Algik
(Pemetrexed disodium)

Lyophilized Powder for Injection
For I.V. Use Only
100mg & 500mg / Vial

COMPOSITION –

[ALGIK Injection 100mg] (1 Vial contains)
Pemetrexed as disodium 100mg
Diluent: Mannitol 106.4mg
Excipients: Hydrochloric acid, Sodium hydroxide, Nitrogen

[ALGIK Injection 500mg] (1 Vial contains)
Pemetrexed as disodium 500mg
Diluent: Mannitol 500mg
Excipients: Hydrochloric acid, Sodium hydroxide, Nitrogen

THERAPEUTIC INDICATIONS

- Nonsquamous Non-Small Cell Lung Cancer – Combination with Cisplatin
In combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer.

- Nonsquamous Non-Small Cell Lung Cancer – Maintenance
Maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

- Nonsquamous Non-Small Cell Lung Cancer – After Prior Chemotherapy
As a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy.

- Mesothelioma
In combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

- Limitations of Use
The treatment of patients with squamous cell non-small cell lung cancer

DOSAGE AND ADMINISTRATION

Combination Use with Cisplatin for Nonsquamous Non-Small Cell Lung Cancer or Malignant Pleural Mesothelioma
The recommended dose of Pemetrexed is 500 mg/m2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m2 infused over 2 hours beginning approximately 30 minutes after the end of Pemetrexed administration. See cisplatin package insert for more information.
Single-Agent Use as Maintenance Following First-Line Therapy, or as a Second-Line Therapy
The recommended dose of Pemetrexed is 500 mg/m2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle**.**
Premedication Regimen and Concurrent Medications
Vitamin Supplementation
Instruct patients to initiate folic acid 400 mcg to 1000 mcg orally once daily beginning 7 days before the first dose of Pemetrexed. Continue folic acid during the full course of therapy and for 21 days after the last dose of Pemetrexed. Administer vitamin B12 1 mg intramuscularly 1 week prior to the first dose of Pemetrexed and every 3 cycles. thereafter. Subsequent vitamin B12 injections may be given the same day as treatment with Pemetrexed.

Corticosteroids
Administer dexamethasone 4 mg by mouth twice daily the day before, the day of, and the day after Pemetrexed administration.

Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations

Monitoring
Complete blood cell counts, including platelet counts, should be performed on all patients receiving Pemetrexed. Patients should be monitored for nadir and recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm3, the platelet count is ≥ 100,000 cells/mm3, and creatinine clearance is ≥45 mL/min. Periodic chemistry tests should be performed to evaluate renal and hepatic function.

Dose Reduction Recommendations
Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in Tables 1-3, which are suitable for using Pemetrexed as a single-agent or in combination with cisplatin.

Table 1: Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin – Hematologic Toxicities

Nadir ANC <500/mm3 and nadir platelets ≥50,000/mm3	75% of previous dose (pemetrexed and cisplatin).
Nadir platelets <50,000/mm3 without bleeding regardless of nadir ANC	75% of previous dose (pemetrexed and cisplatin).
Nadir platelets <50,000/mm3 with bleedinga, regardless of nadir ANC.	50% of previous dose (pemetrexed and cisplatin)

a These criteria meet the CTC version 2.0 (NCI 1998) definition of ≥CTC Grade 2 bleeding

If patients develop nonhematologic 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 guidelines in Table 2.

Table 2: Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin – Nonhematologc Toxicities a,b

	Dose of Pemetrexed (mg/m2)	Dose of Cisplatin (mg/m2)
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

a NCI Common Toxicity Criteria (CTC).
b Excluding neurotoxicity (see Table 3).

In the event of neurotoxicity, the recommended dose adjustments for Pemetrexed and cisplatin are described in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 3: Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin – Neurotoxicity

CTC Grade	Dose of Pemetrexed (mg/m2)	Dose of Cisplatin (mg/m2)
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Discontinuation Recommendation
Pemetrexed therapy should be discontinued if a patient experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.
Renally Impaired Patients
In clinical studies, patients with creatinine clearance ≥45 mL/min required no doseadjustments other than those recommended for all patients. Insufficient numbers ofpatients with creatinine clearance below 45 mL/min have been treated to makedosage recommendations for this group of patients. Therefore, Pemetrexed shouldnot be administered to patients whose

creatinine clearance is <45 mL/min using thestandard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DTPAserum clearance method:
Males: [140 - Age in years] × Actual Body Weight (kg) = mL/min
72 × Serum Creatinine (mg/dL)

Females: Estimated creatinine clearance for males × 0.85

Caution should be exercised when administering Pemetrexed concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min

CONTRAINDICATIONS

Pemetrexed is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Requirement for Premedication and Concomitant Medication to Reduce Toxicity

Vitamin Supplementation Prior to treatment with Pemetrexed, initiate supplementation with oral folic acid and intramuscular vitamin B12 to reduce the severity of hematologic and gastrointestinal toxicity of Pemetrexed. Do not substitute oral vitamin B12 for intramuscular vitamin B12. In clinical studies, the incidence of the following Grade 3-4 toxicities was higher in patients with mesothelioma who were never supplemented as compared to patients who were fully supplemented with folic acid and vitamin B12 prior to and throughout Pemetrexed treatment: neutropenia [38% versus 23%], thrombocytopenia [9% versus 5%], febrile neutropenia [9% versus 0.6%], and infection with neutropenia [6% versus 0].

CorticosteroidsAdminister dexamethasone the day before, the day of, and the day after Pemetrexed administration.

Bone Marrow Suppression

Pemetrexed can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia); myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle.

Decreased Renal Function

Pemetrexed is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance ≥45 mL/min. Insufficient numbers of patients have been studied with creatinine clearance <45 mL/min to give a dose recommendation. Therefore, Pemetrexed should not be administered to patients whose creatinine clearance is <45 mL/min.

One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B12 died of drug-related toxicity following administration of Pemetrexed alone.

Use with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with Mild to Moderate Renal Insufficiency

Caution should be used when administering NSAIDs concurrently with Pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min).

Required Laboratory Monitoring

Obtain a complete blood count and renal function tests at the beginning of each cycle and as needed. Do not initiate a cycle of treatment unless the ANC is ≥1500 cells/mm3, the platelet count is ≥100,000 cells/mm3, and creatinine clearance is ≥45 mL/min.

Pregnancy Category D

Based on its mechanism of action, Pemetrexed can cause fetal harm when administered to a pregnant woman. Pemetrexed administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic and teratogenic in mice at greater than 1/833rd the recommended human dose. If Pemetrexed is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with Pemetrexed.

Pediatric Use

Efficacy of Pemetrexed in pediatric patients has not been demonstrated. Pemetrexed was administered as an intravenous infusion over 10 minutes on Day 1 of a 21-day cycle to pediatric patients with recurrent solid tumors in a Phase 1 study (32 patients) and a Phase 2 study (72 patients). All patients received pretreatment with vitamin B12 and folic acid supplementation and dexamethasone. The dose escalation in the Phase 1 study determined the maximum tolerated dose was 1910 mg/m2 and this dose (or 60 mg/kg for patients <12 months old) was evaluated in the Phase 2 study of patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high grade glioma. No responses were observed among the 72 patients in this Phase 2 trial. The most common toxicities reported were hematolog- ical (leukopenia, neutropenia/granulocytopenia, anemia, thrombocytopenia,and lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea. The single dose pharmacokinetics of Pemetrexed administered in doses ranging from 400 to 2480 mg/m2 were evaluated in the Phase 1 trial in 22 patients (13 males and 9 females) aged 4 to 18 years (average age 12 years). Pemetrexed exposure (AUC and Cmax appeared to increase proportionally with dose.The average pemetrexedclearance (2.30 L/h/m2) and half-life (2.3 hours) in pediatric patients were comparable to values reported in adults.

Geriatric Use

Pemetrexed is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Renal function monitoring is recommended with administration of Pemetrexed. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older of 3,946 patients (34.0% ≥65) studied across the five clinical, the effect of Pemetrexed on survival was similar in patients <65 compared to≥65 years of age. There were no differences in safety with the exception of the following Grade 3-4 adverse reactions, which were noted in at least one of the five trials to be greater in patients 65 years of age and older as compared to younger patients: anemia, fatigue, thrombocytopenia, hypertension, and neutropenia.

Patients with Hepatic Impairment

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, no formal studies have been conducted to examine the pharmacokinetics of pemetrexed in patients with hepatic impairment.

Patients with Renal Impairment Pemetrexed is known to be primarily excreted by the kidneys. Decreased renal function will result in reduced clearance and greater exposure (AUC) to Pemetrexed compared with patients with normal renal function. Cisplatin coadministration with Pemetrexed has not been studied in patients with moderate renal impairment.

Gender

Of 3,946 patients (Male 70.5%) studied across the five registration studies for Pemetrexed indications, the effect of Pemetrexed on survival was similar in female and male patients.

Race

Of 3,946 patients (Caucasian 78.6%) studied across the five registration studies for Pemetrexed indications, the effect of Pemetrexed on survival was similar in the Caucasian and non-Caucasian patients.

DRUG INTERCATIONS

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with Pemetrexed in patients with normal renal function (creatinine clearance ≥80 mL/min). No dose adjustment of Pemetrexed is needed with concomitant NSAIDs in patients with normal renal function. Caution should be used when administering NSAIDs concurrently with Pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of 2 days before, the day of, and 2 days following administration of Pemetrexed.

In the absence of data regarding potential interaction between Pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following Pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

Nephrotoxic Drugs

Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of Pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of Pemetrexed.

EFFCTS ON ABILITY TO DRIVE

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**.**

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Teratogenic Effects – Pregnancy Category D

Based on its mechanism of action, Pemetrexed can cause fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies of Pemetrexed in pregnant women. Pemetrexed was embryotoxic, fetotoxic, and teratogenic in mice. In mice, repeated intraperitoneal doses of pemetrexed when given during organogenesis caused fetal malformations (incomplete ossification of talus and skull bone; about 1/833rd the recommended intravenous human dose on a mg/m2 basis), and cleft palate (1/33rd the recommended intravenous human dose on a mg/ m2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. If Pemetrexed is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use effective contraceptive measures to prevent pregnancy during the treatment with Pemetrexed.

Nursing Mothers

It is not known whether Pemetrexed or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Pemetrexed, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

ADVERSE DRUG REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reactions rates cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.
In clinical trials, the most common adverse reactions (incidence ≥20%) during therapy with Pemetrexed as a single-agent were fatigue, nausea, and anorexia. Additional common adverse reactions (incidence ≥20%) during therapy with Pemetrexed when used in combination with cisplatin included vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Non-Small Cell Lung Cancer (NSCLC) – Pemetrexed in Combination with Cisplatin

Table 4 provides the frequency and severity of adverse reactions that have been reported in >5% of 839 patients with NSCLC who were randomized to study and received Pemetrexed plus cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus cisplatin. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B12.

Table 4: Adverse Reactions in Fully Supplemented Patients Receiving Pemetrexed plus Cisplatin in NSCLCa

Reaction[b]	**Pemetrexed/cisplatin (N=839)**		**Gemcitabine/cisplatin (N=830)**	
	All Grades Toxicity (%)	**Grade 3-4 Toxicity (%)**	**All Grades Toxicity (%)**	**Grade 3-4 Toxicity (%)**
All Adverse Reactions	90	37	91	53
Laboratory				
Hematologic				
Anemia	33	6	46	10
Neutropenia	29	15	38	27
Leukopenia	18	5	21	8
Thrombocytopenia	10	4	27	13
Renal				
Creatinine elevation	10	1	7	1
Clinical				
Constitutional Symptoms				
Fatigue	43	7	45	5
Gastrointestinal				
Nausea	56	7	53	4
Vomiting	40	6	36	6
Anorexia	27	2	24	1
Constipation	21	1	20	0
Stomatitis/Pharyngitis	14	1	12	0
Diarrhea	12	1	13	2
Dyspepsia/Heartburn	5	0	6	0
Neurology				
Neuropathy-sensory	9	0	12	1
Taste disturbance	8	0c	9	0c
Dermatology/Skin				
Alopecia	12	0c	21	1c
Rash/Desquamation	7	0	8	1

a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to Pemetrexed.
b Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity.
c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.
In addition to the lower incidence of hematologic toxicity on the Pemetrexed and cisplatin arm, use of transfusions (RBC and platelet) and hematopoietic growth factors was lower in the Pemetrexed and cisplatin arm compared to the gemcitabine and cisplatin arm. The following additional adverse reactions were observed in patients
with non-small cell lung cancer randomly assigned to receive Pemetrexed plus cisplatin.

Incidence 1% to 5%
Body as a Whole — febrile neutropenia, infection, pyrexia
General Disorders — dehydration
Metabolism and Nutrition — increased AST, increased ALT *Renal* — creatinine clearance decrease, renal failure *Special Senses* — conjunctivitis

Incidence Less than 1% *Cardiovascular* — arrhythmia *General Disorders* — chest pain
Metabolism and Nutrition — increased GGT
Neurology — motor neuropathy

Non-Small Cell Lung Cancer (NSCLC) – Maintenance Pemetrexed Maintenance Following Non-Pemetrexed Containing, Platinum-Based Induction Therapy Table 5 provides the frequency and severity of adverse reactions reported in >5% of the 438 patients with NSCLC who received Pemetrexed maintenance and the 218 patients with NSCLC who received placebo following a platinum-based induction therapy.
All patients received study therapy immediately following 4 cycles of platinum-based treatment for locally advanced or metastatic NSCLC. Patients in both study arms were fully supplemented with folic acid and vitamin B12.

Table 5: Adverse Reactions in Patients Receiving Pemetrexed versus Placebo in NSCLCa Following Platinum-Based Induction Therapy

Reaction[b]	Pemetrexed (N=438)		Placebo (N=218)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	66	16	37	4
Laboratory				
Hematologic				
Anemia	15	3	6	1
Neutropenia	6	3	0	0
Leukopenia	6	2	1	1
Hepatic				
Increased ALT	10	0	4	0
Increased AST	8	0	4	0
Clinical				
Constitutional Symptoms				
Fatigue	25	5	11	1
Gastrointestinal				
Nausea	19	1	6	1
Anorexia	19	2	5	0
Vomiting	9	0	1	0
Mucositis/stomatitis	7	1	2	0
Diarrhea	5	1	3	0
Infection	5	2	2	0
Neurology				
Neuropathy-sensory	9	1	4	0
Dermatology/Skin				
Rash/Desquamation	10	0	3	0

a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to Pemetrexed.
b Refer to NCI CTCAE Criteria version 3.0 for each Grade of toxicity.

No clinically relevant differences in Grade 3/4 adverse reactions were seen in patients based on age, gender, ethnic origin, or histology except a higher incidence of Grade 3/4 fatigue for Caucasian patients compared to non-Caucasian patients (6.5% versus 0.6%).
Safety was assessed by exposure for patients who received at least one dose of Pemetrexed (N=438). The incidence of adverse reactions was evaluated for patients who received ≤6 cycles of Pemetrexed, and compared to patients who received >6 cycles of Pemetrexed. Increases in adverse reactions (all grades) were observed with longer exposure; however, no clinically relevant differences in Grade 3/4 adverse reactions were seen.
Consistent with the higher incidence of anemia (all grades) on the Pemetrexed arm, use of transfusions (mainly RBC) and erythropoiesis stimulating agents (ESAs; erythropoietin and darbepoetin) were higher in the Pemetrexed arm compared to the placebo arm (transfusions 9.5% versus 3.2%, ESAs 5.9% versus 1.8%). The following additional adverse reactions were observed in patients with non-small cell lung cancer who received Pemetrexed.

Incidence 1% to 5%
Dermatology/Skin — alopecia, pruritis/itching
Gastrointestinal — constipation
General Disorders — edema, fever (in the absence of neutropenia)
Hematologic — thrombocytopenia
Renal — decreased creatinine clearance, increased creatinine, decreased glomerular filtration rate
Special Senses — ocular surface disease (including conjunctivitis), increased lacrimation

Incidence Less than 1%
Cardiovascular — supraventricular arrhythmia
Dermatology/Skin — erythema multiforme
General Disorders — febrile neutropenia, allergic reaction/hypersensitivity
Neurology — motor neuropathy
Renal — renal failure

Continuation of Pemetrexed as Maintenance Following Pemetrexed Plus Platinum Induction Therapy
Table 6 provides the frequency and severity of adverse reactions reported in >5% of the 500 patients with nonsquamous NSCLC who received at least one cycle of Pemetrexed maintenance (n=333) or placebo (n=167) on the continuation maintenance trial.
The median of maintenance cycles administered to patients receiving one or more doses of maintenance therapy was 4 on both the pemetrexed and placebo arms. Dose reductions for adverse events occurred in 3.3% of patients in the Pemetrexed arm and 0.6% in the placebo arm. Dose delays for adverse events occurred in 22% of patients in the Pemetrexed arm and 16% in the placebo arm. Patients in both study arms were supplemented with folic acid and vitamin B12.

Table 6: Selected Adversea Reactionsb Occurring in ≥5% of Patients Receiving Pemetrexed in Nonsquamous NSCLC Following Pemetrexed Plus Cisplatin Induction Therapy

Adverse Reaction Organ System and Term	Pemetrexed (N=333)		Placebo (N=167)	
	All Grades[a] Toxicity (%)	Grade 3-4a Toxicity (%)	All Grades[a] Toxicity (%)	Grades 3-4a Toxicity (%)
All Adverse Reactions	53	17	34	4.8
Laboratory				
Hematologic				
Anemia	15	4.8	4.8	0.6
Neutropenia	9	3.9	0.6	0
Clinical				
Constitutional Symptoms				
Fatigue	18	4.5	11	0.6
Gastrointestinal				
Nausea	12	0.3	2.4	0
Vomiting	6	0	1.8	0
Mucositis/stomatitis	5	0.3	2.4	0
General Disorders				
Edema	5	0	3.6	0

a Adverse reaction of any severity (all grades) occurring more frequently (≥5%) or Grade 3-4 adverse reactions occurring more frequently (≥2%) in Pemetrexed-treated patients compared to those receiving placebo.
b NCI CTCAE Criteria version 3.0

Administration of RBC (13% versus 4.8%) and platelet (1.5% versus 0.6%) transfusions, erythropoiesis stimulating agents (12% versus 7%), and granulocyte colony stimulating factors (6% versus 0) were higher in the Pemetrexed arm compared to the placebo arm.
The following additional Grade 3 or 4 adverse reactions were observed more frequently in the Pemetrexed arm.

Incidence 1% to 5%
Blood/Bone Marrow — thrombocytopenia *General Disorders* — febrile neutropenia **Incidence Less than 1%**
Cardiovascular — ventricular tachycardia, syncope
General Disorders — pain
Gastrointestinal — gastrointestinal obstruction
Neurologic — depression
Renal — renal failure
Vascular — pulmonary embolism

Non-Small Cell Lung Cancer (NSCLC) – After Prior Chemotherapy
Table 7 provides the frequency and severity of adverse reactions 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. All patients were diagnosed with locally advanced or metastatic NSCLC and received prior chemotherapy.

Table 7: Adverse Reactions in Fully Supplemented Patients Receiving Pemetrexed versus Docetaxel in NSCLC[a]

Reaction[b]	Pemetrexed (N=265)		Docetaxel (N=276)	
	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)
Laboratory				
Hematologic				
Anemia	19	4	22	4
Leukopenia	12	4	34	27
Neutropenia	11	5	45	40
Thrombocytopenia	8	2	1	0
Hepatic				
Increased ALT	8	2	1	0
Increased AST	7	1	1	0
Clinical				
Gastrointestinal				

Nausea	31	3	17	2
Anorexia	22	2	24	3
Vomiting	16	2	12	1
Stomatitis/Pharyngitis	15	1	17	1
Diarrhea	13	0	24	3
Constipation	6	0	4	0
Constitutional Symptoms				
Fatigue	34	5	36	5
Fever	8	0	8	0
Dermatology/Skin				
Rash/Desquamation	14	0	6	0
Pruritis	7	0	2	0
Alopecia	6	1c	38	2c

[a] For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to Pemetrexed.
b Refer to NCI CTC Criteria for lab values for each Grade of toxicity (version 2.0).
c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.
Clinically relevant adverse reactions occurring in <5% of patients that received Pemetrexed treatment but >5% of patients that received docetaxel include CTC Grade 3/4 febrile neutropenia (1.9% Pemetrexed, 12.7% docetaxel). The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive Pemetrexed.

Incidence 1% to 5%
Body as a Whole — abdominal pain, allergic reaction/hypersensitivity, febrile neutropenia, infection
Dermatology/Skin — erythema multiforme *Neurology* — motor neuropathy, sensory neuropathy *Renal* — increased creatinine
Incidence Less than 1%
Cardiovascular — supraventricular arrhythmias

Malignant Pleural Mesothelioma (MPM)
Table 8 provides the frequency and severity of adverse reactions that have been reported in >5% of 168 patients with mesothelioma who were randomly assigned to receive cisplatin and Pemetrexed and 163 patients with mesothelioma randomly assigned to receive single-agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B12.

Table 8: Adverse Reactions in Fully Supplemented Patients Receiving Pemetrexed plus Cisplatin in MPMa

Reaction[b]	**Pemetrexed/cisplatin (N=168)**		**Cisplatin (N=163)**	
	All Grades Toxicity (%)	**Grade 3-4 Toxicity (%)**	**All Grades Toxicity (%)**	**Grade 3-4 Toxicity (%)**
Laboratory				
Hematologic				
Neutropenia	56	23	13	3
Leukopenia	53	15	17	1
Anemia	26	4	10	0
Thrombocytopenia	23	5	9	0
Renal				
Creatinine elevation	11	1	10	1
Creatinine clearance decreased	16	1	18	2
Clinical				
Eye Disorder				
Conjunctivitis	5	0	1	0
Gastrointestinal				
Nausea	82	12	77	6
Vomiting	57	11	50	4
Stomatitis/Pharyngitis	23	3	6	0
Anorexia	20	1	14	1
Diarrhea	17	4	8	0
Constipation	12	1	7	1
Dyspepsia	5	1	1	0
Constitutional Symptoms				
Fatigue	48	10	42	9
Metabolism and Nutrition				
Dehydration	7	4	1	1
Neurology				
Neuropathy-sensory	10	0	10	1
Taste Disturbance	8	0c	6	0c
Dermatology/Skin				
Rash	16	1	5	0
Alopecia	11	0c	6	0c

a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to Pemetrexed.
b Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity except the term "creatinine clearance decreased" which is derived from the CTC term "renal / genitourinary - other".
c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

The following additional adverse reactions were observed in patients with malignant pleural mesothelioma randomly assigned to receive Pemetrexed plus cisplatin.

Incidence 1% to 5%
Body as a Whole — febrile neutropenia, infection, pyrexia
Dermatology/Skin — urticaria
General Disorders — chest pain
Metabolism and Nutrition — increased AST, increased ALT, increased GGT
Renal — renal failure

Incidence Less than 1% *Cardiovascular* — arrhythmia *Neurology* — motor neuropathy

Effects of Vitamin Supplementations on Toxicity
Table 9 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B12 from the time of enrollment in the study (fully supplemented) with the incidence in patients who never received vitamin supplementation (never supplemented) during the study in the Pemetrexed plus cisplatin arm.

Table 9: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the Pemetrexed plus Cisplatin arm (% incidence)

Adverse Event[a] (%)	**Fully Supplemented Patients** (N=168)	**Never Supplemented Patients** (N=32)
Neutropenia/ granulocytopenia	23	38
Thrombocytopenia	5	9
Vomiting	11	31
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	0	6
Diarrhea	4	9

a Refer to NCI CTC criteria for lab and non-laboratory values for each grade of toxicity (Version 2.0).

The following adverse events were greater in the fully supplemented group compared to the never supplemented group: hypertension (11%, 3%), chest pain (8%, 6%), and
thrombosis / embolism (6%, 3%).
No relevant effect for Pemetrexed safety due to gender or race was identified, except an increased incidence of rash in men (24%) compared to women (16%).
Additional Experience Across Clinical Trials
Sepsis, which in some cases was fatal, occurred in approximately 1% of patients Esophagitis occurred in less than 1% of patients.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Pemetrexed. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
These reactions occurred with Pemetrexed when used as a single-agent and in combination therapies.

Blood and Lymphatic System — immune-mediated hemolytic anemia Gastrointestinal — colitis, pancreatitis General Disorders and Administration Site Conditions — edema

Injury, poisoning, and procedural complications — Radiation recall has been reported in patients who have previously received radiotherapy.
Respiratory — interstitial pneumonitis

Skin — Bullous conditions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Some cases were fatal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 at pv@searlecompany.com

OVERDOSE

There have been few cases of Pemetrexed overdose. Reported toxicities included neutropenia, anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anemia. In addition, infection with or without fever, diarrhea, and mucositis may be seen. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician.In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting ≥3 days, CTC Grade 4 neutropenia lasting ≥3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or4 mucositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100 mg/m2, intravenously once, followed by leucovorin, 50 mg/ m2, intravenously every 6 hours for 8 days.

The ability of Pemetrexed to be dialyzed is unknown.

PRECAUTIONS FOR ADMINISTRATION

Preparation and Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of Pemetrexed. The use of gloves is recommended. If a solution of Pemetrexed contacts the skin, wash the skin immediately and thoroughly with soap and water. If Pemetrexed contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.

Pemetrexed is not a vesicant. There is no specific antidote for extravasation of Pemetrexed. To date, there have been few reported cases of Pemetrexed extravasation, which were not assessed as serious by the investigator. Pemetrexed extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

Preparation for Intravenous Infusion Administration

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

(2) Calculate the dose of Pemetrexed and determine the number of vials needed. Vials contain either 100 mg or 500 mg of Pemetrexed. The vials contain an excess of Pemetrexed to facilitate delivery of label amount.

(3) Reconstitute each 100-mg vial with 4.2 ml of 0.9% Sodium Chloride Injection (preservative free). Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives 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 color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted Pemetrexed solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.

(4) Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.

(5) An appropriate quantity of the reconstituted Pemetrexed solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml. Pemetrexed is administered as an intravenous infusion over 10 minutes.

(6) Chemical and physical stability of reconstituted and infusion solutions of Pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated. When prepared as directed, reconstitution and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Discard any unused portion.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection and Ringer's Injection and therefore these should not be used. Coadministration of Pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended. Pemetrexed is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of Action

Pemetrexed, pemetrexed for injection, is a folate analog metabolic inhibitor that exerts its action by disrupting folatedependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

Pharmacodynamics

Preclinical studies have shown that pemetrexed inhibits the in vitro growth of mesothelioma cell lines (MSTO211H, NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined concurrently with cisplatin.

Absolute neutrophil counts (ANC) following single-agent administration of Pemetrexed to patients not receiving folic acid and vitamin B12 supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, correlates with the systemic exposure, or area under the curve (AUC) of pemetrexed. It was also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or

homocysteine concentrations. The levels of these substances can be reduced by folic acid and vitamin B12 supplementation. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to9.6 days over a range of exposures from 38.3 to 316.8 mcg•hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

Pharmacokinetic properties

Absorption
The pharmacokinetics of Pemetrexed administered as a single-agent in doses ranging from 0.2 to 838 mg/m2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (Cmax) increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles.
Distribution
Pemetrexed has a steady-state volume of distribution of 16.1 liters. In

vitro studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Metabolism and Excretion

Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. The clearance decreases, and exposure (AUC) increases, as renal function decreases. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min).

The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in controlled and single arm studies.

In vitro studies indicate that pemetrexed is a substrate of OAT3 (organic anion transporter 3), a transporter that may play a role in active secretion of pemetrexed.

Effect of Age, Gender or Race

No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26 to 80 years. The pharmacokinetics of pemetrexed were not different in male and female patients. The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. Insufficient data are available to compare pharmacokinetics for other ethnic groups.

Effect of Hepatic Insufficiency

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted.

Effect of Renal Insufficiency

Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min.

Effect of Third Space Fluid

The effect of third space fluid, such as pleural effusion and ascites, on Pemetrexed is not fully defined. A study of Pemetrexed 500 mg/ m2 was performed in 31 solid tumor patients with stable third space fluid (All but 2 of the 31 patients included in study had mild or moderate amounts of third space fluid). Moderate pleural effusion was defined in the study as less than 1/3 the way up on one side with obscuring of the entire hemidiaphragm. Moderate ascites was defined as that detectable on physical exam. The pemetrexed plasma concentrations in these patients were comparable to those observed in previous clinical trials in patients without third space fluid collections. Thus, drainage of mild or moderate third space fluid collection prior to Pemetrexed treatment should be considered, but is probably not necessary. The effect of severe third space fluid on pharmacokinetics is not known.

Effect of Ibuprofen

Ibuprofen doses of 400 mg four times a day reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown. **Effect of Aspirin**

Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Effect of Cisplatin

Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum are unaltered by pemetrexed.

Effect of Vitamins

Coadministration of oral folic acid or intramuscular vitamin B12 does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes

Results from in vitro studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/ m2 basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

PRESENTATION

White to pale yellow or yellow-green lyophilized powder for injection in vial

IDENTIFICATION

Algik Injection is a lyophilized powder supplied in single-dose vials for reconstitution

for intravenous infusion.

Algik Injection 100 mg:

Carton containing one (1) single-dose vial of 100 mg pemetrexed.

Algik Injection 500 mg:

Carton containing one (1) single-dose vial of 500 mg pemetrexed.

STORAGE INSTRUCTIONS

- To be sold on prescription of a registered medical practitioner only.
- Store below 30°C, after reconstitution store at 2-8°C.
- Protect from heat and sunlight.
-Keep all medicines out of sight and reach of children

REGISTRATION NUMBER

Algik Injection 100 mg: 090534
Algik Injection 500 mg: 090535

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE INSTRUCTIONS

Manufactured by:

Imported and Marketed by:

The Searle Company Limited,
F-319, S.I.T.E., Karachi - Pakistan.

Manufactured by:

25, Gongdan 1-ro, Anseong-si, Gyeonggi-do, Korea.
Mfg. Lic. No.: 1293

DATE OF PUBLICATION OF THE PACKAGE INSERT

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