Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pemetrexed Waverley 100 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of pemetrexed (as pemetrexed disodium).

Excipients with known effect:
Each vial contains approximately 11 mg sodium.

After reconstitution (see section 6.6), each vial contains 25 mg/ml of pemetrexed.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to either light yellow or green-yellow lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Malignant pleural mesothelioma:
Pemetrexed Waverley in combination with cisplatin is indicated for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer:
Pemetrexed Waverley in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology (see section 5.1).

Pemetrexed Waverley is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy (see section 5.1).

Pemetrexed Waverleyis indicated as monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1).

4.2 Posology and method of administration

Posology
Pemetrexed Waverleymust only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

Pemetrexed Waverley *in combination with cisplatin*
The recommended dose of Pemetrexed Waverley is 500 mg/m^2 of 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 two 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 (see also cisplatin Summary of Product Characteristics for specific dosing advice).

Pemetrexed Waverley *as single agent*
In patients treated for non-small cell lung cancer after prior chemotherapy, the recommended dose of Pemetrexed Waverleyis 500 mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Pre-medication Regimen
To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day (see section 4.4).
To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1,000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B12 (1,000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

Monitoring
Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration, blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: absolute neutrophil count (ANC) should be ≥ 1,500 cells/mm3 and platelets should be ≥ 100,000 cells/mm3.
Creatinine clearance should be ≥ 45 ml/min.
The total bilirubin should be ≤ 1.5-times upper limit of normal. Alkaline phosphatase (AP), aspartate aminotransferase (AST or SGOT), and alanine aminotransferase (ALT or SGPT) should be ≤ 3-times upper limit of normal. Alkaline phosphatase, AST, and ALT ≤ 5-times upper limit of normal is acceptable if liver has tumour involvement.

Dose Adjustments
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 re-treated using the guidelines in Tables 1, 2, and 3, which are applicable for Pemetrexed Waverleyused as a single agent or in combination with cisplatin.

Table 1. Dose Modification Table for Pemetrexed (as Single Agent or in Combination) and Cisplatin - Haematologic Toxicities

Nadir ANC < 500/mm3 and nadir platelets ≥ 50,000/mm3	75% of previous dose (both pemetrexed and cisplatin)
Nadir platelets < 50,000/mm3 regardless of nadir ANC	75% of previous dose (bothpemetrexed and cisplatin)
Nadir platelets < 50,000/mm3 with bleeding[a] , regardless of nadir ANC	50% of previous dose (both pemetrexed and cisplatin)
[a] These criteria meet the National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998) definition of ≥ CTC Grade 2 bleeding.	

If patients develop non-haematologic toxicities ≥ Grade 3 (excluding neurotoxicity), **Pemetrexed Waverley** 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 Table for Pemetrexed (as Single Agent or in Combination) and Cisplatin - Non-Haematologic Toxicities [a, b]

	Dose of pemetrexed (mg/m^2)	Dose for 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] National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998) [b] Excluding neurotoxicity		

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

Table 3. Dose Modification Table for Pemetrexed(as Single Agent or in Combination) and Cisplatin - Neurotoxicity		
CTC a Grade	Dose of pemetrexed (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
[a] National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998)		

Treatment with Pemetrexed Waverleyshould 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
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 population
There is no relevant use of Pemetrexed Waverleyin the paediatric population in malignant pleural mesothelioma and non-small cell lung cancer.

Patients with renal impairment (standard Cockcroft and Gault formula or Glomerular Filtration Rate measured Tc99m DPTA serum clearance method)
Pemetrexed is primarily eliminated unchanged by renal excretion. In clinical studies, patients with creatinine clearance of ≥ 45 ml/min required no dose adjustments other than those recommended for all patients. There are insufficient data on the use of pemetrexed in patients with creatinine clearance below 45 ml/min; therefore, the use of pemetrexed is not recommended (see section 4.4).

Patients with hepatic impairment
No relationships between AST (SGOT), ALT (SGPT), or total bilirubin and pemetrexed pharmacokinetics were identified. However, patients with hepatic impairment, such as bilirubin > 1.5-times the upper limit of normal and/or aminotransferase > 3.0-times the upper limit of normal (hepatic metastases absent) or > 5.0-times the upper limit of normal (hepatic metastases present), have not been specifically studied.

Method of administration
Precautions to be taken before handling or administeringPemetrexed Waverley, see section 6.6.
Pemetrexed Waverleyshould be administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. For instructions on reconstitution and dilution of Pemetrexed Waverleybefore administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding (see section 4.6).
Concomitant yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Pemetrexed can suppress bone marrow function as manifested by neutropenia, thrombocytopenia, and anaemia (or pancytopenia) (see section 4.8). 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 ≥ 1,500 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 from the previous cycle (see section 4.2).

Less toxicity and reduction 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 B12 was administered. Therefore, all patients treated with pemetrexed must be instructed to take folic acid and vitamin B12 as a prophylactic measure to reduce treatment-related toxicity (see section 4.2).

Skin reactions have been reported in patients not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions (see section 4.2).
An insufficient number of patients has been studied with creatinine clearance of below 45 ml/min. Therefore, the use of pemetrexed in patients with creatinine clearance of <45 ml/min is not recommended (see section 4.2).

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, and acetylsalicylic acid (>1.3g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.5).

In patients with mild to moderate renal insufficiency eligible for pemetrexed therapy, NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.5).

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. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with pemetrexed alone or with other chemotherapeutic agents. Most of these events resolved after pemetrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).

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 tumour 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.

Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate anti-emetic 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 (see section 4.8).

Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended (see section 4.3 and 4.5).

Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended. Owing to the possibility of pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

Women of childbearing potential must use effective contraception during treatment with pemetrexed (see section 4.6).

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (e.g., aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of substances that are also tubularly secreted (e.g., probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed. If necessary, creatinine clearance should be closely monitored.

In patients with normal renal function (creatinine clearance ≥ 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and acetylsalicylic acid at higher doses (≥ 1.3g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or acetylsalicylic acid, concurrently with pemetrexed to patients with normal function (creatinine clearance ≥ 80 ml/min).

In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min), the concomitant administration of pemetrexed with NSAIDs (e.g., ibuprofen) or acetylsalicylic acid at higher doses should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.4).

In the absence of data regarding potential interaction with NSAIDs having longer half-lives such as piroxicam or rofecoxib, the concomitant administration with pemetrexed in patients with mild to moderate renal insufficiency should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.4). If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

Pemetrexed undergoes limited hepatic metabolism. Results from in vitro studies with human liver microsomes indicated that pemetrexed would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Interactions Common to all Cytotoxics

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anti-cancer chemotherapy require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Concomitant Use Contraindicated: Yellow fever vaccine: Risk of fatal generalised vaccinale disease (see section 4.3).

Concomitant Use Not Recommended: Live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated): Risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential must use effective contraception during treatment with pemetrexed. Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment, and up to 6 months thereafter. Contraceptive measures or abstinence are recommended.

Pregnancy

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

Breast-feeding

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions
The table below provides the frequency and severity of undesirable effects that have been reported in >5% of 168 patients with mesothelioma who were randomised to receive cisplatin and pemetrexed, and 163 patients with mesothelioma randomised to receive single-agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B12.

Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System 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/ Granulocytes decreased	56.0	23.2	13.5	3.1
		Leukocytes decreased	53.0	14.9	16.6	0.6
		Haemoglobin decreased	26.2	4.2	10.4	0.0
		Platelets decreased	23.2	5.4	8.6	0.0
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***
Eye disorders	Common	Conjunctivitis	5.4	0.0	0.6	0.0
		Diarrhoea	16.7	3.6	8.0	0.0

Gastro-intestinal disorders	Very common					
		Vomiting	56.5	10.7	49.7	4.3
		Stomatitis/ Pharyngitis	23.2	3.0	6.1	0.0
		Nausea	82.1	11.9	76.7	5.5
		Anorexia	20.2	1.2	14.1	0.6
		Constipation	11.9	0.6	7.4	0.6
	Common	Dyspepsia	5.4	0.6	0.6	0.0
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***
Renal and urinary disorders	Very common	Creatinine elevation	10.7	0.6	9.8	1.2
		Creatinine clearance decreased**	16.1	0.6	17.8	1.8
General disorders and administration site conditions	Very common	Fatigue	47.6	10.1	42.3	9.2

* Refer to National Cancer Institute CTC version 2 for each grade of toxicity except the term "creatinine clearance decreased".
** Which is derived from the term "renal/genitourinary other".
*** According to National Cancer Institute CTC (v2.0; NCI 1998), taste disturbance and alopecia should only be reported as Grade 1 or 2.

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 toxicities that were reported in ≥ 1% and ≤ 5% of the patients that were randomly assigned to receive cisplatin and pemetrexed include: renal failure, infection, pyrexia, febrile neutropenia, increased AST, ALT, and GGT, urticaria and chest pain.
Clinically relevant CTC toxicities that were reported in < 1% of the patients that were randomly assigned to receive cisplatin and pemetrexed include arrhythmia and motor neuropathy.
The table below 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 B12 supplementation, and 276 patients randomly assigned to receive single-agent docetaxel in studies. All patients were diagnosed with locally advanced or metastatic non-small cell lung cancer and received prior chemotherapy.

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	Neutrophils/ Granulocytes decreased	10.9	5.3	45.3	40.2
		Leukocytes decreased	12.1	4.2	34.1	27.2
		Haemoglobin decreased	19.2	4.2	22.1	4.3
	Common	Platelets decreased	8.3	1.9	1.1	0.4
	Very common	Diarrhoea	12.8	0.4	24.3	2.5

Gastrointestinal disorders						
		Vomiting	16.2	1.5	12.0	1.1
		Stomatitis/ Pharyngitis	14.7	1.1	17.4	1.1
		Nausea	30.9	2.6	16.7	1.8
		Anorexia	21.9	1.9	23.9	2.5
	Common	Constipation	5.7	0.0	4.0	0.0
Hepatobiliary disorders	Common	SGPT (ALT) elevation	7.9	1.9	1.4	0.0
		SGOT (AST) elevation	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**
General disorders and administration site conditions	Very common	Fatigue	34.0	5.3	35.9	5.4
	Common	Fever	8.3	0.0	7.6	0.0

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity.
**According to National Cancer Institute CTC (v2.0; NCI 1998), alopecia should only be reported as Grade 1 or 2.

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 toxicities that were reported in ≥ 1% and ≤ 5% of the patients that were randomly assigned to pemetrexed include: infection without neutropenia, febrile neutropenia, allergic reaction/hypersensitivity, increased creatinine, motor neuropathy, sensory neuropathy, erythema multiforme, and abdominal pain.
Clinically relevant CTC toxicities that were reported in < 1% 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 both chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

The table below provides the frequency and severity of undesirable effects considered possibly related to pemetrexed that have been reported in > 5% of 839 patients with NSCLC who were randomized to receive cisplatin and pemetrexed and 830 patients with NSCLC who were randomized to receive cisplatin and gemcitabine according to studies. 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 B12.

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 decreased	33.0*	5.6*	45.7*	9.9*
		Neutrophils/ Granulocytes decreased	29.0*	15.1*	38.4*	26.7*
		Leukocytes decreased	17.8	4.8*	20.6	7.6*
		Platelets decreased	10.1*	4.1*	26.6*	12.7*

Nervous system disorders	Common	Neuropathy-sensory	8.5*	0.0*	12.4*	0.6*
		Taste disturbance	8.1	0.0***	8.9	0.0***
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
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
Renal and urinary disorders	Very common	Creatinine elevation	10.1*	0.8	6.9*	0.5
General disorders and administration site conditions	Very common	Fatigue	42.7	6.7	44.9	4.9

*p-values < 0.05 comparing pemetrexed/cisplatin to gemcitabine/cisplatin, using Fisher Exact test.
**Refer to National Cancer Institute CTC (v2.0; NCI 1998) for each Grade of Toxicity.
***According to National Cancer Institute CTC (v2.0; NCI 1998), taste disturbance and alopecia should only be reported as Grade 1 or 2.

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% 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% of the patients that were randomly assigned to receive cisplatin and pemetrexed include: GGT increase, chest pain, arrhythmia, and motor neuropathy.
Clinically relevant toxicities with respect to gender were similar to the overall population in patients receiving pemetrexed plus cisplatin.
The table below provides the frequency and severity of undesirable effects considered possibly related to pemetrexed 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 pemetrexed maintenance (JMEN: N= 663) and continuation pemetrexed maintenance (PARAMOUNT: N=539) studies. 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 B12.

System organ class	**Frequency***	**Event****	**Pemetrexed *** (N = 800)**		**Placebo *** (N = 402)**	
			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

Nervous system disorders	Common	Neuropathy-sensory	7.4	0.6	5.0	0.2
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
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	Common	Rash/ desquamation	8.1	0.1	3.7	0.0
General disorders and administration site conditions	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
Renal Disorders	Common	Renal disorders****	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 aminotransferase; SGPT = serum glutamic pyruvic aminotransferase. *Definition of frequency terms: 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. **Refer to NCI CTCAE Criteria (Version 3.0; NCI 2003) for each grade of toxicity. The reporting rates shown are according to CTCAE version 3.0. ***Integrated adverse reactions table combines the results of the JMEN pemetrexed maintenance (N=663) and PARAMOUNT continuation pemetrexed maintenance (N=539) studies. **** 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% of the patients that were randomly assigned to pemetrexed include: febrile neutropenia, infection, decreased platelets, diarrhoea, constipation, alopecia, pruritus/itching, fever (in the absence of neutropenia), ocular surface disease (including conjunctivitis), increased lacrimation, dizziness and motor neuropathy.

Clinically relevant CTC toxicity that was reported in < 1% of the patients that were randomly assigned to pemetrexed include: allergic reaction/hypersensitivity, erythema multiforme, supraventricular arrhythmia and pulmonary embolism.

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.

Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident, and transient ischaemic attack, 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.

Rare cases of hepatitis, potentially serious, have been reported during clinical studies with pemetrexed. Pancytopenia has been uncommonly reported during clinical trials with pemetrexed.
In clinical trials, cases of colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis) have been reported uncommonly in patients treated with pemetrexed.

In clinical trials, cases of interstitial pneumonitis with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed.

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

Oesophagitis/ radiation oesophagitis has been uncommonly reported during clinical trials with pemetrexed. Sepsis, sometimes fatal, has been commonly reported during clinical trials with pemetrexed.
During post-marketing surveillance, the following adverse reactions have been reported in patients treated with pemetrexed:
Hyperpigmentation has been commonly reported.
Uncommon cases of acute renal failure have been reported with pemetrexed alone or in association with other chemotherapeutic agents (see section 4.4). Nephrogenic diabetes insipidus and renal tubular necrosis have been reported in post marketing setting with an unknown frequency.

Uncommon cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy (see section 4.4).

Rare cases of radiation recall have been reported in patients who have received radiotherapy previously (see section 4.4).
Uncommon cases of peripheral ischaemia leading sometimes to extremity necrosis have been reported.
Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.

Rarely, immune-mediated haemolytic anaemia has been reported in patients treated with pemetrexed. Rare cases of anaphylactic shock have been reported.
Erythematous oedema mainly of the lower limbs has been reported with an unknown frequency. Infectious and non-infectious disorders of the dermis, the hypodermis and/or the subcutaneous tissue have been reported with an unknown frequency (e.g. acute bacterial dermo-hypodermitis, pseudocellulitis, dermatitis).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **Antineoplastic agents,** Folic acid analogues. ATC code: L01BA04.

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

In vitro studies have shown that pemetrexed behaves as a 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. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing pemetrexed in all subsets of the paediatric population for the granted indication (see section 4.2 for information on paediatric use).

Clinical efficacy

Mesothelioma

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

During the study, low-dose folic acid and vitamin B12 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 B12 supplementation during the entire course of study therapy (fully supplemented). The results of these analyses of efficacy are summarised in the table below.

Efficacy ofpemetrexed 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 (months) (95% CI)	12.1 (10.0-14.4)	9.3 (7.8-10.7)	13.3 (11.4-14.9)	10.0 (8.4-11.9)
Log rank p-value*	0.020		0.051	
Median time to tumour progression (months) (95% CI)	5.7 (4.9-6.5)	3.9 (2.8-4.4)	6.1 (5.3-7.0)	3.9 (2.8-4.5)
Log rank p-value*	0.001		0.008	
Time to treatment failure (months) (95% CI)	4.5 (3.9-4.9)	2.7 (2.1-2.9)	4.7 (4.3-5.6)	2.7 (2.2-3.1)
Log rank p-value*	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	

Abbreviation: CI = confidence interval.

*p-value refers to comparison between arms.

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

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the pemetrexed /cisplatin arm (212 patients) versus the cisplatin arm alone (218 patients) was demonstrated using the Lung Cancer Symptom Scale. Statistically significant differences in pulmonary function tests were also

observed. The separation between the treatment arms was achieved by improvement in lung function in the pemetrexed /cisplatin arm and deterioration of lung function over time in the control arm.

There are limited data in patients with malignant pleural mesothelioma treated with pemetrexed powder for concentrate for solution for infusion alone. Pemetrexed at a dose of 500 mg/m2 was studied as a single agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1%.

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

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

Efficacy of Pemetrexed vs. Docetaxel in NSCLC - ITT population

	Pemetrexed	**Docetaxel**
Survival time (months) • Median (m) • 95% CI for median	(N = 283) 8.3 (7.0-9.4)	(N = 288) 7.9 (6.3-9.2)
• HR • 95% CI for HR • Non-inferiority p-value (HR)	0.99 (0.82-1.20) 0.226	
Progression-free survival (months) • Median • HR (95% CI)	(N = 283) 2.9 0.97 (0.82-1.16)	(N = 288) 2.9
Time to treatment failure (TTTF - months) • Median • HR (95% CI)	(N = 283) 2.3 0.84 (0.71-0.997)	(N = 288) 2.1
Response (n: qualified for response) • Response rate (%) (95% CI) • Stable disease (%)	(N = 264) 9.1 (5.9-13.2) 45.8	(N = 274) 8.8 (5.7-12.8) 46.4
Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; N = total population size.		

NSCLC, first-line treatment
A multi-centre, randomised, open-label, Phase 3 study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with locally advanced or metastatic (Stage IIIb or IV) non-small cell lung cancer (NSCLC) showed thatpemetrexed 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 (HR) 0.94; 95% CI= 0.84-1.05). All patients included in this study had an ECOG performance status 0 or 1.

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

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

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

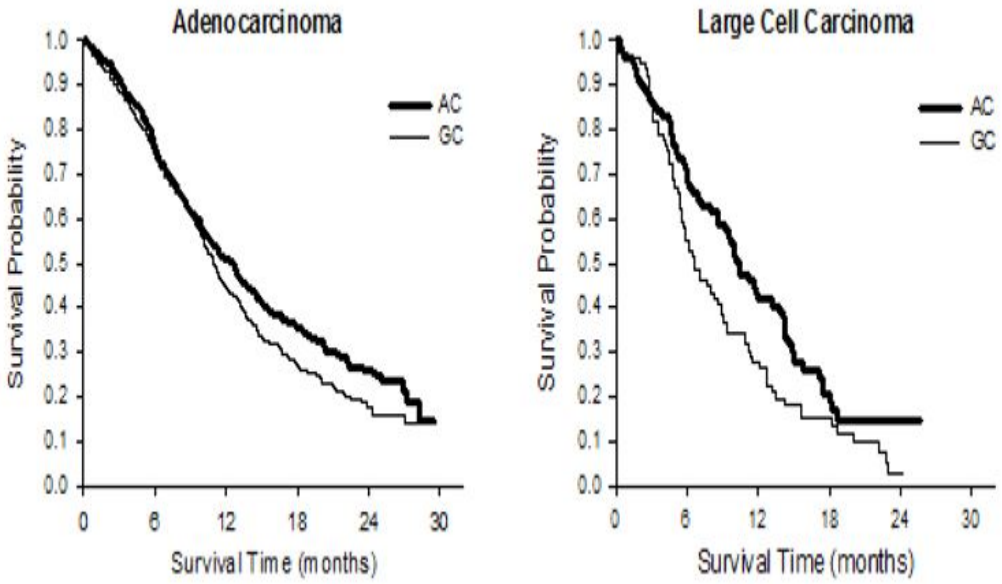
Efficacy ofpemetrexed + cisplatin vs. gemcitabine + cisplatin in first-line non-small cell lung cancer – ITT population and histology subgroups

ITT population and histology subgroups	**Median overall survival in months (95% CI)**				**Adjusted hazard ratio (HR) (95% CI)**	**Superiority p-value**
	Pemetrexed + Cisplatin		**Gemcitabine + Cisplatin**			
ITT population (N = 1725)	10.3 (9.8 – 11.2)	N = 862	10.3 (9.6 – 10.9)	N = 863	0.94a (0.84 – 1.05)	0.259
Adenocarcinoma (N = 847)	12.6 (10.7 – 13.6)	N = 436	10.9 (10.2 –11.9)	N = 411	0.84 (0.71–0.99)	0.033
Large cell (N = 153)	10.4 (8.6 – 14.1)	N = 76	6.7 (5.5 – 9.0)	N = 77	0.67 (0.48–0.96)	0.027
Other (N = 252)	8.6 (6.8 – 10.2)	N = 106	9.2 (8.1 – 10.6)	N = 146	1.08 (0.81–1.45)	0.586
Squamous cell (N = 473)	9.4 (8.4 – 10.2)	N = 244	10.8 (9.5 – 12.1)	N = 229	1.23 (1.00–1.51)	0.050

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

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

Kaplan-Meier plots of overall survival by histology



There were no clinically relevant differences observed for the safety profile of pemetrexedplus cisplatin within the histology subgroups.
Patients treated with pemetrexed and cisplatin required fewer transfusions (16.4% versus 28.9%, p < 0.001), red blood cell transfusions (16.1% versus 27.3%, p < 0.001) and platelet transfusions (1.8% versus 4.5%, p = 0.002). Patients also required lower administration of erythropoietin/darbopoietin (10.4% versus 18.1%, p < 0.001), G-CSF/GM-CSF (3.1% versus 6.1%, p = 0.004), and iron preparations (4.3% versus 7.0%, p = 0.021).

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

The study met its primary endpoint and showed a statistically significant improvement in PFS in the pemetrexed arm over the placebo arm (N = 581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (hazard ratio = 0.60, 95% CI = 0.49-0.73, p < 0.00001). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. The median OS for the overall population (N = 663) was 13.4 months for thepemetrexed arm and 10.6 months for the placebo arm, hazard ratio = 0.79 (95% CI= 0.65-0.95, p = 0.01192).

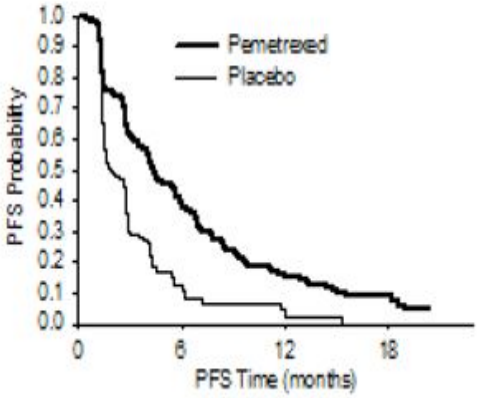
Consistent with other pemetrexed studies, a difference in efficacy according to NSCLC histology was observed in JMEN. For patients with NSCLC other than predominantly squamous cell histology (N = 430, independently reviewed population) median PFS was 4.4 months for the pemetrexedarm and 1.8 months for the placebo arm, hazard ratio = 0.47 (95% CI = 0.37-0.60, p = 0.00001). The median OS for patients with NSCLC other than predominantly squamous cell histology (N = 481) was 15.5 months for thepemetrexed arm and 10.3 months for the placebo arm, hazard ratio = 0.70 (95% CI = 0.56-0.88, p = 0.002). Including the induction phase, the median OS for patients with NSCLC other than predominantly squamous cell histology was 18.6 months for thepemetrexed arm and 13.6 months for the placebo arm, hazard ratio = 0.71 (95% CI = 0.56-0.88, p = 0.002).

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

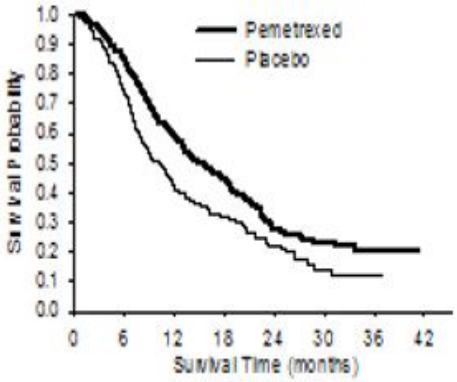
There were no clinically relevant differences observed for the safety profile of pemetrexed within the histology subgroups.

JMEN: 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



PARAMOUNT

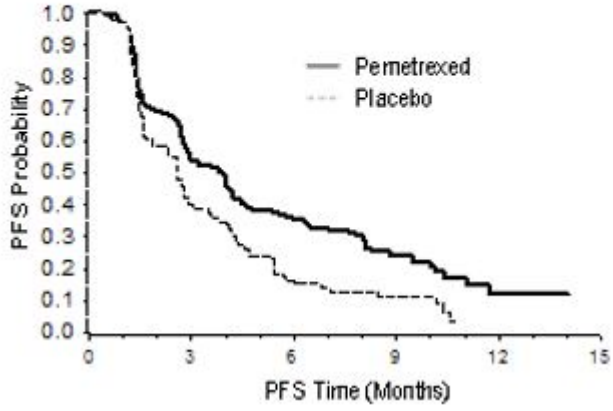
A multi-centre, randomised, double-blind, placebo-controlled Phase 3 study (PARAMOUNT), compared the efficacy and safety of continuation maintenance treatment with pemetrexed plus BSC (N = 359) with that of placebo plus BSC (N = 180) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC other than predominantly squamous cell histology who did not progress after 4 cycles of first-line doublet therapy of pemetrexed in combination with cisplatin. Of the 939 patients treated with pemetrexed plus cisplatin induction, 539 patients were randomised to maintenance treatment with pemetrexed or placebo. Of the randomised patients, 44.9% had a complete/partial response and 51.9% had a response of stable disease to pemetrexedplus cisplatin induction. Patients randomised to maintenance treatment were required to have an ECOG performance status 0 or 1. The median time from the start of pemetrexedplus cisplatin induction therapy to the start of maintenance treatment was 2.96 months on both the pemetrexed arm and the placebo arm. Randomised 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 4 cycles of maintenance treatment with pemetrexed powder for concentrate for solution for infusion and 4 cycles of placebo. A total of 169 patients (47.1%) completed ≥ 6 cycles maintenance treatment with pemetrexedrepresenting at least 10 total cycles of pemetrexed.

The study met its primary endpoint and showed a statistically significant improvement in PFS in the pemetrexed arm over the placebo arm (N = 472, independently reviewed population; 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 confirmed the findings of the investigator assessment of PFS. For randomised patients, as measured from the start ofpemetrexed plus cisplatin first-line induction treatment, the median investigator-assessed PFS was 6.9 months for the pemetrexedarm and 5.6 months for the placebo arm (hazard ratio = 0.59, 95% CI = 0.47-0.74).

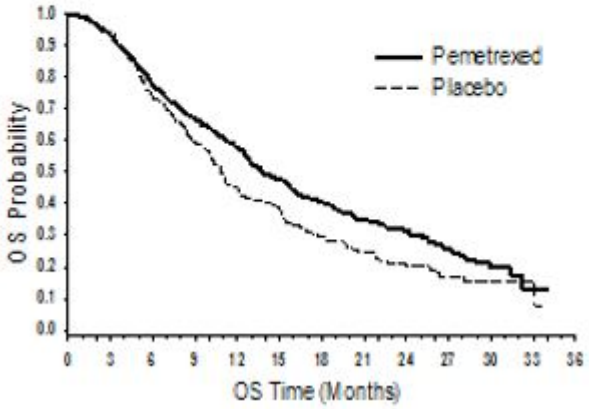
Following pemetrexedplus cisplatin induction (4 cycles), treatment withpemetrexedwas statistically superior to placebo for OS (median 13.9 months versus 11.0 months, hazard ratio = 0.78, 95%CI=0.64-0.96, p=0.0195). At the time of this final survival analysis, 28.7% of patients were alive or lost to follow up on the pemetrexed arm versus 21.7% on the placebo arm. The relative treatment effect of pemetrexed 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 pemetrexedwere 58% and 32% respectively, compared to 45% and 21% for patients on placebo. From the start of pemetrexed plus cisplatin first-line induction treatment, the median OS of patients was 16.9 months for the pemetrexedarm 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-study treatment was 64.3% for pemetrexedand 71.7% for placebo.

PARAMOUNT: Kaplan-Meier plot of progression-free survival (PFS) and Overall Survival (OS) for continuation pemetrexed maintenance versus placebo in patients with NSCLC other than predominantly squamous cell histology (measured from randomisation)

Progression Free Survival



Overall Survival



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

5.2 Pharmacokinetic properties

The pharmacokinetic properties 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 9 l/m2. 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. In vitro studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter).

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.

The pharmacokinetic properties of pemetrexed are not influenced by concurrently administered cisplatin. Oral folic acid and intramuscular vitamin B12 supplementation do not affect the pharmacokinetics of pemetrexed.

5.3 Preclinical safety data

Administration of pemetrexed to pregnant mice resulted in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures, and cleft palate.

Administration of pemetrexed to male mice resulted in reproductive toxicity characterised by reduced fertility rates and testicular atrophy. In a study conducted in beagle dog by intravenous bolus injection for 9 months, testicular findings (degeneration/necrosis of the seminiferous epithelium) have been observed. This suggests that pemetrexed may impair male fertility. Female fertility was not investigated.

Pemetrexed was not mutagenic in either the in vitro chromosome aberration test in Chinese hamster ovary cells, or the Ames test. Pemetrexed has been shown to be clastogenic in the in vivo micronucleus test in the mouse.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Hydrochloric acid (E507) (for pH adjustment)

Sodium hydroxide (E524) (for pH adjustment)

6.2 Incompatibilities

Pemetrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection. In the absence of other compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial
2 years.

Reconstituted and infusion solutions
When prepared as directed, reconstituted and infusion solutions of **Pemetrexed Waverley** contain no antimicrobial preservatives. Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2°C to 8°C.

6.4 Special precautions for storage

Unopened vial
This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml Type I clear glass vial with chlorobutyl grey rubber stopper containing 100 mg of pemetrexed, sealed with dark grey aluminium flip off seal.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.

2. Calculate the dose and the number of Pemetrexed Waverley vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

3. Reconstitute 100 mg vials with 4.2 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed. 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 solution is between 6.6 and 7.8. **Further dilution is required.**

4. The appropriate volume of reconstituted pemetrexed solution must be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, and administered as an intravenous infusion over 10 minutes.

5. Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride- and polyolefin- lined administration sets and infusion bags.

6. Parenteral medicinal products must be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

7. Pemetrexed solutions are for single use only. Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

Preparation and administration precautions

As with other potentially toxic anti-cancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. There have been few reported cases of pemetrexed extravasation, which were not assessed as serious by the investigator. Extravasation should be managed by local standard practice as with other non-vesicants.

7 MARKETING AUTHORISATION HOLDER

Waverley Pharma Europe Limited
Alexandra House, Office # 234, The Sweepstakes
Ballsbridge
Dublin 4
D04 C7H2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2260/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st February 2020

10 DATE OF REVISION OF THE TEXT

August 2020