NEW ZEALAND DATA SHEET

PEMETREXED ACCORD (PEMETREXED POWDER FOR INFUSION)

1 PRODUCT NAME

Pemetrexed Accord 100 mg powder for infusion

Pemetrexed Accord 500 mg powder for infusion

Pemetrexed Accord 1000 mg powder for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in Pemetrexed Accord powder for infusion is pemetrexed (as pemetrexed disodium hemipentahydrate).

Pemetrexed disodium is a white to off white crystalline powder.

Pemetrexed Accord is supplied in 1000 mg, 500 mg and 100 mg vials.

- Each 100 mg vial of Pemetrexed Accord contains pemetrexed disodium equivalent to 100 mg pemetrexed.
- Each 500 mg vial of Pemetrexed Accord contains pemetrexed disodium equivalent to 500 mg pemetrexed.
- Each 1000 mg vial of Pemetrexed Accord contains pemetrexed disodium equivalent to 1000 mg pemetrexed.

For the full list of excipients, see **Section 6.1 List of Excipients.**

3 PHARMACEUTICAL FORM

Pemetrexed Accord is supplied as a sterile lyophilised powder for intravenous infusion available in single dose clear glass vials. The product is a white to either light yellow or green-yellow lyophilised solid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Malignant Pleural Mesothelioma

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

Non-Small Cell Lung Cancer

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

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Pemetrexed Accord in combination use with cisplatin

Adults - The recommended dose of Pemetrexed Accord 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 Accord 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. See cisplatin Product Information document for specific dosing advice.

Single agent use

Adults - The recommended dose of Pemetrexed Accord 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 Accord 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 Accord, and dosing should continue during the full course of therapy and for 21 days after the last dose of Pemetrexed Accord. Patients must also receive one intramuscular injection of vitamin B_{12} during the week preceding the first dose of Pemetrexed Accord and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as Pemetrexed Accord. In clinical trials, the dose of folic acid studied ranged from 350 to 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 Accord 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 1-3 which are suitable for using Pemetrexed Accord as a single agent or in combination with cisplatin.

Table 1: Dose Modification for Pemetrexed Accord (single agent or in combination) and Cisplatin Haematologic Toxicities

Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose (Pemetrexed Accord and cisplatin)
Nadir platelets ≤50,000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose (Pemetrexed Accord and cisplatin)
Nadir platelets <50,000/mm^3 with bleeding[a], regardless of nadir ANC	50% of previous dose (Pemetrexed Accord 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 2.

Table 2: Dose Modification for Pemetrexed Accord (single agent or in combination) and Cisplatin Non-haematologic Toxicities [a, b]

	Dose of Pemetrexed Accord (mg/m^2)	**Dose of cisplatin (mg/m^2)**
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhoea requiring hospitalisation (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 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 3: Dose Modification for Pemetrexed Accord (single agent or in combination) and Cisplatin Neurotoxicity

CTC Grade	Dose for Pemetrexed Accord (mg/m^2)	Dose for cisplatin (mg/m^2)
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Pemetrexed Accord therapy should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after 2 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.

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

Renally impaired patients - In clinical studies, patients with creatinine clearance of at least 45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 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].

Hepatically impaired patients - No relationship between AST (SGOT), ALT (SGPT), or total bilirubin on the pharmacokinetics of pemetrexed were identified. However, patients with hepatic impairment such as bilirubin >1.5 times the upper limit of normal (ULN) or aminotransferase >3 times the ULN (hepatic metastases absent) or >5 time the ULN (hepatic metastases present) have not been specifically studied.

Method of Administration

For instructions on reconstitution and dilution of Pemetrexed Accord, see **Section 6.6 Special Precautions for Disposal and Other Handling**.

The product is for single use in one patient on one occasion only. Discard any residue.

4.3 CONTRAINDICATIONS

Pemetrexed is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any excipients in this product. Pemetrexed is contraindicated in women of childbearing age unless adequate contraception is used.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pemetrexed can suppress bone marrow function as manifested by anaemia, neutropenia, thrombocytopenia, or pancytopenia (see **Section 4.8 Undesirable 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 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-haematologic toxicity seen in the previous cycle (see **Dose reduction recommendations** *under* **Section 4.2 Dose and Method of Administration**).

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 **Section 4.2 Dose and Method of Administration**). In the Phase 3 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.

Skin reactions have been reported in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions (see **Section 4.2 Dose and Method of Administration**).

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) should avoid taking nonsteroidal anti-inflammatory drugs (NSAIDs) with short elimination half-lives for at least 2 days prior to, on the day of, and at least 2 days after administration of pemetrexed. All patients eligible for Pemetrexed Accord therapy should avoid taking NSAIDs with long elimination half-lives at least 5 days prior to, on the day of, and at least 2 days after pemetrexed administration (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Use in hepatic impairment

Pemetrexed is not extensively metabolised by the liver. However, patients with hepatic impairment such as bilirubin >1.5 times the upper limit of normal (ULN) or aminotransferase >3 times the ULN (hepatic metastases absent) or >5 time 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 **Section 4.2 Dose and Method of Administration**).

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is not fully defined. A phase 2 study of pemetrexed in 31 solid tumor patients with stable third space fluid demonstrated no difference in pemetrexed dose-normalized plasma concentrations or clearance compared to patients without third space fluid collections. Thus, drainage of third space fluid collection prior to pemetrexed treatment should be considered, but may not be 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 **Dose reduction recommendations** *under* **Section 4.2 Dose and Method of Administration**).

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.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Nephrotoxic drugs

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 is not fully understood. Concomitant administration of nephrotoxic drugs and/or substances that are tubularly secreted could result in delayed clearance of pemetrexed.

Cytochrome P450

Pemetrexed undergoes limited hepatic metabolism. Results from *in vitro* studies with human liver microsomes suggest that pemetrexed would not be predicted cause clinically significant interactions with drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Concomitant cytotoxic therapy

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.

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.

Asprin

Acetylsalicylic acid, administered in low to moderate doses (325 mg orally every 6 hours) does not affect the pharmacokinetics of pemetrexed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy

Pregnancy Category D

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). Therefore, the use of pemetrexed must be avoided in pregnant women because of the potential hazard to the foetus. Women must be advised to avoid becoming pregnant while being treated with Pemetrexed Accord.

Use in lactation

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

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 machinery if this event occurs.

4.8 UNDESIRABLE EFFECTS

Single agent pemetrexed (NSCLC)

Table 4 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 4

System Organ Class	Frequency	Event*	Pemetrexed (N=265)		Docetaxel (N=276)	
			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/ Granulocyte	10.9	5.3	45.3	40.2

System Organ Class	Frequency	Event*	Pemetrexed (N=265)		Docetaxel (N=276)	
			All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)	All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)
	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	Pruritus	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4**	37.7	2.2**

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

** According to NCI CTC Criteria (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 2 results from three single agent pemetrexed studies (n=164) and the Phase 3 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 2 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 5 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 cisplatin and pemetrexed 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 5

Class organ class	Frequency	Event*	Pemetrexed /cisplatin (N=168)		Cisplatin (N=163)	
			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 Disorders	Very Common	Creatinine Clearance Decreased**	10.7	0.6	9.8	1.2
		Genitourinary Other	16.7	0.6	18.4	2.5
Skin and Subcutaneous Tissue Disorders	Very Common	Rash	16.1	0.6	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 Criteria (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 cisplatin and pemetrexed include: increased AST (SGOT), ALT (SGPT), and GGT, infection, febrile neutropenia, renal failure, chest pain, pyrexia and urticaria.

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

Combination with cisplatin (NSCLC)

Table 6 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 cisplatin and pemetrexed and 830 patients with NSCLC who were randomised to study and received cisplatin and gemcitabine. 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 6

System Organ Class	Frequency	Event*	Pemetrexed/cisplatin (N=839)		Gemcitabine/ cisplatin (N=830)	
			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 and administration site conditions	Very Common	Fatigue	42.7	6.7	44.9	4.9
Nervous System Disorders	Common	Neuropathy-sensory	8.5*	0.0*	12.4*	0.6*
		Taste disturbance	8.1	0.0***	8.9	0.0***
Renal and urinary disorders	Very Common	Creatinine increased	10.1*	0.8	6.9*	0.5
Skin and Subcutaneous	Very Common	Alopecia	11.9*	0***	21.4*	0.5***
Tissue disorder	Common	Rash/ desquamation	6.6	0.1	8.0	0.5

*P-values <0.05 comparing pemetrexed/cisplatin to gemcitabine/cisplatin, using Fisher Exact test

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

*** According to NCI CTC Criteria (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 cisplatin and pemetrexed include: AST increase, ALT increase, infection, febrile neutropenia, renal failure, pyrexia, dehydration, conjunctivitis, and creatinine clearance decrease.

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

Single agent pemetrexed (NSCLC maintenance)

Table 7 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 (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 7

System Organ Class	**Frequency [a]**	**Event [b]**	**Pemetrexed (N = 800)**		**Placebo (N = 402)**	
			All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
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
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	0.0	1.5	0.0
Hepatobiliary Disorders	Common	ALT (SGPT) elevation	6.5	0.1	2.2	0.0
		AST (SGOT) elevation	5.9	0.0	1.7	0.0
Skin and Subcutaneous Tissue Disorders	Very Common	Rash/ Desquamation	8.1	0.1	3.7	0.0
Nervous System Disorders	Common	Neuropathy-sensory	7.4	0.6	5.0	0.2
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 oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

[a] Definition of frequency terms: Very common - ≥ 10%; Common - > 5% and < 10%. For the purpose of this table, a cutoff of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.
[b] Refer to NCI CTCAE Criteria (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, edema, alopecia, increased creatinine, pruritus/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 Grade 3-4 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 DATA:

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.

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

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

Rare - ≤0.1% of patients treated with pemetrexed.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicine is important. It allows continued monitoring of the benefit-risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

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.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pemetrexed is an antifolate antineoplastic 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 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 thymidylate synthase (TS) correlates with reduced sensitivity to pemetrexed in antifolate-resistant cell lines. Results in a study with specimens from chemonaive patients with NSCLC demonstrated lower levels of TS expression in adenocarcinoma as compared to squamous cell carcinoma tumors. 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.

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 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. 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. On 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 8 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 8: Efficacy of Pemetrexed plus Cisplatin vs. Cisplatin in Malignant Pleural Mesothelioma

	Randomised 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 (95% CI)	12.1 mos (10.0-14.4)	9.3 mos (7.8-10.7)	13.3 mos (11.4-14.9)	10.0 mos (8.4-11.9)
Hazard ratio	0.77		0.75	
Log Rank p-value*	0.020		0.051	
Percent censored	35.8	28.4	43.5	36.8
Median Time to Tumour Progression (95% CI)	5.7 mos (4.9-6.5)	3.9 mos (2.8-4.4)	6.1 mos (5.3-7.0)	3.9 mos (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 mos (3.9-4.9)	2.7 mos (2.1-2.9)	4.7 mos (4.3-5.6)	2.7 mos (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 because of any cause, or discontinuation because of any other reason.

*** In the pemetrexed /cis arm, randomised and treated (N=225) and fully supplemented (N=167).

Table 9 summarises the number of cycles of treatment completed by randomised 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 9: Summary of Cycles Given

	Randomised and Treated Patients		**Fully Supplemented Patients**	
Cycle Statistics	**Pemetrexed / cis (N=226)**	**Cisplatin (N=222)**	**Pemetrexed / cis (N=168)**	**Cisplatin (N=163)**
Median Cycles Completed	6.0	4.0	6.0	4.0
Range	(1-12)	(1-9)	(1-12)	(1-9)
Total Cycles Completed	1066	877	825	650
Cycles given at full dosage	1030	874	802	648
(%)	(96.6%)	(99.7%)	(97.2%)	(99.7%)

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 (LCCS). By the end of treatment (after 6 cycles), there was a statistically significant difference in favour of pemetrexed/cis 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/cis 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 /cis 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 3 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) 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). Refer to following figure.

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

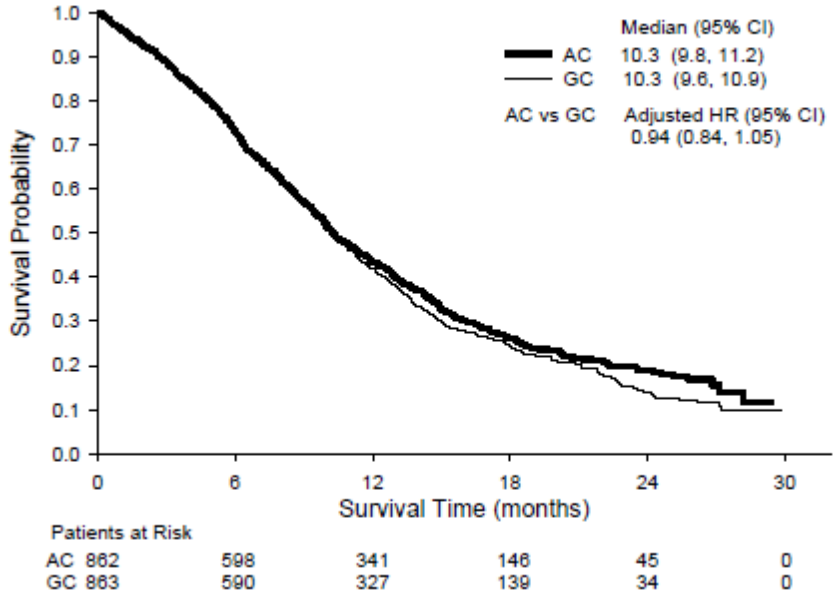


Table 10: Efficacy of Pemetrexed + Cisplatin vs. Gemcitabine + Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population

	Pemetrexed + Cisplatin (N= 862)	**Gemcitabine + Cisplatin (N= 863)**
Median overall survival (95% CI)	10.3 mos (9.8 – 11.2)	10.3 mos (9.6 – 10.9)
Adjusted hazard ratio (HR) (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)
Median Progression free survival (95% CI)	4.8 mos (4.6 – 5.3)	5.1 mos (4.6 – 5.5)
Adjusted hazard ratio (HR) (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%)

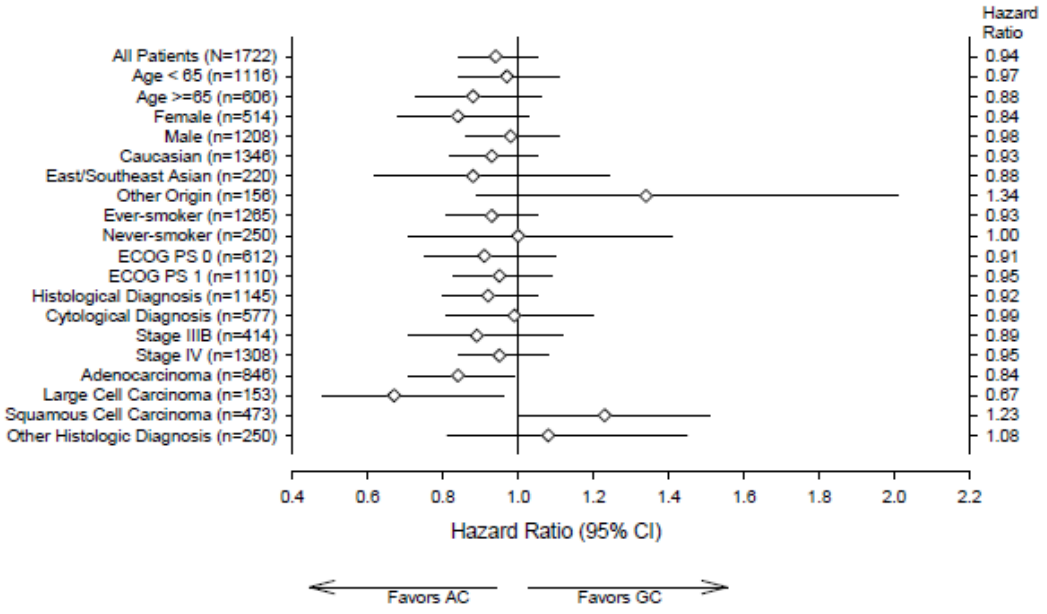
a Statistically significant for non-inferiority

b Number of tumor-qualified patients on the AC arm (N=762) and GC arm (N=755). Investigator assessed

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

A series of subsets of patients were examined in pre-specified adjusted analyses as shown in the following figure:

Figure 2: Forest Plot for Overall Survival Adjusted Hazard Ratios of Subgroups pemetrexed + Cisplatin vs. Gemcitabine + Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population

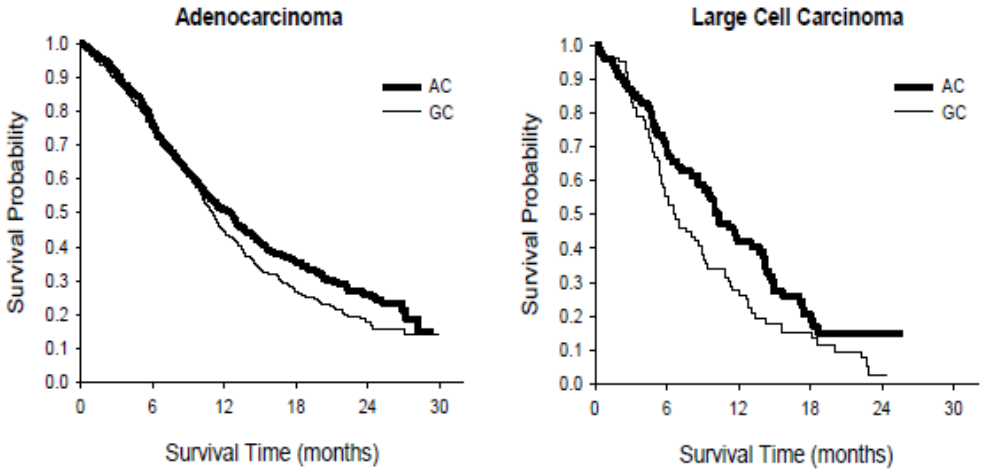


Results based on Cox adjusted analyses for ECOG PS, disease stage, gender, and basis for diagnosis (histological vs cytological). In the analysis by group, pertaining to each of these 4 covariates, the variable depicting the group was excluded from the model.
3 patients were missing ECOG performance status and are excluded from the Cox adjusted analyses; 209 patients were missing smoking status

Abbreviations: AC = pemetrexed plus cisplatin; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine plus cisplatin.

The analysis of the impact of NSCLC histology on overall survival demonstrated statistically significant superiority for pemetrexed + cisplatin in the adenocarcinoma (n=846, 12.6 versus 10.9 months, adjusted HR = 0.84; 95% CI =0.71-0.99, p =0.033) and large cell carcinoma subgroups (n=153, 10.4 versus 6.7, adjusted HR = 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 HR = 1.23; 95% CI =1.00-1.51, p =0.050) or patients with other histologies (n=250, 8.6 versus 9.2, adjusted HR = 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 the figures below:

Figure 3: Kaplan-Meier Curves for Overall Survival - Pemetrexed + Cisplatin (AC) vs. Gemcitabine + Cisplatin (GC) in First-line Non-Small Cell Lung Cancer – Adenocarcinoma and Large Cell Carcinoma



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

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

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. 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.

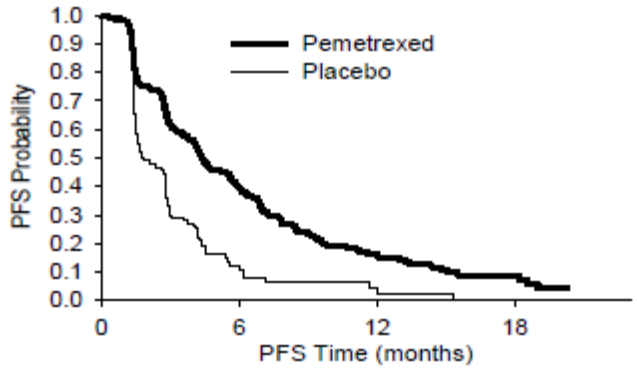
In the overall study population, pemetrexed was statistically superior to placebo in terms of overall survival (OS) (median 13.4 months versus 10.6 months, HR=0.79 (95% CI: 0.65-0.95), p-value=0.012) and PFS (median 4.0 months versus 2.0 months, HR=0.60 (95% CI: 0.49-0.73), p-value <0.00001). Consistent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

The PFS and OS results in patients with squamous cell histology suggested no advantage for pemetrexed over placebo.

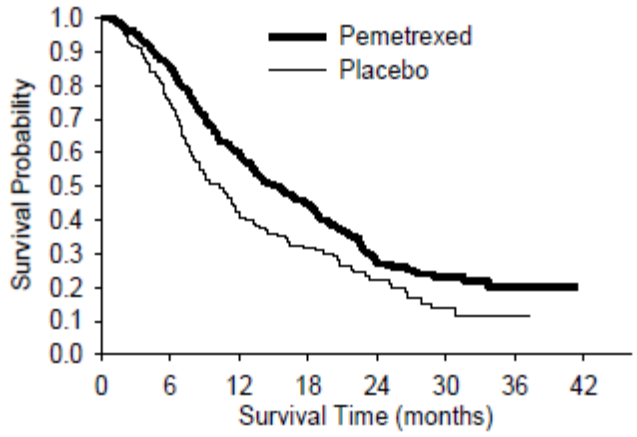
There were no clinically relevant differences observed for the safety profile of pemetrexed within the histology subgroups.

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:

Progression-free Survival



Overall Survival



A multicentre, randomised, double-blind, placebo-controlled Phase 3 study (PARAMOUNT), compared the efficacy and safety of continuation maintenance treatment with pemetrexed disodium injection plus BSC (n = 359) with that of placebo plus BSC (n = 180) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC other than predominantly squamous cell histology who did not progress after 4 cycles of first line doublet therapy of pemetrexed disodium injection in combination with cisplatin. Of the 939 patients treated with pemetrexed disodium injection us cisplatin induction, 539 patients were randomised to maintenance treatment with pemetrexed disodium injection or placebo. Of the randomised patients, 44.9% had a complete/partial response and 51.9% had a response of stable disease to pemetrexed disodium injection plus cisplatin induction. Patients randomised to treatment were required to have an ECOG performance status 0 or 1. The median time from the start of pemetrexed disodium injection plus cisplatin induction therapy to the start of maintenance treatment was 2.96 months on both the pemetrexed disodium injection arm and the placebo arm. Randomised patients received maintenance treatment until disease progression. For statistical purposes, efficacy and safety were measured from the time of randomisation after completion

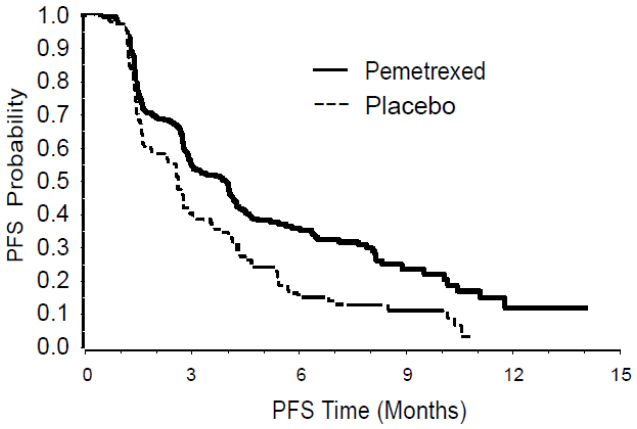
of first line (induction) therapy. Patients received a median of 4 cycles of maintenance treatment with pemetrexed disodium injection and 4 cycles of placebo. A total of 169 patients (47.1%) completed ≥ 6 cycles maintenance treatment with pemetrexed disodium injection, representing at least 10 total cycles of pemetrexed disodium injection.

Independent review of the imaging of 472 of the 539 randomised patients showed that the study met its primary endpoint (PFS) and showed a statistically significant improvement in PFS in the pemetrexed disodium injection arm over the placebo arm – median of 3.9 months and 2.6 months respectively (hazard ratio = 0.64, 95% CI = 0.51-0.81, p = 0.0002). The independent review of patient scans showed consistent results to the findings of the investigator assessment of PFS. In addition, for randomised patients, as measured from the start of pemetrexed disodium injection plus cisplatin first line induction treatment, the median investigator-assessed PFS was 6.9 months for the pemetrexed disodium injection arm and 5.6 months for the placebo arm (hazard ratio = 0.59, 95% CI = 0.47-0.74).

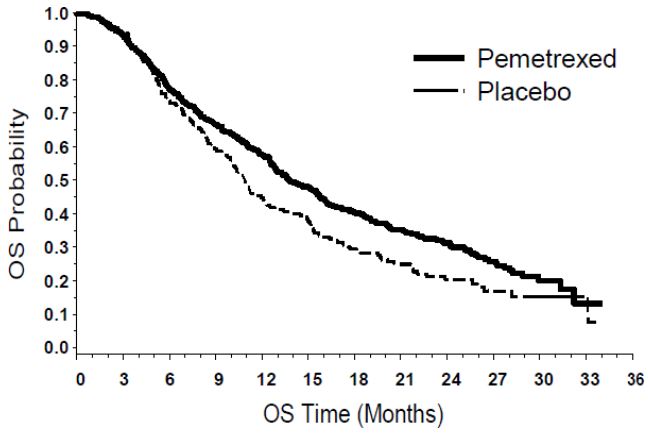
Following pemetrexed disodium injection plus cisplatin induction (4 cycles), treatment with pemetrexed disodium injection was statistically superior to placebo for OS (median 13.9 months versus 11.0 months, hazard ratio= 0.78, 95% CI = 0.64-0.96, p = 0.0195). At the time of final survival analysis, 28.7% of patients were alive or lost to follow up on the pemetrexed disodium injection arm versus 21.7% on the placebo arm. The relative treatment effect of pemetrexed disodium injection was internally consistent across subgroups (including disease stage, induction response, ECOG PS, smoking status, gender, histology and age) and similar to that observed in the unadjusted OS and PFS analyses. The 1 year and 2 year survival rates for patients on pemetrexed disodium injection were 58% and 32% respectively, compared to 45% and 21% for patients on placebo. From the start of pemetrexed disodium injection plus cisplatin first line induction treatment, the median OS of patients was 16.9 months for the pemetrexed disodium injection arm and 14.0 months for the placebo arm (hazard ratio = 0.78, 95% CI = 0.64-0.96). The percentage of patients that received post-discontinuation chemotherapy was 64.3% for pemetrexed disodium injection and 71.7% for placebo.

Kaplan Meier Plots of Progression- Free Survival (PFS) and Overall Survival (OS) for Continuation Pemetrexed Disodium Injection Maintenance versus Placebo in Patients with NSCLC other than Predominantly Squamous Cell Histology (measured from randomization):

Progression-Free Survival



Overall Survival



The pemetrexed disodium injection maintenance safety profiles from the two studies JMEN and PARAMOUNT were similar.

A multicentre, randomised, open label phase 3 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 (Intent To Treat population n = 283) and 7.9 months for patients treated with docetaxel (ITT n = 288) which is not statistically significantly different. These data, as outlined in Table 11, indicate comparable efficacy between pemetrexed and docetaxel.

Table 11: 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)
• Hazard Ratio	0.99	
• 95 % CI for Hazard Ratio	(0.82 - 1.20)	
• Non-inferiority p-value (Hazard Ratio)	0.226	
• % of docetaxel's survival benefit retained*	102 %	
• 95 % CI for % retention	(52 - 157%)	
• Non-inferiority p-value (% retention)	0.047	
Progression free survival (months)	(n = 283)	(n = 288)
• Median	2.9	2.9
• Hazard Ratio (95 % CI)	0.97 (.82 - 1.16)	
Time to treatment failure (TTTF – months)	(n = 283)	(n = 288)
• Median	2.3	2.1
• Hazard Ratio (95 % CI)	0.84 (.71 - .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.

On this study, treatment was administered until disease progression.

An analysis of the impact of NSCLC histology on overall survival was in favor of pemetrexed versus docetaxel for other than predominantly squamous histology (n=399, 9.3 versus 8.0 months, adjusted HR = 0.78; 95% CI =0.61-1.00, p =0.047) and was in favor 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.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of pemetrexed following single agent administration have been evaluated in 426 cancer patients with a variety of solid tumours at doses ranging from 0.2 to 838 mg/m2 infused over a 10-minute period. 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 was not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism. Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered dose being recovered unchanged in urine within the first 24 hours following administration. Pemetrexed total systemic clearance is 91.8 mL/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). Between-patient variability in clearance is moderate at 19.3 %. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

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% to 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 3.5 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 2 studies, 70 patients from the Phase 3 malignant pleural mesothelioma EMPHACIS trial, and 47 patients from a Phase 1 renal study.

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

Hepatic Insufficiency - No effect of AST (SGOT), ALT (SGPT), or total bilirubin on the pharmacokinetics of pemetrexed was observed. However, specific studies of hepatically impaired patients have not been conducted (see **Section 4.4 Special Warnings and Precautions for Use**).

Renal Insufficiency - 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 **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.2 Dose and Method of Administration**).

5.3 PRECLINICAL SAFETY DATA

Administration of pemetrexed to pregnant mice resulted in decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate. The use of pemetrexed must therefore be avoided in pregnant women (**see Section 4.6 Fertility, Pregnancy and Lactation**).

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Each 1000 mg vial of Pemetrexed Accord 1000 mg of mannitol.
- Each 500 mg vial of Pemetrexed Accord contains 500 mg of mannitol.
- Each 100 mg vial of Pemetrexed Accord contains 100 mg of mannitol.

Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

The product contains no preservative and is for single use in one patient on one occasion only. Discard any residue.

6.2 INCOMPATIBILITIES

See **Section 6.6 Special Precautions for Disposal and Other Handling**, Preparation and administration instructions.

6.3 SHELF LIFE

The shelf life for Pemetrexed Accord is 3 years.

Chemical and physical stability of reconstituted and infusion solutions of Pemetrexed Accord was demonstrated for up to 72 hours after reconstitution of the original vial when refrigerated between 2 to 8°C. However, because Pemetrexed Accord and the recommended diluent contain no antimicrobial preservatives, to reduce antimicrobial hazard, reconstituted and infusion solutions should be used immediately.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Pemetrexed Accord is not light sensitive.

6.5 NATURE AND CONTENTS OF CONTAINER

Pemetrexed Accord, pemetrexed disodium powder for infusion is available in sterile single-use glass vials containing: 100 mg, 500 mg or 1000 mg pemetrexed (pack size 1 vial).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

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 Accord is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection and Ringer's Injection. Coadministration of Pemetrexed Accord 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 Accord for intravenous infusion administration.
2. Calculate the dose and the number of Pemetrexed Accord vials needed. A 1000 mg vial contains 1000 mg of pemetrexed. A 500 mg vial contains 500 mg of pemetrexed. A 100 mg vial contains 100 mg of pemetrexed. The vial contains an excess of pemetrexed to facilitate delivery of label amount.
3. Prior to administration, reconstitute 1000 mg vials with 40 mL of 0.9% Sodium Chloride Injection to give a solution containing 25 mg/mL pemetrexed. Reconstitute 500 mg vials with 20 mL of 0.9%

Sodium Chloride Injection to give a solution containing 25 mg/mL pemetrexed. Reconstitute 100 mg vials with 4.2 mL of 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 Accord solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
5. The appropriate volume of reconstituted Pemetrexed Accord 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.

Pemetrexed Accord is a cytotoxic medicine, appropriate handling and disposal procedures should be used. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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