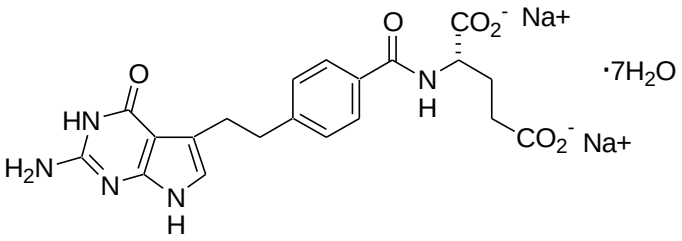
RELADDIN® (pemetrexed disodium)

NAME OF THE MEDICINE
RELADDIN® (pemetrexed disodium)

The active ingredient in RELADDIN powder for injection is pemetrexed disodium. Pemetrexed disodium has the chemical name L-glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It has an empirical formula of $C_{20}H_{19}N_5O_6 \bullet 2Na \bullet 7H_2O$ and a molecular weight of 597.49. The structural formula is as follows:



The CAS number for pemetrexed disodium is 357166-29-1.

DESCRIPTION
Pemetrexed disodium is a white to almost white solid.

RELADDIN is supplied as a sterile lyophilised powder for intravenous infusion available in single dose vials. The product is a white to either light yellow or green-yellow lyophilised solid. RELADDIN is supplied in 500 mg and 100 mg vials. Each 500 mg vial of RELADDIN contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH. Each 100 mg vial of RELADDIN contains pemetrexed disodium equivalent to 100 mg pemetrexed and 106.4 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

PHARMACOLOGY
Pharmacodynamic Properties
Pemetrexed is an antifolate antineoplastic agent. *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.

Pharmacokinetic Properties
Absorption: RELADDIN is for intravenous administration only.

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

Metabolism: RELADDIN undergoes limited hepatic metabolism.

Elimination: RELADDIN 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 RELADDIN 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 RELADDIN in special populations included 287 patients with a variety of advanced tumor 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 RELADDIN 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 RELADDIN was observed. However, specific studies of hepatically impaired patients have not been conducted (*see* **PRECAUTIONS**).

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

CLINICAL TRIALS

Malignant Pleural Mesothelioma - The safety and efficacy of RELADDIN 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 RELADDIN plus cisplatin versus cisplatin in chemonaive patients with malignant pleural mesothelioma, has shown that patients treated with RELADDIN and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone. RELADDIN 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 RELADDIN. 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 1 summarises the efficacy results for all patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrolment in the trial.

Table 1: Efficacy of RELADDIN plus Cisplatin vs. Cisplatin in Malignant Pleural Mesothelioma

Efficacy Parameter	**Randomised and Treated Patients**		**Fully Supplemented Patients**	
	RELADDIN/cis (N=226)	Cisplatin (N=222)	RELADDIN/cis (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 Tumor 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 RELADDIN/cis arm, randomised and treated (N=225) and fully supplemented (N=167).

Table 2 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 2: Summary of Cycles Given

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

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the RELADDIN/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 RELADDIN/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 RELADDIN/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 RELADDIN/cis arm and deterioration of lung function over time in the control arm.

Non-Small Cell Lung Cancer **-** The safety and efficacy of RELADDIN 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 RELADDIN 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 RELADDIN 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.

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

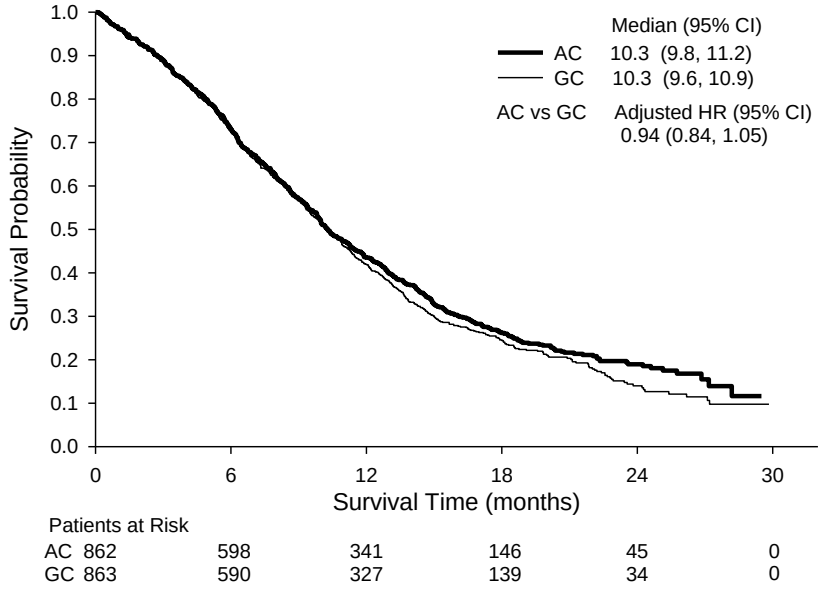


Table 3. Efficacy of RELADDIN + Cisplatin vs. Gemcitabine + Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population

	RELADDIN + 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%

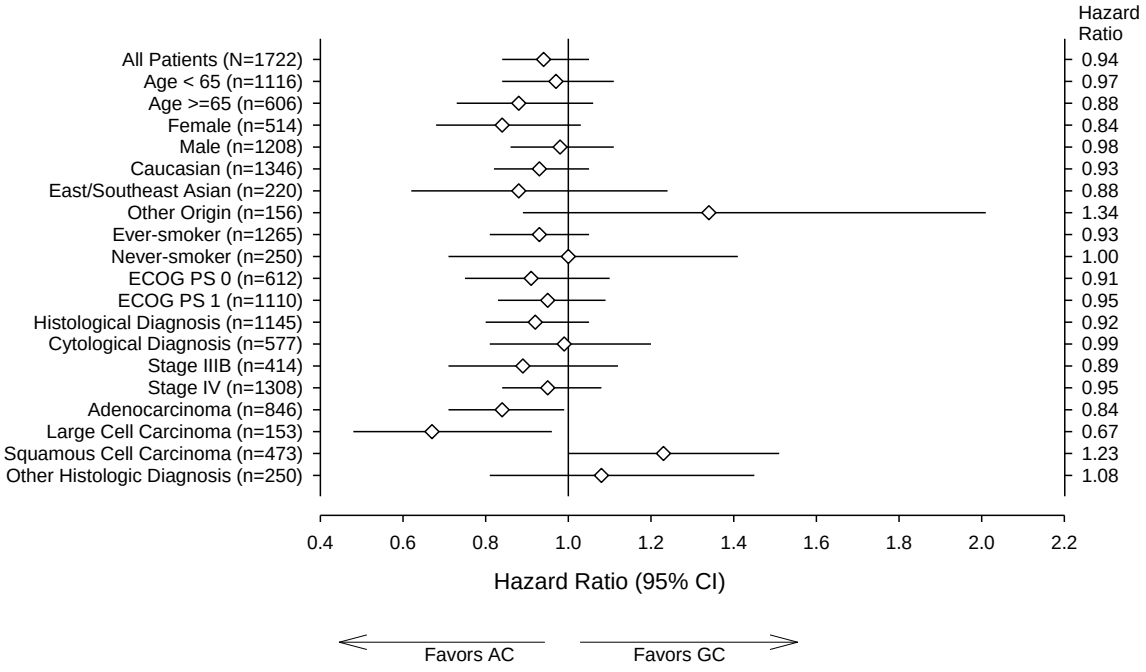
Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = total population size; mos = months.

[a] Statistically significant for non-inferiority

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

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

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

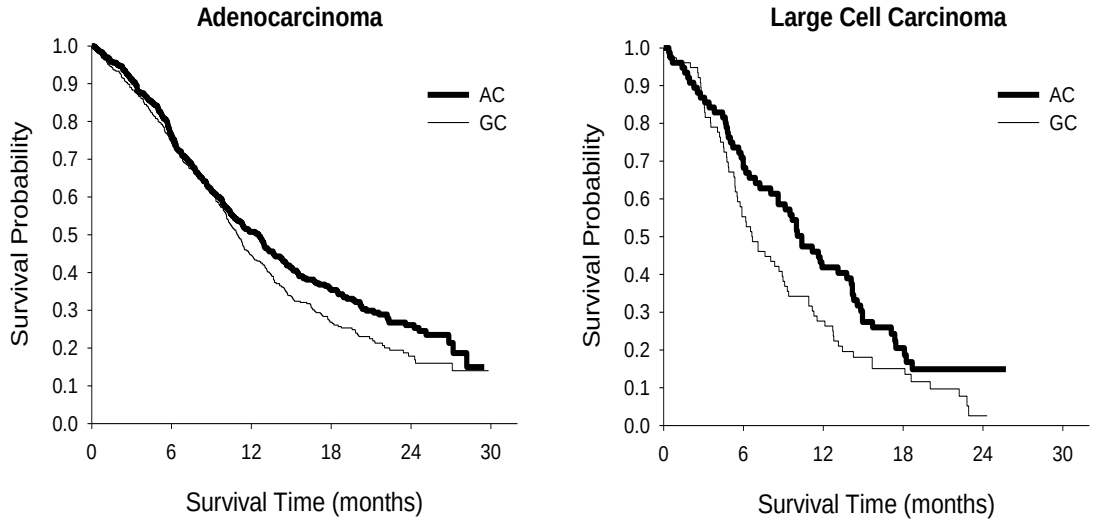


Results based on Cox adjusted analyses for ECOG PS, disease stage, gender, and basis for diagnosis (histological vs cytological). In the analysis by group, pertaining to each of these 4 covariates, the variable depicting the group was excluded from the model.
3 patients were missing ECOG performance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

Kaplan-Meier Curves for Overall Survival - RELADDIN + 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 RELADDIN 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 RELADDIN 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 RELADDIN 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 RELADDIN.

In the overall study population, RELADDIN 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 RELADDIN 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,

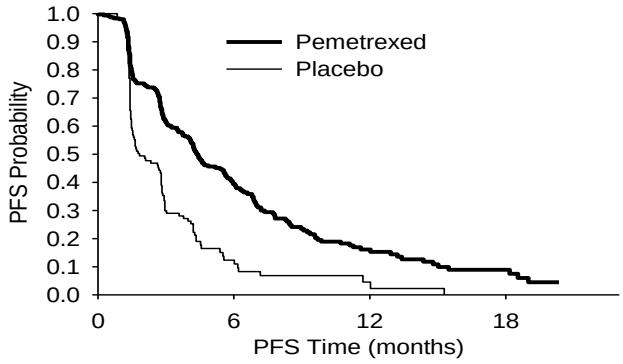
RELADDIN was superior to placebo for OS (median 15.5 months versus 10.3 months, HR=0.70 (95% CI: 0.56-0.88)) and PFS (median 4.4 months versus 1.8 months, HR=0.47 (95% CI: 0.37-0.60)).

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

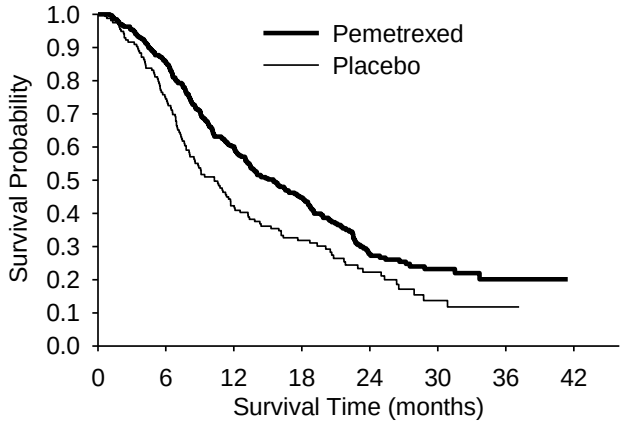
There were no clinically relevant differences observed for the safety profile of RELADDIN within the histology subgroups.

Kaplan Meier Plots of Progression-Free Survival (PFS) and Overall Survival RELADDIN 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 RELADDIN 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 RELADDIN in

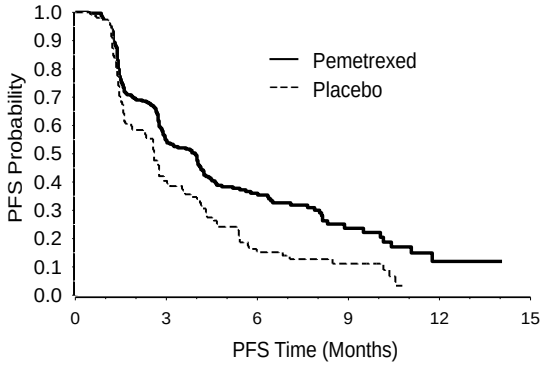
combination with cisplatin. Of the 939 patients treated with RELADDIN plus cisplatin induction, 539 patients were randomised to maintenance treatment with RELADDIN or placebo. Of the randomised patients, 44.9% had a complete/partial response and 51.9% had a response of stable disease to RELADDIN plus cisplatin induction. Patients randomised to treatment were required to have an ECOG performance status 0 or 1. The median time from the start of RELADDIN plus cisplatin induction therapy to the start of maintenance treatment was 2.96 months on both the RELADDIN 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 RELADDIN and 4 cycles of placebo. A total of 169 patients (47.1%) completed ≥ 6 cycles maintenance treatment with RELADDIN, representing at least 10 total cycles of RELADDIN.

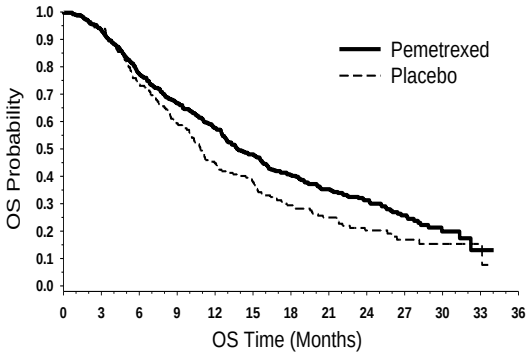
Independent review of the imaging of 472 of the 539 randomised patients showed that the study met its primary endpoint (PFS) and showed a statistically significant improvement in PFS in the RELADDIN arm over the placebo arm – median of 3.9 months and 2.6 months respectively (hazard ratio = 0.64, 95% 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 RELADDIN plus cisplatin first line induction treatment, the median investigator-assessed PFS was 6.9 months for the RELADDIN arm and 5.6 months for the placebo arm (hazard ratio = 0.59, 95% CI = 0.47-0.74).

Following RELADDIN plus cisplatin induction (4 cycles), treatment with RELADDIN 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 RELADDIN arm versus 21.7% on the placebo arm. The relative treatment effect of RELADDIN 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 RELADDIN were 58% and 32% respectively, compared to 45% and 21% for patients on placebo. From the start of RELADDIN plus cisplatin first line induction treatment, the median OS of patients was 16.9 months for the RELADDIN 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 RELADDIN and 71.7% for placebo.

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

Progression-Free Survival **Overall Survival**





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

A multicentre, randomised, open label phase 3 study of RELADDIN 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 RELADDIN (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 4, indicate comparable efficacy between pemetrexed and docetaxel.

Table 4 . Efficacy of RELADDIN vs docetaxel in NSCLC - ITT Population

	RELADDIN	**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 RELADDIN 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 RELADDIN within the histology subgroups.

INDICATIONS

Malignant Pleural Mesothelioma

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

Non-Small Cell lung Cancer

RELADDIN 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.

RELADDIN 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.

CONTRAINDICATIONS

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

PRECAUTIONS

RELADDIN can suppress bone marrow function as manifested by anaemia, neutropenia, thrombocytopenia, or pancytopenia. (*see* **ADVERSE REACTIONS**). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and RELADDIN 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 nonhaematologic toxicity seen in the previous cycle (*see* **Dose Reduction Recommendations** *under* **DOSAGE AND ADMINISTRATION**).

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

Renally Impaired Patients — RELADDIN is primarily eliminated unchanged by renal excretion. Insufficient numbers of patients have been studied with creatinine clearance below 45 mL/min. Therefore, RELADDIN should not be administered to patients whose creatinine clearance is <45 mL/min (*see* **Dose Reduction Recommendations** *under* **DOSAGE AND ADMINISTRATION**).

Hepatically Impaired Patients — RELADDIN 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.

RELADDIN 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 RELADDIN seen in clinical trials have been reversible. Skin rash has been reported in patients not pretreated with a corticosteroid in clinical trials. Pre-treatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction (*see* **DOSAGE AND ADMINISTRATION**).

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

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

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*).

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.

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

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

Paediatric Use
RELADDIN 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

Elderly Use
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.

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

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

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

The pharmacokinetics of RELADDIN 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 RELADDIN administration.

Although NSAIDs in moderate doses can be administered with RELADDIN 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 RELADDIN 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 RELADDIN.
In the absence of data regarding potential interaction between RELADDIN 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 RELADDIN administration. If concomitant

administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

ADVERSE EFFECTS

Single agent RELADDIN (NSCLC):

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

Table 5

System Organ Class	Frequency	Event*	RELADDIN (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
	Common	Platelets	8.3	1.9	1.1	0.4
Gastrointestinal Disorders	Very Common	Nausea	30.9	2.6	16.7	1.8
		Anorexia	21.9	1.9	23.9	2.5
		Vomiting	16.2	1.5	12.0	1.1
		Stomatitis/ Pharyngitis	14.7	1.1	17.4	1.1
		Diarrhoea	12.8	0.4	24.3	2.5
	Common	Constipation	5.7	0.0	4.0	0.0
General Disorders	Very Common	Fatigue	34.0	5.3	35.9	5.4
	Common	Fever	8.3	0.0	7.6	0.0
Hepatobiliary Disorders	Common	ALT (SGPT)	7.9	1.9	1.4	0.0
		AST (SGOT)	6.8	1.1	0.7	0.0
Skin and Subcutaneous Tissue Disorders	Very Common	Rash/ desquamation	14.0	0.0	6.2	0.0
	Common	Pruritis	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4**	37.7	2.2**

* Refer to National Cancer Institute Common Toxicity (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 RELADDIN)

Clinically relevant CTC toxicity that was reported in ≥1% and ≤5% (common) of the patients that were randomly assigned to RELADDIN 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 RELADDIN include supraventricular arrhythmias.

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single agent RELADDIN studies (n=164) and the Phase 3 single agent RELADDIN 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 6 provides the frequency and severity of undesirable effects that have been reported in >5% of 168 patients with mesothelioma who were randomly assigned to receive cisplatin and RELADDIN and 163 patients with mesothelioma randomly assigned to receive single agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B_{12}.

Table 6						
System Organ Class	**Frequency**	**Event***	**RELADDIN/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: $\geq$ 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 RELADDIN and cisplatin).

Clinically relevant toxicity that was reported in ≥1% and ≤5% (common) of the patients that were randomly assigned to receive cisplatin and RELADDIN 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 RELADDIN include arrhythmia and motor neuropathy.

Combination with cisplatin (NSCLC)

Table 7 provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in >5% of 839 patients with NSCLC who were randomised to study and received 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 7

System Organ Class	Frequency	Event*	RELADDIN/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 RELADDIN (NSCLC maintenance)
Table 8 provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in >5% of 800 patients randomly assigned to receive single agent pemetrexed and 402 patients randomly assigned to receive placebo in the single-agent maintenance pemetrexed study (JMEN: N=663) and continuation pemetrexed maintenance study (PARAMOUNT: N=539). All patients were diagnosed with Stage IIIB or IV NSCLC and had received prior platinum-based chemotherapy. Patients in both study arms were fully supplemented with folic acid and vitamin B12.

Table 8						
			Pemetrexed (N = 800)		Placebo (N = 402)	
System Organ Class	Frequency[a]	Event[b]	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Blood and Lymphatic System Disorders	Very Common	Hemoglobin 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
		Edema	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 oxaloacectic 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, pruritis/itching, fever (in the absence of neutropenia), ocular surface disease (including conjunctivitis), increased lacrimation, and decreased glomerular filtration rate.

Clinically relevant CTC toxicity that was reported in <1% (uncommon) of the patients that were randomly assigned to pemetrexed include: febrile neutropenia, allergic

reaction/hypersensitivity, motor neuropathy, erythema multiforme, renal failure, and supraventricular arrhythmia.

Safety was assessed for patients who were randomised to receive pemetrexed (N=800). The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed maintenance (N=519), and compared to patients who received > 6 cycles of pemetrexed (N=281). Increases in adverse reactions (all grades) were observed with longer exposure. A significant increase in the incidence of possibly study drug-related 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 RELADDIN.

General disorders and administration site conditions — Rare cases of oedema have been reported in patients treated with RELADDIN.

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 RELADDIN.

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 RELADDIN.

Rare - ≤0.1% of patients treated with RELADDIN

DOSAGE AND ADMINISTRATION
RELADDIN should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.

RELADDIN in combination use with cisplatin:
Adults - The recommended dose of RELADDIN 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 RELADDIN 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 RELADDIN 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 pretreated 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 RELADDIN administration.

To reduce toxicity, patients treated with RELADDIN 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 RELADDIN, and dosing should continue during the full course of therapy and for 21 days after the last dose of RELADDIN. Patients must also receive one intramuscular injection of vitamin B_{12} during the week preceding the first dose of RELADDIN and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as RELADDIN. 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 RELADDIN 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 nonhaematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in Tables 9 - 11 which are suitable for using RELADDIN as a single agent or in combination with cisplatin.

e 9. Dose Modification for RELADDIN (single agent or in combination) and Cisplatin natologic Toxicities	
Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3.	75% of previous dose (RELADDIN and cisplatin).
Nadir platelets ≤50,000/mm^3 without bleeding regardless of nadir ANC.	75% of previous dose (RELADDIN and cisplatin).
Nadir platelets <50,000/mm^3 with bleeding[a], regardless of nadir ANC.	50% of previous dose (RELADDIN 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 nonhaematologic toxicities (excluding neurotoxicity) ≥ Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guidelines in Table 10.

Table 10: Dose Modification for RELADDIN (single agent or in combination) and Cisplatin Nonhaematologic Toxicities[a,b]		
	Dose of RELADDIN (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 Table11. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 11. Dose Modification for RELADDIN (single agent or in combination) and Cisplatin Neurotoxicity		
CTC Grade	Dose for RELADDIN (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

RELADDIN therapy should be discontinued if a patient experiences any haematologic or nonhaematologic 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.

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 RELADDIN whose creatinine clearance is <45 mL/min [using the standard Cockcroft and Gault formula or GFR measured by Tc99m-DPTA serum clearance method].

Preparation and administration instructions: Use aseptic technique.
Reconsititution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection. RELADDIN is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection and Ringer's Injection. Coadministration of RELADDIN 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 RELADDIN for intravenous infusion administration.
2. Calculate the dose and the number of RELADDIN vials needed. 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 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 RELADDIN solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
5. The appropriate volume of reconstituted RELADDIN solution should be further diluted to 100 mL with 0.9% Sodium Chloride Injection and administered as an intravenous infusion over 10 minutes.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

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

OVERDOSAGE
Reported symptoms of RELADDIN 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 RELADDIN overdose should include consideration of the use of leucovorin or thymidine rescue.

PRESENTATION AND STORAGE CONDITIONS
RELADDIN® pemetrexed disodium for injection contains 100 mg or 500 mg pemetrexed (pack size 1 vial).

It is supplied in sterile, single-use clear Type I glass vials. The closure consists of a siliconised bromobutyl stopper and an aluminium seal with a plastic flip-off cap.

Store below 25°C. RELADDIN is not light sensitive.

NAME AND ADDRESS OF SPONSOR
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SUPPLIED IN AUSTRALIA BY
Alphapharm Pty Limited
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Australia

POISON SCHEDULE OF THE MEDICINE
S4.

DATE of FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)
7 October 2015

DATE of MOST RECENT AMENDMENT
6 November 2015