For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

PEMOTIDE

1. Generic Name

Pemetrexed Injection I.P.

2. Qualitative and quantitative composition

PEMOTIDE 100

Each vial contains:

Pemetrexed Disodium Heptahydrate I.P.

Equivalent to Pemetrexed……100 mg

Excipients…….q.s.

The excipients used are Mannitol, Hydrochloric Acid, Sodium Hydroxide and Water for injection.

PEMOTIDE 500

Each vial contains:

Pemetrexed Disodium Heptahydrate I.P.

Equivalent to Pemetrexed……500 mg

Excipients…….q.s.

The excipients used are Mannitol and Water for injection.

3. Dosage form and strength

Dosage Form: Powder for injection

Strength: 100mg, 500mg

4. Clinical particulars

4.1 Therapeutic indication

PEMOTIDE 100

In combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

As monotherapy for the second -line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

PEMOTIDE 500

In combination with cisplatin it is indicated for the treatment of chemotherapy naive patients with unrespectable malignant pleural mesothellioma, indicated as monotherapy in locally advanced or metastatic non-small cell lung cancer.

4.2 Posology and method of administration

Posology

PEMOTIDE must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

PEMOTIDE in combination with cisplatin

The recommended dose of PEMOTIDE is 500 mg/m of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin.

PEMOTIDE as single agent

In patients treated for non-small cell lung cancer after prior chemotherapy, the recommended dose of PEMOTIDE is 500 mg/m BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Pre-medication regimen

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day.

To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation. Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B injections may be given on the same day as pemetrexed.

Monitoring

Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following:

- Absolute neutrophil count (ANC) should be ≥ 1500 cells/mm and platelets should be ≥ 100,000 cells/mm.
- Creatinine clearance should be ≥ 45 ml/min.
- The total bilirubin should be ≤ 1.5 times upper limit of normal. Alkaline phosphatase (AP), aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) should be ≤ 3 times upper limit of normal. Alkaline phosphatase, AST and ALT ≤ 5 times upper limit of normal is acceptable if liver has tumour involvement.

Dose adjustments

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy.

Treatment may be delayed to allow sufficient time for recovery. Upon recovery patients

should be retreated using the guidelines in below tables, which are applicable for PEMOTIDE used as a single agent or in combination with cisplatin.

Dose modification table for PEMOTIDE (as single agent or in combination) and cisplatin – Haematologic toxicities	
Nadir ANC < 500 /mm and nadir platelets ≥ 50,000 /mm3	75 % of previous dose (both PEMOTIDE and cisplatin)
Nadir platelets <50,000 /mm regardless of nadir	75 % of previous dose (both PEMOTIDE and cisplatin)
Nadir platelets <50,000/mm with bleeding[a], regardless of nadir	50% of previous dose (both PEMOTIDE and cisplatin)

a These criteria meet the National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998) definition of ≥CTC Grade 2 bleeding

If patients develop non-haematologic toxicities ≥ Grade 3 (excluding neurotoxicity), PEMOTIDE 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 below table.

Dose modification table for PEMOTIDE (as single agent or in combination) and cisplatin– Nonhaematologic toxicities [a,b]		
	Dose of PEMOTIDE (mg/m)	Dose for cisplatin (mg/m)
Any Grade 3 or 4 toxicities except	75 % of previous dose	75 % of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or grade 3 or 4 diarrhoea	75 % of previous dose	75 % of previous dose
Grade 3 or 4 mucositis	50 % of previous dose	100 % of previous dose

a National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998)

b Excluding neurotoxicity

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

Dose modification table for PEMOTIDE (as single agent or in combination) and cisplatin – Neurotoxicity		
CTC[a] Grade	Dose of PEMOTIDE (mg/m)	Dose for cisplatin (mg/m)
0-1	100 % of previous dose	100 % of previous dose
2	100 % of previous dose	50 % of previous dose

[a] National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998)

Treatment with PEMOTIDE should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after 2 dose reductions or

immediately if Grade 3 or 4 neurotoxicity is observed.

Elderly

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

Paediatric population

There is no relevant use of PEMOTIDE in the paediatric population in malignant pleural mesothelioma and non-small cell lung cancer.

Patients with renal impairment (Standard Cockcroft and Gault formula or Glomerular Filtration Rate measured Tc99m-DPTA serum clearance method)

Pemetrexed is primarily eliminated unchanged by renal excretion. In clinical studies, patients with creatinine clearance of ≥ 45 ml/min required no dose adjustments other than those recommended for all patients. There are insufficient data on the use of pemetrexed in patients with creatinine clearance below 45 ml/min; therefore the use of pemetrexed is not recommended.

Patients with hepatic impairment

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

Method of administration

PEMOTIDE should be administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Breast-feeding.
- Concomitant yellow fever vaccine.

4.4 Special warnings and precautions for use

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

Less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade ¾ neutropenia were reported when pre-treatment with folic acid and vitamin B was administered. Therefore, all patients treated with pemetrexed must be instructed to take folic acid and vitamin B as a prophylactic measure to reduce treatment-related toxicity.

Skin reactions have been reported in patients not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin

reactions.

An insufficient number of patients has been studied with creatinine clearance of below 45 ml/min. Therefore, the use of pemetrexed in patients with creatinine clearance of < 45 ml/min is not recommended.

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

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

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with pemetrexed alone or with other chemotherapeutic agents. Most of these events resolved after pemetrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is not fully defined. A reported study of pemetrexed in 31 solid tumour patients with stable third space fluid demonstrated no difference in pemetrexed dose normalized plasma concentrations or clearance compared to patients without third space fluid collections. Thus, drainage of third space fluid collection prior to pemetrexed treatment should be considered, but may not be necessary.

Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate 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.

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

Women of childbearing potential must use effective contraception during treatment with pemetrexed.

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.

4.5 Drugs interactions

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

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

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

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

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

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

<u>Interactions common to all cytotoxics</u>

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

Concomitant use contraindicated: Yellow fever vaccine: risk of fatal generalised vaccinale disease.

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

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Contraception in males and females

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

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The table below lists the adverse drug events regardless of causality associated with pemetrexed used either as a monotherapy treatment or in combination with cisplatin from the pivotal registration studies (JMCH, JMEI, JMBD, JMEN and PARAMOUNT) and from the post marketing period.

ADRs are listed by MedDRA body system organ class. The following convention has been used for classification of frequency: very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥ 1/10,000 to < 1/1,000; very rare: < 1/10,000) and not known (cannot be estimated from the available data).

Frequencies of all grades adverse drug events regardless of causality from the pivotal registration studies: JMEI (ALIMTA vs Docetaxel), JMDB (ALIMTA and Cisplatin

versus GEMZAR and Cisplatin, JMCH (ALIMTA plus Cisplatin versus Cisplatin), JMEN and PARAMOUNT (Pemetrexed plus Best Supportive Care versus Placebo plus Best Supportive Care) and from post-marketing period.

System Organ Class (MedDRA)	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and infestations	Infection[a] Pharyngitis	Sepsis[b]			Dermo-hypodermitis	
Blood and lymphatic system disorders	Neutropenia Leukopenia Haemoglobin decreased	Febrile neutropenia Platelet count decreased	Pancytopenia	Autoimmune haemolytic anaemia		
Immune System disorders		Hypersensitivity		Anaphylactic shock		
Metabolism and nutrition disorders		Dehydration				
Nervous system disorders		Taste disorder Peripheral motor neuropathy Peripheral sensory neuropathy Dizziness	Cerebrovascular accident Ischaemic stroke Haemorrhage intracranial			
Eye disorders		Conjunctivitis Dry eye Lacrimation increased Keratoconjunctivitis sicca Eyelid oedema Ocular surface disease				
Cardiac disorders		Cardiac failure Arrhythmia	Angina Myocardial infarction Coronary artery disease Arrhythmia supraventricular			

Vascular disorders			Peripheral ischaemia[c]			
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism Interstitial pneumonitis[bd]			
Gastrointes-tinal disorders	Stomatitis Anorexia Vomiting Diarrhoea Nausea	Dyspepsia Constipation Abdominal pain	Rectal haemorrhage Gastrointestinal haemorrhage Intestinal perforation Oesophagitis Colitis [e]			
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased		Hepatitis		
Skin and subcutaneous tissue disorders	Rash Skin exfoliation	Hyperpigmentation Pruritus Erythema multiforme Alopecia Urticaria		Erythema	Stevens-Johnson syndrome[b] Toxic epidermal necrolysis[b] Pemphigoid Dermatitis bullous Acquired epidermolysis bullosa Erythematous oedema[f] Pseudocellu-litis Dermatitis Eczema Prurigo	
Renal and urinary disorders	Creatinine clearance decreased Blood creatinine increased[e]	Renal failure Glomerular filtration rate decreased				Nephroge-nic diabetes insipidus Renal tubular necrosis
General	Fatigue	Pyrexia				

disorders and administration site conditions		Pain Oedema Chest pain Mucosal inflammation				
Investigations		Gamma-glutamyltransferase increased				
Injury, poisoning and procedural complications			Radiation oesophagitis Radiation pneumonitis	Recall pheno-menon		

a with and without neutropenia

b in some cases fatal

c sometimes leading to extremity necrosis

d with respiratory insufficiency

eseen only in combination with cisplatin

f mainly of the lower limbs

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

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

5. Pharmacological properties

5.1. Mechanism of Action

Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA04

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

In vitro studies have shown that pemetrexed behaves as a multi-targeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport

systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

5.2. Pharmacodynamic properties

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

During the study, low-dose folic acid and vitamin B 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). The results of these analyses of efficacy are summarised in the table below:

Efficacy of PEMOTIDE plus cisplatin vs. cisplatin in malignant pleural mesothelioma				
	Randomized and treated patients		**Fully supplemented patients**	
Efficacy parameter	**PEMOTIDE/ cisplatin**	**Cisplatin**	**PEMOTIDE/ cisplatin**	**Cisplatin**
	(N = 226)	**(N = 222)**	**(N = 168)**	**(N = 163)**
Median overall survival	**12.1 (10.0 - 14.4)**	**9.3 (7.8 - 10.7)**	**13.3 (11.4 - 14.9)**	**10.0 (8.4 - 11.9)**
Log Rank p-value	**0.020**		**0.051**	
Median time to tumour progression (month	**5.7 (4.9 - 6.5)**	**3.9 (2.8 - 4.4)**	**6.1 (5.3 - 7.0)**	**3.9 (2.8 - 4.5)**
Log Rank p-value	**0.001**		**0.008**	

Time to treatment failure	**4.5 (3.9 - 4.9)**	**2.7 (2.1 - 2.9)**	**4.7 (4.3 - 5.6)**	**2.7 (2.2 - 3.1)**
Log Rank p-value	**0.001**		**0.001**	
Overall response rate*	**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	**< 0.001**		**< 0.001**	

Abbreviation: CI = confidence interval

* p-value refers to comparison between arms.

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

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

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

There are limited data in patients with malignant pleural mesothelioma treated with PEMOTIDE alone. PEMOTIDE at a dose of 500 mg/m was studied as a single-agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1 %.

NSCLC, second-line treatment

A multicentre, randomised, open label phase 3 study of PEMOTIDE versus docetaxel in patients with locally advanced or metastatic NSCLC after prior chemotherapy has shown median survival times of 8.3 months for patients treated with PEMOTIDE (Intent To Treat population n = 283) and 7.9 months for patients treated with docetaxel (ITT n = 288). Prior chemotherapy did not include PEMOTIDE An analysis of the impact of NSCLC histology on the treatment effect on overall survival was in favour of PEMOTIDE versus docetaxel for other than predominantly squamous histologies (n = 399, 9.3 versus 8.0 months, adjusted HR = 0.78; 95% CI = 0 .61-1.00, p = 0.047) and was in favour of docetaxel for squamous cell carcinoma histology (n =172, 6.2 versus 7.4 months, adjusted HR = 1.56; 95% CI = 1.08-2.26, p = 0.018). There were no clinically relevant differences observed for the safety profile of PEMOTIDE within the histology subgroups.

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

receive previous docetaxel treatment (n = 540).

Efficacy of PEMOTIDE vs docetaxel in NSCLC - ITT population

	PEMOTIDE	**Docetaxel**
Survival Time (months) ▪ **Median (m)** **95 % CI f**	**(n = 283)** **8.3** **(7.0 - 9.4)**	**(n = 288)** **7.9** **(6.3 - 9.2)**
▪ HR ▪ 95 % CI for HR ▪ Non-inferiority p-value (	**0.99** **(.82 - 1.20)** **.226**	
Progression free survival (months) - Median	**(n = 283)** **2.9**	**(n = 288)** **2.9**
HR (95 % CI)	**0.97 (.82 – 1.16)**	
Time to treatment failure (TTTF – months) - Median	**(n = 283)** **2.3**	**(n = 288)** **2.1**
▪ HR (95 % CI)	**0.84 (.71 - .997)**	
Response (n: qualified for response) ▪ Response rate (%) (95	**(n = 264)** **9.1 (5.9 - 13.2)** **45.8**	**(n = 274)** **8.8 (5.7 - 12.8)** **46.4**

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

NSCLC, first-line treatment

A multicentre, randomised, open-label, Phase 3 study of PEMOTIDE plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with locally advanced or metastatic (Stage IIIb or IV) non-small cell lung cancer (NSCLC) showed that PEMOTIDE 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). All patients included in this study had an ECOG performance status 0 or 1.

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

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

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

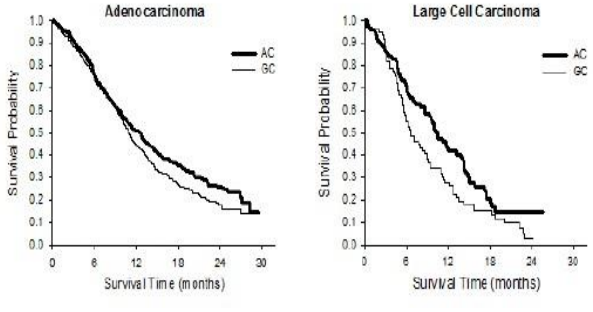
Efficacy of PEMOTIDE + cisplatin vs. gemcitabine + cisplatin in first-line non-small cell lung cancer – ITT population and histology subgroups.

ITT population and histology subgroups	**Median overall survival in months (95% CI)**				**hazard ratio (HR) (95**	**Superiority p-value**
	PEMOTIDE + cisplati		Gemcitabine + cisplatin			
ITT population (N = 1725)	**10.3 (9.8-11.2)**	**N=862**	**10.3 (9.6-10.9)**	**N=863**	**0.943 (0.84 – 1.05)**	**0.259**
Adenocarcinoma (N=847)	**12.6 (10.7 – 13.6)**	**N=436**	**10.9 (10.2-11.9)**	**N=411**	**0.84 (0.71– 0.99)**	**0.033**
Large cell (N=153)	**10.4 (8.6 – 14.1)**	**N=76**	**6.7 (5.5 -9.0)**	**N=77**	**0.67 (0.48– 0.96)**	**0.027**
Other (N=252)	**8.6 (6.8 – 10.2)**	**N=106**	**9.2 (8.1 - 10.6)**	**N=146**	**1.08 (0.81– 1.45)**	**0.586**
Squamous cell (N=473)	**9.4 (8.4 – 10.2)**	**N=244**	**10.8 (9.5 - 12.1)**	**N=229**	**1.23 (1.00– 1.51)**	**0.050**

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

Statistically significant for noninferiority, with the entire confidence interval for HR well below the 1.17645 noninferiority margin (p <0.001).

Kaplan Meier plots of overall survival by histology



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

Patients treated with PEMOTIDE and cisplatin required fewer transfusions (16.4% versus 28.9%, p<0.001), red blood cell transfusions (16.1% versus 27.3%, p<0.001) and platelet transfusions (1.8% versus 4.5%, p=0.002). Patients also required lower administration of erythropoietin/darbopoietin (10.4% versus 18.1%, p<0.001), G-CSF/GM-CSF (3.1% versus 6.1%, p=0.004), and iron preparations (4.3% versus 7.0%, p=0.021).

NSCLC, maintenance treatment JMEN

A multicentre, randomised, double-blind, placebo-controlled Phase 3 study (JMEN), compared the efficacy and safety of maintenance treatment with PEMOTIDE plus best supportive care (BSC) (n = 441) with that of placebo plus BSC (n = 222) in patients with

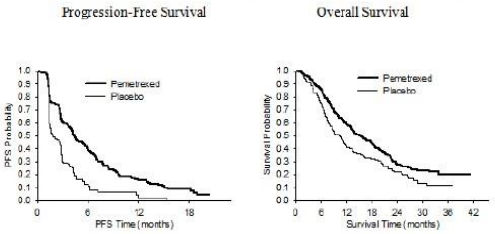
locally advanced (Stage IIIB) or metastatic (Stage IV) Non-Small Cell Lung Cancer (NSCLC) who did not progress after 4 cycles of first line doublet therapy containing Cisplatin or Carboplatin in combination with Gemcitabine, Paclitaxel, or Docetaxel. First line doublet therapy containing PEMOTIDE was not included. All patients included in this study had an ECOG performance status 0 or 1. Patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomisation after completion of first line (induction) therapy. Patients received a median of 5 cycles of maintenance treatment with PEMOTIDE 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 PEMOTIDE The study met its primary endpoint and showed a statistically significant improvement in PFS in the PEMOTIDE arm over the placebo arm (n = 581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (hazard ratio = 0.60, 95% CI = 0.49-0.73, p < 0.00001). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. The median OS for the overall population (n = 663) was 13.4 months for the PEMOTIDE arm and 10.6 months for the placebo arm, hazard ratio = 0.79 (95% CI = 0.65-0.95, p = 0.01192).

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

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

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

JMEN: Kaplan Meier plots of progression-free survival (PFS) and overall survival PEMOTIDE versus placebo in patients with NSCLC other than predominantly squamous cell histology:



PARAMOUNT

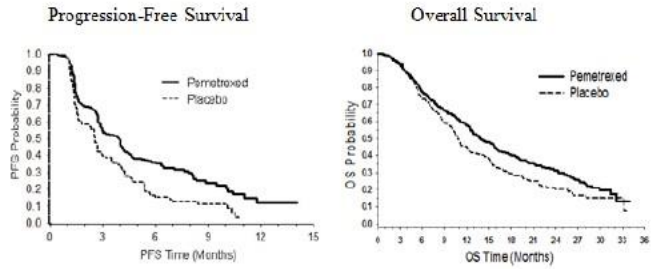
A multicentre, randomised, double-blind, placebo-controlled Phase 3 study (PARAMOUNT), compared the efficacy and safety of continuation maintenance treatment with PEMOTIDE plus BSC (n = 359) with that of placebo plus BSC (n = 180) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV)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

The study met its primary endpoint and showed a statistically significant improvement in PFS in the PEMOTIDE arm over the placebo arm (n = 472, independently reviewed population;median of 3.9 months and 2.6 months, respectively) (hazard ratio = 0.64, 95% CI = 0.51-0.81, p = 0.0002). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. For randomised patients, as measured from the start of PEMOTIDE plus cisplatin first line induction treatment, the median investigator-assessed PFS was 6.9 months for the PEMOTIDE arm and 5.6 months for the placebo arm (hazard ratio = 0.59 95% CI = 0.47-0.74).

Following PEMOTIDE plus cisplatin induction (4 cycles), treatment with PEMOTIDE 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 this final survival analysis, 28.7% of patients were alive or lost to follow up on the PEMOTIDE arm versus 21.7% on the placebo arm. The relative treatment effect of PEMOTIDE 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 PEMOTIDE were 58% and 32% respectively, compared to 45% and 21% for patients on placebo. From the start of PEMOTIDE plus cisplatin first line induction treatment, the median OS of patients was 16.9 months for the PEMOTIDE 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

study treatment was 64.3% for PEMOTIDE and 71.7% for placebo.

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



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

5.3. Pharmacokinetic properties

The pharmacokinetic properties of pemetrexed following single-agent administration have been evaluated in 426 cancer patients with a variety of solid tumours at doses ranging from 0.2 to 838 mg/m infused over a 10-minute period. Pemetrexed has a steady-state volume of distribution of 9 l/m2 . In vitro studies indicate that pemetrexed is approximately 81 % bound to plasma proteins. Binding was not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism. Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered dose being recovered unchanged in urine within the first 24 hours following administration. In Vitro studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter. Pemetrexed total systemic clearance is 91.8 ml/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90 ml/min). Between patient variability in clearance is moderate at 19.3 %. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

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

6. Nonclinical properties

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

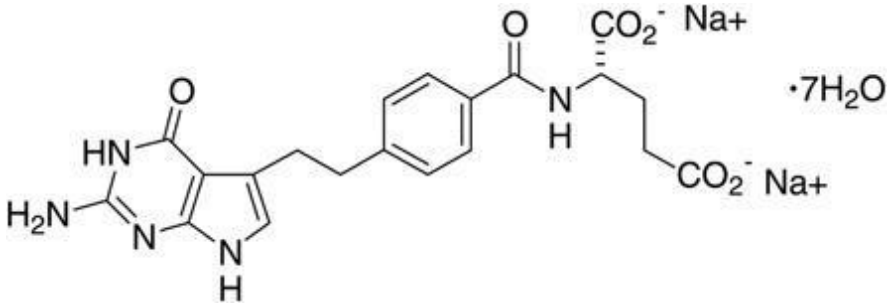
Administration of pemetrexed to male mice resulted in reproductive toxicity characterised by reduced fertility rates and testicular atrophy. In a study conducted in beagle dog by intravenousbolus injection for 9 months, testicular findings (degeneration/necrosis of the seminiferous epithelium) have been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

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

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

7. Description

Pemetrexed disodium heptahydrate, has the chemical name disodium (2S)-2-[[4-[2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]amino] pentanedioate heptahydrate with a molecular formula of $C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$ and a molecular weight of 597.49. The structural formula is as follows:



Pemetrexed disodium heptahydrate is a white or almost white powder which is freely soluble in water; very slightly soluble in anhydrous ethanol; practically insoluble in methylene chloride.

PEMOTIDE 100

Pemotide 100 is a white to either light yellow or green-yellow lyophilized solid. The excipients used are Mannitol, Hydrochloric Acid, Sodium Hydroxide and Water for injection.

PEMOTIDE 500

Pemotide 500 is a white to either light yellow or green-yellow lyophilized solid. The excipients used are Mannitol and Water for injection.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

PEMOTIDE is available in sterile single dose vial.

8.4 Storage and handing instructions

Store protected from moisture at a temperature not exceeding 30°C.

Store the reconstituted and infusion solution below 25°C excursion permitted to 15-30°C.

9. Patient counselling information

Package leaflet:

PEMOTIDE

Pemetrexed Injection I.P.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

9.1. What PEMOTIDE is and what it is used for

9.2. What you need to know before you take PEMOTIDE

9.3. How to take PEMOTIDE

9.4. Possible side effects

9.5. How to store PEMOTIDE

9.6. Contents of the pack and other information

9.1. What PEMOTIDE is and what it is used for

PEMOTIDE is a medicine used in the treatment of cancer.

PEMOTIDE is given in combination with cisplatin, another anti-cancer medicine, as treatment for malignant pleural mesothelioma, a form of cancer that affects the lining of the lung, to patients who have not received prior chemotherapy.

PEMOTIDE is also given in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer.

PEMOTIDE can be prescribed to you if you have lung cancer at an advanced stage if your disease has responded to treatment or it remains largely unchanged after initial chemotherapy.

PEMOTIDE is also a treatment for patients with advanced stage of lung cancer whose disease has progressed after other initial chemotherapy has been used.

9.2. What you need to know before you take PEMOTIDE

Do not use PEMOTIDE

- If you are allergic (hypersensitive) to pemetrexed or any of the other ingredients of this medicine.
- If you are breast-feeding; you must discontinue breast-feeding during treatment with PEMOTIDE
- If you have recently received or are about to receive a vaccine against yellow fever.

Warnings and precautions

Talk to your doctor or hospital pharmacist before receiving PEMOTIDE

If you currently have or have previously had problems with your kidneys, talk to your

doctor or hospital pharmacist as you may not be able to receive PEMOTIDE

Before each infusion you will have samples of your blood taken to evaluate if you have sufficient kidney and liver function and to check that you have enough blood cells to receive PEMOTIDE. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low. If you are also receiving cisplatin, your doctor will make sure that you are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting.

If you have had or are going to have radiation therapy, please tell your doctor, as there may be an early or late radiation reaction with PEMOTIDE.

If you have been recently vaccinated, please tell your doctor, as this can possibly cause bad effects with PEMOTIDE.

If you have heart disease or a history of heart disease, please tell your doctor.

If you have an accumulation of fluid around your lungs, your doctor may decide to remove the fluid before giving you PEMOTIDE.

Children and adolescents

There is no relevant use of PEMOTIDE in the pediatric population.

Other medicines and PEMOTIDE

Please tell your doctor if you are taking any medicine for pain or inflammation (swelling), such as medicines called “nonsteroidal anti-inflammatory drugs” (NSAIDs), including

Medicines purchased without a doctor’s prescription (such as ibuprofen). There are many sorts of NSAIDs with different durations of activity. Based on the planned date of your infusion of PEMOTIDE and/or on the status of your kidney function, your doctor needs to advise you on which medicines you can take and when you can take them. If you are unsure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor. The use of PEMOTIDE should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking PEMOTIDE during pregnancy. Women must use effective contraception during treatment with PEMOTIDE.

Breast-feeding

If you are breast-feeding, tell your doctor.

Breast-feeding must be discontinued during PEMOTIDE treatment

Fertility

Men are advised not to father a child during and up to 6 months following treatment with PEMOTIDE and should therefore use effective contraception during treatment with PEMOTIDE and for up to 6 months afterwards. If you would like to father a child during the treatment or in the 6 months following receipt of treatment, seek advice from your doctor or pharmacist. You may want to seek counselling on sperm storage before starting your therapy.

Driving and using machines

PEMOTIDE may make you feel tired. Be careful when driving a car or using machines

9.3. How to take PEMOTIDE

The dose of PEMOTIDE is 500 milligrams for every square metre of your body's surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dose may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition. A hospital pharmacist, nurse or doctor will have mixed the PEMOTIDE powder with 9 mg/ml (0.9 %) sodium chloride solution for injection before it is given to you.

You will always receive PEMOTIDE by infusion into one of your veins. The infusion will last approximately 10 minutes.

When using PEMOTIDE in combination with cisplatin:

The doctor or hospital pharmacist will work out the dose you need based on your height and weight. Cisplatin is also given by infusion into one of your veins, and is given approximately 30 minutes after the infusion of PEMOTIDE has finished. The infusion of cisplatin will last approximately 2 hours.

You should usually receive your infusion once every 3 weeks

Additional medicines:

Corticosteriods: your doctor will prescribe you steroid tablets (equivalent to 4 milligram of dexamethasone twice a day) that you will need to take on the day before, on the day of, and the day after PEMOTIDE treatment. This medicine is given to you to reduce the frequency and severity of skin reactions that you may experience during your anticancer treatment.

Vitamin supplementation: your doctor will prescribe you oral folic acid (vitamin) or a multivitamin containing folic acid (350 to 1000 micrograms) that you must take once a day while you are taking PEMOTIDE. You must take at least 5 doses during the seven days before the first dose of PEMOTIDE. You must continue taking the folic acid for 21 days after the last dose of PEMOTIDE .You will also receive an injection of vitamin B12 (1000 micrograms) in the week before administration of PEMOTIDE and then approximately every 9 weeks (corresponding to 3 courses of PEMOTIDE treatment). Vitamin B12 and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You must contact your doctor immediately if you notice any of the following:

- Fever or infection (common): if you have a temperature of 38ºC or greater, sweating or other signs of infection(since you might have less white blood cells than normal which is very common). Infection (sepsis) may be severe and could lead to death.
- If you start feeling chest pain (common) or having a fast heart rate (uncommon).
- If you have pain, redness, swelling or sores in your mouth (very common).
- Allergic reaction: if you develop skin rash (very common) / burning or prickling sensation (common), or fever (common). Rarely, skin reactions may be severe and could lead to death.
- Contact your doctor if you get a severe rash, or itching, or blistering (Stevens - Johnson syndrome or Toxic epidermal necrolysis).

- If you experience tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal which is very common).
- If you experience bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal which is very common).
- If you experience sudden breathlessness, intense chest pain or cough with bloody sputum (uncommon) (may indicate a blood clot in the blood vessels of the lungs).

Side effects with PEMOTIDE may include:

Very common (may affect more than 1 in 10 people)

- Low white blood cells
- Low haemoglobin level (anaemia) Low platelet count
- Diarrhoea
- Vomiting
- Pain, redness, swelling or sores in your mouth
- Nausea
- Loss of appetite
- Fatigue (tiredness)
- Skin rash
- Hair loss
- Constipation
- Loss of sensation
- Kidney: abnormal blood tests

Common (may affect up to 1 in 10 people)

- Allergic reaction: skin rash / burning or prickling sensation
- Infection including sepsis
- Fever
- Dehydration
- Kidney failure
- Irritation of the skin and itching
- Chest pain
- Muscle weakness
- Conjunctivitis (inflamed eye)
- Upset stomach
- Pain in the abdomen
- Taste change
- Liver: abnormal blood tests

- Watery eyes
- Increased skin pigmentation

Uncommon (may affect up to 1 in 100 people)

- Acute renal failure
- Fast heart rate
- Inflammation of the lining of the oesophagus (gullet) has been experienced with PEMOTIDE / radiation therapy.
- Colitis (inflammation of the lining of the large bowel, which may be accompanied by intestinal or rectal bleeding)
- Interstitial pneumonitis (scarring of the air sacs of the lung)
- Oedema (excess fluid in body tissue, causing swelling) Some patients have experienced a heart attack, stroke or "mini-stroke" while receiving PEMOTIDE usually in combination with another anticancer therapy.
- Pancytopenia- combined low counts of white cells, red cells and platelets.
- Radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy) may occur in patients who are also treated with radiation either before, during or after their PEMOTIDE therapy.
- Extremity pain, low temperature and discolouration have been reported. Blood clots in the lung blood vessels (pulmonary embolism).

Rare (may affect up to 1 in 1,000 people)

- Radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy, from days to years after the radiation.
- Bullous conditions (blistering skin diseases)-including Stevens-Johnson syndrome and Toxic epidermal necrolysis. Immune mediated haemolytic anaemia (antibody-mediated destruction of red blood cells).
- Hepatitis (inflammation of the liver).
- Anaphylactic shock (severe allergic reaction).

Not known: frequency cannot be estimated from the available data

- Lower limb swelling with pain and redness
- Increased urine output
- Thirst and increased water consumption
- Hypernatraemia – increased sodium in blood
- Inflammation of the skin, mainly of the lower limb with swelling, pain and redness
- You might have any of these symptoms and/or conditions. You must tell your doctor as soon as possible when you start experiencing any of these side effects.
- If you are concerned about any side effects, talk to your doctor.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point

of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5. How to store PEMOTIDE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton.

Reconstituted and Infusion Solutions: The product should be used immediately. When prepared as directed**,** chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature.

This medicine is for single use only; any unused solution must be disposed of in accordance with local requirement.

Do not refrigerate after reconstitution.

9.6. Contents of the pack and other information

What PEMOTIDE contains

The active substance is Pemetrexed Disodium Heptahydrate.

PEMOTIDE 100

Each vial contains 100 milligrams of pemetrexed (as pemetrexed disodium heptahydrate).

The excipients used are Mannitol, Hydrochloric Acid, Sodium Hydroxide and Water for injection.

PEMOTIDE 500

Each vial contains 500 milligrams of pemetrexed (as pemetrexed disodium heptahydrate). The excipients used are Mannitol and Water for injection.

After reconstitution, the solution contains 25 mg/ml of pemetrexed. Further dilution by a healthcare provider is required prior to administration.

What PEMOTIDE looks like and contents of the pack

PEMOTIDE is a powder for concentrate for solution for infusion in a vial. It is a white to either light yellow or green-yellow lyophilised powder.

Each pack of PEMOTIDE consists of one PEMOTIDE vial.

Not all pack sizes may be marketed**.**

10. Details of manufacturer

Manufactured in India by:

BDR Pharmaceuticals International Pvt Ltd.

At: Plot No.58 to 67, Sector B-1 Umariya – Dungaria Tehsil – Shahpura

Jabalpur MP., India

11. Details of permission or licence number with date

Mfg Lic No. 28-A/25/2018 issued on 29.06.2020

12. Date of revision

JUL 2022

13. MARKETED BY