Summary of Product Characteristics

1 Name of the medicinal product

Emetex 100 mg powder for concentrate for solution for infusion

2. Qualitative and quantitative composition

Each vial contains 100 mg of pemetrexed (as pemetrexed disodium 2.5 hydrate)

After reconstitution, each vial contains 25 mg/ml of pemetrexed.

3. Pharmaceutical form

Powder for concentrate for solution for infusion.
Off-white or light yellow to green-yellow lyophilized powder.

4. Clinical particulars

4.1 Therapeutic indications

Malignant Plueral Mesothelioma
Pemetrexed in combination with cisplatin is indicated for the treatment of chemotherapy native patients with unresectable malignant pleural mesothelioma.
Non-small cell lung cancer
Pemetrexed 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.
Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.
Pemetrexed is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

4.2 Posology and method of administration

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

Pemetrexed in combination with cisplatin
The recommended dose of pemetrexed is 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin (see also cisplatin Summary of Product Characteristics for specific dosing advice).

Pemetrexed as single agent

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

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

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_{12} (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.

Monitoring
Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: Absolute Neutrophil Count (ANC) should be ≥ 1,500 cells/mm^3 and platelet should be ≥ 100,000 cells/mm^3.
Creatinine clearance should be ≥ 45 mL/min.
The total bilirubin should be ≤ 1.5 times upper limit of normal. Alkaline phosphatase (AP), aspartate transaminase (AST or SGOT) and alanine transaminase (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 Tables 1, 2 and 3 which are applicable for pemetrexed used as a single agent or in combination with cisplatin.

Table 1 - Dose Modification for Pemetrexed (as single agent or in combination) and Cisplatin - Hematologic Toxicities.	
Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose (both pemetrexed and cisplatin)
Nadir platelets <50,000/mm^3 without bleeding regardless of nadir ANC.	75% of previous dose (both pemetrexed and cisplatin)
Nadir platelets <50,000/mm^3 with bleeding[a] regardless of nadir ANC.	50% of previous dose (both pemetrexed and cisplatin)

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

If patients develop non-haematologic toxicities ≥ Grade 3 (excluding neurotoxicity), treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guideline in Table 2.

Table 2 - Dose Modification table for Pemetrexed (as single agent or in combination) and Cisplatin – Non-hematologic Toxicities[a,b]		
	Dose of Pemetrexed (mg/m^2)	**Dose for Cisplatin (mg/m^2)**
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization (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 v 2.0; NCI 1998)
[b] Excluding neurotoxicity

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

Table 3 - Dose modification for pemetrexed (as single agent or in combination) and Cisplatin - Neurotoxicity		
CTC[a] Grade	**Dose of Pemetrexed (mg/m^2)**	**Dose for Cisplatin (mg/m^2)**
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

[a] National Cancer Institute Common Toxicity Criteria (CTC v 2.0; NCI 1998)

Treatment with pemetrexed should be discontinued if a patient experiences any haematologic or non-haematologic grade 3 or 4 toxicity after 2 doses reductions or immediately if grade 3 or 4 neurotoxicity is observed.

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

Paediatric population
There is no relevant use of pemetrexed 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. Patients with creatinine clearance of $\geqslant$ 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.

Preparation for Intravenous Infusion Administration
Reconstitution and dilution process should be sterile operation.
Calculate the dose of pemetrexed and the number of vials needed. Each vial contains 100 mg of pemetrexed.
Dissolve 100 mg vial with 4 ml of 0.9% Sodium Chloride Injection (preservative free) to get a solution containing 25 mg/ml Emetex. Gently swirl each vial until the powder is completely dissolved. The reconstituted solution is clear and ranges in color from colorless to yellow or green-yellow. The pH of the reconstituted Emetex solution is between 6.6 and 7.8.

Further dilution is required.
The Emetex solution should be inspected visually for particulate matter and discoloration before administration. If particulate matter or discoloration is observed, do not administer.

Diluted reconstituted Emetex solution with 0.9% Sodium Chloride Injection (preservative free) to 100 ml and administered as an intravenous infusion over 10 minutes.
Chemical and physical stability of reconstituted and infusion solutions of Emetex were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or room temperature (15-30°C) and lighting. When prepared as directed, reconstitution and infusion solution of Emetex 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).

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

4.3 Contraindication

Hypersensitivity to pemetrexed or to any of the excipients.
Breast-feeding must be discontinued during pemetrexed therapy.
Concomitant yellow fever vaccine.

4.4 Special warnings and special precautions for use

Pemetrexed can suppress bone marrow function as manifested by neutropenia, thrombocytopenia and anemia. 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 $\geq$ 1500 cells/mm^3 and platelet count returns to $\geq$ 100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle.
Less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Therefore, all patients

treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} 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 aspirin (> 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.

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is not fully defined. In 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.

4.5 Interaction with other medicinal products and other forms of interaction

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, cyclosporine) 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 $\geqslant$ 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and aspirin 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 aspirin, 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 aspirin 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 should be avoided for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

4.6 Fertility, pregnancy and lactation

Pregnancy
Pregnancy Category D.
Pemetrexed may cause fetal harm when administered to a pregnant woman. Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. There are no studies of pemetrexed in pregnant women. Patients should be advised to avoid becoming pregnant. If pemetrexed is used during pregnancy, or if the patient becomes pregnant while using pemetrexed, the patient should be apprised of the potential hazard to the fetus.

Lactation
It is not known whether pemetrexed or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pemetrexed, it is recommended that nursing should be discontinued if the mother is treated with pemetrexed.

Contraception in males and females during treatment with pemetrexed
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.

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 fatique, therefore patients should be cautioned against driving or operation machines.

4.8 Undesirable effects

Pemetrexed of malignant pleural mesothelioma treated with pemetrexed in combination with cisplatin, the adverse reactions have been observed as below:

Incidence	Adverse reactions	
Very common (≥ 10%)	Blood and lymphatic system abnormality	Neutrophil, Leukocyte, Hemoglobin, Platelet
	Gastrointestinal abnormality	Nausea, Vomiting, Stomatitis/Pharyngitis, Anorexia, Diarrhea , Constipation

	General abnormality	Fatigue
	Nervous system abnormality	Nerve/Sense
	Renal abnormality	Creatinine clearance rate lower, Renal/Urinary system obstacle
	Skin and subcutaneous tissue abnormality	Rash, Alopecia
Common (> 5% and < 10%)	Eyes abnormality	Conjunctivitis
	Gastrointestinal abnormality	Dyspepsia
	Metabolic nutrition abnormality	Dehydration
> 1% and ≤ 5%	AST, ALT and GGT increasing, infection, fever, neutropenia with fever, renal failure, chest pain, and urticaria.	
≤ 1%	Heart rate abnormality and motor neuron disease.	

Patients of non-small cell lung cancer treated with single-agent pemetrexed supplemented with folic acid and vitamin B_{12}, as second-line therapy, the adverse reactions have been observed as below:

Incidence	Adverse reactions	
Very common (≥ 10%)	Blood and lymphatic system abnormality	Hemoglobin, Leukocyte, Neutrophil/granulocytes, Platelet
	Gastrointestinal abnormality	Nausea, Anorexia,Vomiting, Stomatitis/Pharyngitis, Diarrhea
	General abnormality	Fatigue
	Skin and subcutaneous tissue abnormality	Rash, Desquamation
Common (> 5% and < 10%)	Gastrointestinal abnormality	Constipation
	General abnormality	Fever
	Hepatobiliary abnormality	SGPT（ALT）, SGOT（AST）
	Skin and subcutaneous tissue abnormality	Pruritus, Alopecia
> 1% and ≤ 5%	Nerve disorders, motor neuron disease, abdominal pain, creatinine increasing, neutropenia with fever, infections with non-neutropenia, allergy and erythema multiforme	
≤ 1%	Supraventricular arrhythmia	

4.9 Overdose

There have been few cases of pemetrexed overdose. Reported toxicities included neutropenia, anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include myelosuppression as manifested by neutropenia, thrombocytopenia, and anemia. In addition, infection with or without fever, diarrhea, and mucositis may be observed. If 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, or CTC Grade 4 neutropenia lasting ≥ 3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The dosage and administration of leucovorin were recommended as following: 100 mg/m^2, intravenously once, followed by 50 mg/m^2, intravenously every 6 hours for 8 days.

The ability of pemetrexed to be dialyzed is unknown.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pemetrexed is primarily a thymidylate synthase inhibitor like raltitrexed but it also inhibits other folate-dependent enzymes involved in purine synthesis such as dihydrofolate reductase and glycinamide ribonucleotide formyltransferase.

5.2 Pharmacokinetic Properties

Pemetrexed has a steady-state volume of distribution of 9 l/m^2. *In vitro* studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding was not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism. Pemetrexed is primarily eliminated in the urine, with 70% to 90% of the administered dose being recovered unchanged in urine within the first 24 hours following administration. Pemetrexed total systemic clearance is 91.8 mL/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). 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_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

5.3 Pre-clinical Safety Data

. Administration of pemetrexed to pregnant mice resulted in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate.
Administration of pemetrexed to male mice resulted in reproductive toxicity characterized by resuced fertility rates and testicular atrophy. 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 vitro micronucleus test in the mouse.
Studies to assess the carcinogenic potential of pemetrexed have not been conducted.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol

6.2 Incompatibilities

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection. Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Co-administration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended.
A study found pemetrexed disodium 20 mg/ml to be physically incompatible with 24 drugs resulting in precipitation or colour change during simulated Y-site administration. These drugs include amphotericin B, some cephalosporin and cephamycin antibacterials, chlorpromazine hydrochloride, ciprofloxacin, dobutamine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, gemcitabine hydrochloride, gentamicin sulfate, irinotecan hydrochloride, metronidazole, minocycline hydrochloride, mitoxantrone hydrochloride, nalbuphine hydrochloride, ondansetron hydrochloride, prochlorperazine edisilate, tobramycin sulfate, and topotecan hydrochloride.

6.3 Shelf-life

Unopened vial: 2 years, store below 30°C.

Reconstituted and infusion solutions: 24 hours when stored at refrigerated or room temperature (15-30°C).

6.4 Special precautions for storage

Unopened vial: Store below 30°C. Preserve in tightly closed containers, stored in a dry place, protected from light.

Reconstituted and infusion solutions: when prepared as directed, reconstitution and infusion solutions of Emetex contain no antimicrobial preservatives. Chemical and physical in-use stability of reconstituted and infusion solutions of Emetex were demonstrated for up to 24 hours when stored at refrigerated or room temperature (15-30°C) and lighting, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours.

6.5 Nature and contents of the container

Neutral borosilicate glass vial type 1 and halogenated butyl rubber stopper, sealed with aluminium-plastic caps, box of 1 vial.

7. Marketing authorization holder

Manufactured by: Shanghai Chemo Wanbang Biopharma Co., Ltd., Shanghai, China

Imported by: Exeltis (Thailand) Co., Ltd., Bangkok, Thailand

8. Marketing authorization numbers

On process of registration

9. Date of first authorization/renewal of the authorization

Draft version

10. Date of revision of the text

Draft version