	1.6	1.8	0.0
Nervous System Disorders	Common	Neuropathy – sensory	7.4	0.6	5.0	0.2
Skin and Subcutaneous Tissue Disorders	Very Common	Rash/ Desquamation	8.1	0.1	3.7	0.0
Renal disorders	Common	Renal disorders[c]	7.6	0.9	1.7	0.0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Event; NCI = National Cancer Institute; SGOT = serum glutamic oxaloacectic transaminase; SGPT = serum glutamic pyruvic transaminase.

[a] Very Common (≥ 10%); Common (> 5% and < 10%). For the purpose of this table, a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

[b] Refer to NCI CTCAE (version 3.0, NCI 2003) for each Grade of toxicity.

[c] Combined term includes increased serum/blood creatinine, decreased glomerular filtration rate, renal failure and renal/genitourinary – other.

Clinically relevant CTC toxicity of any grade that was reported in ≥ 1% and ≤ 5% (common) of the patients that were randomly assigned to pemetrexed include decreased platelets, decreased creatinine clearance, constipation, oedema, alopecia, increased creatinine, pruritis/itching, fever (in the absence of neutropenia), ocular surface disease (including conjunctivitis), increased lacrimation and decreased glomerular filtration rate.

Clinically relevant CTC toxicity that was reported in < 1% (uncommon) of the patients that were randomly assigned to pemetrexed include febrile neutropenia, allergic reaction/hypersensitivity, motor neuropathy, erythema multiforme, renal failure and supraventricular arrhythmia.

Safety was assessed for patients who were randomised to receive pemetrexed (N=800). The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed maintenance (N=519), and compared to patients who received > 6 cycles of pemetrexed (N=281). Increases in adverse reactions (all grades) were observed with longer exposure. A significant increase in the incidence of possibly study drug related Grade3-4 neutropenia was observed with longer exposure to pemetrexed (≤6 cycles: 3.3%, >6 cycles: 6.4%, p=0.046).; No statistically significant differences in any other individual Grade 3/4/5 adverse reactions were seen with longer exposure.
In clinical trials, sepsis which in some cases was fatal occurred in approximately 1% of patients.

Cases of oesophagitis have been reported uncommonly in clinical trials with pemetrexed.

Post–Marketing Experience

Rare: ≤ 0.1% of patients treated with pemetrexed.

Blood and Lymphatic System

Rare cases of immune-mediated haemolytic anaemia have been reported in patients treated with pemetrexed.

Gastrointestinal Disorders

Rare cases of colitis have been reported in patients treated with pemetrexed.

General Disorders and administration site conditions

Rare cases of oedema have been reported in patients treated with pemetrexed.

Injury, Poisoning and Procedural Complications

Rare cases of radiation recall have been reported in patients who have previously received radiotherapy.

Respiratory Disorders

Rare cases of interstitial pneumonitis have been reported in patients treated with pemetrexed.

Skin

Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and toxic epidermal necrolysis which in some cases were fatal.

Hepatobiliary Disorders

Rare cases of hepatitis, potentially serious, have been reported during clinical trials with pemetrexed.

DOSAGE AND ADMINISTRATION

Pemetrexed should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.

Pemetrexed in Combination use with Cisplatin

Adults – the recommended dose of pemetrexed is 500 mg/m^2 as body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

The recommended dose of cisplatin is 75 mg/m^2 BSA infused over 2 hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin. Refer to cisplatin Product Information document for specific dosing advice.

Single Agent Pemetrexed

Adults – the recommended dose of pemetrexed is 500 mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Premedication Regimen

Skin rash has been reported in patients not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of and the day after pemetrexed administration.

To reduce toxicity, patients treated with pemetrexed must be instructed to take a low-dose oral folic acid preparation or a multivitamin containing folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive one intramuscular injection of vitamin B_{12} during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as pemetrexed. In clinical trials, the dose of folic acid studied ranged from 350–1000 µg, and the dose of vitamin B_{12} received was 1000 µg. The most commonly used dose of oral folic acid was 400 µg.

Laboratory Monitoring and Dose Reduction Recommendations

Monitoring

It is recommended that patients receiving pemetrexed be monitored before each dose with a complete blood count, including a differential and platelet count. Periodic blood chemistry tests should be collected to evaluate renal and hepatic function.

Absolute neutrophil count (ANC) should be ≥ 1500 cells/mm^3 and platelets ≥ 100,000 cells/mm^3 prior to scheduled administration of any cycle.

Dose Reduction Recommendations

Dose adjustments at the start of a subsequent 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, patients should be retreated using the guidelines in Tables 9–11 which are suitable for using pemetrexed as a single agent or in combination with cisplatin.

Table 9: Dose Modification for Pemetrexed (Single Agent or in Combination) and Cisplatin Haematological Toxicities

nadir platelets ≥ 50,000/mm^3 and nadir ANC < 500/mm^3	75% of previous dose (pemetrexed and cisplatin)
nadir platelets ≤ 50,000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose (pemetrexed and cisplatin)
nadir platelets < 50,000/mm^3 with bleeding[a], regardless of nadir ANC	50% of previous dose (pemetrexed and cisplatin)

a These criteria meet the ((National Cancer Institute Common Toxicity Criteria version 2.0 (NCI 1998) definition of ≥ CTC Grade 2 bleeding.

If patients develop non-haematologic toxicities (excluding neurotoxicity) ≥ Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guidelines in Table 10.

Table 10: Dose Modification for Pemetrexed (Single Agent or in Combination) and Cisplatin Nonhaematologic Toxicities[a,b]

	Pemetrexed Dose (mg/m^2)	Cisplatin Dose (mg/m^2)
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhoea requiring hospitalization (irrespective of grade) or grade 3 or 4 diarrhoea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

a NCI CTC

b Excluding neurotoxicity.

In the event of neurotoxicity, the recommended dose adjustment for pemetrexed and cisplatin is documented in Table 11. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 11: Dose Modification for Pemetrexed (Single Agent or in Combination) and Cisplatin Neurotoxicity

CTC Grade	Pemetrexed Dose (mg/m^2)	Cisplatin Dose (mg/m^2)
0–1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Pemetrexed therapy should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after two dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Elderly Patients

In clinical trials, there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared with patients younger than 65. No dose reductions other than those recommended for all patients are necessary.

Renally Impaired Patients

In clinical studies, patients with creatinine clearance of ≥ 45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance < 45 mL/min have been treated to make dosage recommendations for this group of patients. Therefore, patients should not receive pemetrexed whose creatinine clearance is < 45 mL/min [using the standard Cockcroft and Gault formula or GFR measured by Tc99m-DPTA serum clearance method].

Preparation and Administration Instructions – Use Aseptic Technique

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection. Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection and Ringer's Injection. Co-administration of pemetrexed with other drugs and diluents has not been studied and therefore is not recommended.

1. Use appropriate aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose and the number of pemetrexed vials needed. A 500 mg vial contains 500 mg pemetrexed. A 100 mg vial contains 100 mg pemetrexed. The vial contains an excess of pemetrexed to facilitate delivery of label amount.
3. Prior to administration, reconstitute 500 mg vials with 20 mL 0.9% Sodium Chloride Injection to give a solution containing 25 mg/mL pemetrexed.

Reconstitute 100 mg vials with 4.05 mL 0.9% Sodium Chloride Injection to give a solution containing 25 mg/mL pemetrexed.

4. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted pemetrexed solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
5. The appropriate volume of reconstituted pemetrexed solution should be further diluted to 100 mL with 0.9% Sodium Chloride Injection and administered as an intravenous infusion over 10 minutes.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Chemical and physical stability of reconstituted and infusion solutions of pemetrexed was demonstrated for up to 24 hours after reconstitution of the original vial when refrigerated between 2–8°C. However, because pemetrexed and the recommended diluent contain no antimicrobial preservatives, to reduce antimicrobial hazard, reconstituted and infusion solutions should be used immediately. Discard any unused portion.

OVERDOSAGE

Symptoms

Reported symptoms of pemetrexed overdose include neutropenia, anaemia, thrombocytopenia, mucositis 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 mucositis may be seen.

Treatment

If overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Management of pemetrexed overdose should include consideration of the use of leucovorin or thymidine rescue.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Pemetrexed APOTEX powder for injection is intended for intravenous infusion.

100 mg: white to either light yellow or green-yellow powder.
Pack size: 1 vial, single use.
AUST R 210429.

500 mg: white to either light yellow or green-yellow powder.
Pack size: 1 vial, single use.
AUST R 210440.

Not all strengths may be marketed.

Storage

Store below 25°C.

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

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