ELUZER®
Pemetrexed Disodium for Injection

Please read this package insert carefully and administration under the guidance of qualified physicians.

【Name】

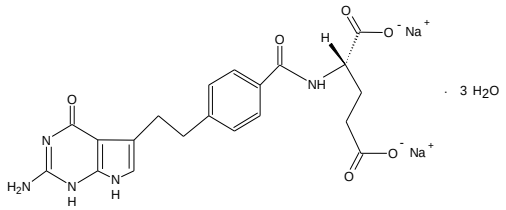
Generic name: Pemetrexed disodium for injection

Trade name: ELUZER®

【Composition】 Each 100mg vial of pemetrexed disodium for injection contains Pemetrexed disodium equivalent to 100mg pemetrexed and 100mg mannitol.

Pemetrexed disodium trihydrate has the chemical name L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-Pyrrolo[2,3-d] pyrimidin-5-yl) ethy1] benzoyl]-, disodium salt, trihydrate.

The structural formula is as follows:



Molecular Formula: $C_{20}H_{19}N_5Na_2O_6 \cdot 3H_2O$

Molecular Weight: 525.43

【Physical Character】 An almost white to either light yellow or green-yellow lyophilized solid, hydroscopic.

【Strength】 1 vial 100mg.

【Indication】

1) Combined with cisplatin, pemetrexed disodium for injection is indicated for the treatment of patients with malignant pleural mesothelioma who are not candidates for curative surgery.
2) Pemetrexed disodium for injection is used as a single-agent for the treatment of patients with nonsquamous non-small cell lung cancer after prior chemotherapy. Not indicated for squamous cell non-small lung cancer's treatment.

【Dosage and Administration】

The drug should be used under the guidance of qualified physicians with anticancer drug application experience. The drug can only be used in intravenous infusion, the solution must be prepared in accordance with the instruction of "Preparation of Intravenous Solution".

Malignant Pleural Mesothelioma:

The recommended dose of pemetrexed disodium for injection in combination with cisplatin for the treatment of malignant pleural mesothelioma is 500mg/m^2 on Day 1 of each 21-day cycle, infused intravenously over 10 minutes. According to the recommended dose of 75mg/m^2, cisplatin is administered intravenously over 2 hours beginning approximately 30 minutes after the end of administration of pemetrexed disodium for injection. Accepting cisplatin for the treatment needs a hydration protocol. See the details in the package insert of "Cisplatin".

Nonsquamous non-small cell lung cancer:

The recommended dose of pemetrexed disodium for injection for the treatment of nonsquamous non-small cell lung cancer is 500mg/m^2 on Day 1 of each 21-day cycle, infused intravenously over 10 minutes.

Premedication Regimen:

Corticosteroid—Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. Dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after Pemetrexed disodium for injection administration.

Vitamin Supplementation—Patients treated with Pemetrexed disodium for injection must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis in order to reduce toxicity. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed disodium for injection, and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed disodium for injection. Patients must also receive one intramuscular injection of vitamin B_{12} during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as pemetrexed disodium for injection.

The dose of folic acid: 350-1000μg, the commonly used dose is 400μg.

The dose of vitamin B_{12}: 1000μg (see Warnings)

Laboratory Monitoring and Dose Adjustment Recommendations

Monitoring—All patients must be performed with complete blood cell counts, including platelet counts before administration with pemetrexed disodium for injection. Patients should be monitored for nadir hematologic counts and recovery, which were

tested before each dose and on Day-8 and 15 of each cycle in the clinical study. Patients should not begin a new cycle of treatment unless the absolute neutrophilic granulocyte count(ANC)≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 ml/min. Periodic biochemical tests should be performed to evaluate renal and hepatic function.

Dose Adjustment Recommendations—Dose adjustments should be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. If the patient could not recover from the adverse effect in 21-day cycle, the treatment should be delayed. After recovery, patients should be retreated according to the guidelines in Tables 1-3.

Table 1. Dose Adjustment for Pemetrexed(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 drugs)
Nadir platelets〈50，000/mm^3 regardless of nadir ANC	50% of previous dose (both drugs)

If patients develop non-hematologic toxicities (excluding neurotoxicity) ≥Grade 3 (except Grade 3 transaminase elevations), pemetrexed 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 Adjustment for Pemetrexed(single-agent or in combination) and Cisplatin – Non-hematologic Toxicities[a,b]

	Dose of Pemetrexed (mg/m^2)	Dose of Cisplatin(mg/m^2)
Any Grade 3[c] 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

c Except Grade 3 transaminase elevation

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

Table 3. Dose Adjustment for Pemetrexed(single-agent or in combination) and Cisplatin Neurotoxicity

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

If a patient experiences dose adjustment twice, but hematologic of Grade 3/4 or nonhematologic toxicity (except Grade 3 transaminase elevations) appeared again, or neurotoxicity of Grade 3/ 4 is observed, pemetrexed therapy should be discontinued immediately.

Elderly Patients— No special dose adjustments other than those recommended for all patients as above for patients≥65 years of age.

Children— Pemetrexed is not recommended for use in children, as safety and efficacy have not been established in children.

Renally Impaired Patients—Patients with creatinine clearance ≥45 ml/min required no special dose adjustments other than those recommended for all patients. Dose adjustments in the patients with creatinine clearance below 45 ml/min have not been established. Therefore, pemetrexed should not be administered to patients whose creatinine clearance is <45 ml/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:

$$\text{Males:}\quad \frac{[\,140-\text{Age in years}\,]\times\text{Actual Body Weight（kg）}}{72\times\text{Serum Creatinine（mg/dL）}} = \text{ml/min}$$

Females：Estimated creatinine clearance for males×0.85

Patients whose creatinine clearance is <80 mL/min, should be cautious to be monitored when administering pemetrexed concurrently with NSAIDs.(see **Drug Interaction**】).

Hepatically Impaired Patients—Pemetrexed is not extensively metabolized by the liver. Dose adjustments in patients with hypohepatia are provided in Table 2 (see Patients with hypohepatia under【**Precautions**】).

Preparation and Administration Precautions

Pemetrexed is an anticancer agent. As with other potentially toxic anticancer agents, it should be cautious in handling and preparation of infusion solutions. The use of gloves is recommended. If a solution of pemetrexed contacts the skin, wash the skin with soap and water immediately and thoroughly. If pemetrexed contacts the mucous membranes, flush thoroughly with water. There is no uniform standard to be recommended on the disposal of anticancer drugs currently.

Pemetrexed is not a vesicant, and there is no specific antidote for extravasation. To date, there have been few reported cases of pemetrexed extravasation, which were not evaluated seriously 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. Reconstitution and dilution process should be sterile operation.
2. Calculate the dose of pemetrexed and the number of vials needed. Each vial contains 100 mg of pemetrexed.
3. Dissolve 100 mg vials with 4 ml of 0.9% Sodium Chloride Injection (preservative free) to get a solution containing 25 mg/ml pemetrexed. 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 pemetrexed solution is between 6.6 and 7.8. Further dilution is required.
4. The pemetrexed solution should be inspected visually for particulate matter and discoloration before administration. If particulate matter or discoloration is observed, do not administer.
5. Diluted reconstituted pemetrexed solution with 0.9% Sodium Chloride Injection (preservative free) to 100 ml and 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 at refrigerated or room temperature (15-30℃) with no requirement of dark. When prepared as directed, reconstitution and infusion solution 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, USP and Ringer's Injection, USP and therefore these should not be used. Coadministration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended.

【Adverse Reaction】

1. 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	Neutropenia, Leucopenia, Reduced hemoglobin, Thrombocytopenia
	Gastrointestinal abnormality	Nausea, Vomiting, Stomatitis/Pharyngitis, Anorexia, Diarrhea, Constipation
	General abnormality	Fatigue
	Nervous system abnormality	Nerve/Sense abnormality
	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
	Nervous system abnormality	Dysgeusia
>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.	

2. 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	Leucopenia, Reduced hemoglobin, Neutropenia/Granulopenia
	Gastrointestinal abnormality	Nausea, Anorexia, Vomiting, Stomatitis/Pharyngitis, Diarrhea
	General abnormality	Fatigue
	Skin and subcutaneous tissue abnormality	Rash, Desquamation
Common (>5% and <10%)	Blood and lymphatic system abnormality	Thrombocytopenia
	Gastrointestinal abnormality	Constipation
	General abnormality	Fever
	Hepatobiliary abnormality	SGPT（ALT）, SGOT（AST）increasing
	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	

3. Other reports of adverse reaction observed in clinical usage with marketed pemetrexed disodium for injection, such as colitis, injection site edema, interstitial pneumonia, and radiation recall reaction occurred in patients who have been treated with radiotherapy.

【Contraindications】

ELUZER is contraindicated in patients who have been known hypersensitivity to pemetrexed or to any other ingredients in the composition.

【Precautions】

Warnings

Decreased renal function

Pemetrexed is primarily eliminated unchanged by renal excretion. No dosage adjustment is necessary for 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 (see Dose Adjustment Recommendations under **【Dosage and Administration】**).

In foreign clinical studies, one patient with severe renal impairment (creatinine clearance is 19 ml/min) who did not receive folic acid and vitamin B_{12} supplementation, died of drug-related toxicity after administered with pemetrexed single-agent treatment.

Myelosuppression

Pemetrexed can suppress bone marrow function, manifested by neutropenia, thrombocytopenia, and anemia(or pancytopenia) (see **【Adverse Reaction】**). Myelosuppression is a common dose-limited toxicity. Dose adjustments for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle (see Dose Adjustment Recommendations under **【Dosage and Administration】**).

Need for Folic acid and Vitamin B_{12} Supplementation

Patients treated with pemetrexed must be administered with folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related hematologic or gastrointestinal adverse effects. (see **【Dosage and Administration】**). In clinical studies, overall toxicity reduced by supplementation with folic acid and vitamin B_{12} when treated with pemetrexed, including Grade 3/4 hematologic and non-hematologic toxicities such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia.

Precautions

General

Pemetrexed should be administered under the guidance of a qualified physician experienced in the use of antineoplastic agents, and should be used in the qualified medical institutions with experienced diagnostic and therapeutic techniques to assure appropriate management of complications are readily available. Treatment-related adverse events of pemtrexed seen in clinical trials have been reversible. Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pemetrexed with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction (see **【Dosage and Administration】**).

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

Laboratory Tests

All the patients receiving pemetrexed should be performed with complete blood cell test, including platelet counts and blood biochemical examination. Patients should be monitored for nadir of blood cells and recovery, which should be tested before each dose and on day 8 and 15 of each cycle in the clinical study. Patients should not begin a new cycle of treatment unless the ANC is ≥ 1500 cells/mm^3, the platelet count is ≥ 100,000 cells/mm^3, and creatinine clearance is ≥ 45 ml/min.

Patients with Hypohepatia

Patients with bilirubin >1.5 times the upper limit of normal were excluded from clinical trials of pemetrexed. Patients had no evidence of hepatic metastases if with transaminase >3.0 times the upper limit of normal were excluded from clinical trials. Patients with transaminase from 3 to 5 times the upper limit of normal were included in the clinical trial of pemetrexed if they had hepatic metastases.

Dose adjustments for Patients with hypohepatia are provided in table 2 (see Special Populations under **【Pharmacokinetics】**).

Patients with Renal Insufficiency

Pemetrexed is primarily excreted by the kidney. 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 (see Special Populations under **【Pharmacokinetics】**).

The Interaction between the Drug and the Laboratory Test

Has not been established yet.

No study shows whether taking pemetrexed will influence on the patients' driving and machine operation. However, studies showed that pemetrexed may lead to fatigue, when it occurs, patients should be cautious to drive and operate machines.

【Pregnancy and Nursing mothers】

Pregnancy

Pregnancy Category D.

Pemetrexed may cause fetal harm when administered to a pregnant woman. Embryotoxicity was characterized by increased embryo-fetal deaths and fetal growth retardation. 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.

Nursing Mothers

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.

【Pediatric Use】

The safety and effectiveness of pemetrexed in perdiatric patients have not been established.

【Geriatric Use】

Dose adjustments are recommended as that for all patients, special adjustments are not necessary (see Special Populations under **【Pharmacokinetics】**).

【Drug Interactions】

Chemotherapeutic Agents—Cisplatin does not alter the pharmacokinetics of pemetrexed and pemetrexed does not affect the pharmacokinetics of all platinum drugs.

Vitamins—Coadministration of oral folic acid or intramuscular vitamin B_{12} 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 decrease the metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No studies were conducted to assess the cytochrome P450 isozyme influenced by pemetrexed, because pemetrexed used as recommended (once every 21 days) would not cause any significant enzyme induction.

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.

Ibuprofen—Daily ibuprofen doses of 400 mg qid 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.

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

Ibuprofen (400 mg qid) can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥80 ml/min), but should be cautious when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-life for a period of 2 days before, the day of, and 2 days following administration of pemetrexed.

It have not been known regarding potential interaction between pemetrexed and NSAIDs with longer half-life, all 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 an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

【Overdosage】

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.

【Pharmacological and Toxicology】

Pharmacological Action

Pemetrexed is an antifolate containing the pyrrolopyrimidine-based nucleus that exerts its antineoplastic activity by disrupting folate-dependent 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), all the three enzymes are necessary for folic acid biosynthesis and involve in the re-biosynthesis of thymidine and purine nucleotide. Pemetrexed is transported into cells by both the 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, to a lesser concentration in normal tissues. Polygutamated metabolites have an increased intracellular half-life

resulting in prolonged drug action in malignant cells.
Preclinical studies have shown that in vitro pemetrexed inhibits the growth of mesothelioma cell lines (MSTO-211H, 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 B_{12} supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the level of the ANC nadirs, is inversely proportional to the systemic exposure of pemetrexed. It was also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or homocysteine concentrations. The levels of these two substrates can be reduced by folic acid and vitamin B_{12} supplementation. There is no cumulative effect of ANC over multiple treatment cycles of pemetrexed.
Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days over a range of exposures from 38.3 to 316.8 μg•hr/ml. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.
Toxicological Studies
Genetic toxicity: Pemetrexed was a clastogen in the vivo micronucleus assay in mouse bone marrow but was not mutagenic reaction in multiple in vitro tests (Ames assay, CHO cell assay).
Reproductive toxicity: Pemetrexed administered at i.v. doses of 0.1 mg/kg/day or greater (about 1/1666 the recommended human dose on a mg/m^2 basis) to male mice resulted in reduced fertility, hypospermia, and testicular atrophy.
Carcinogenic Effect: No research on the carcinogenic effect of pemetrexed.

【Pharmacokinetics】
There is no pharmacokinetics datas from Chinese people using pemetrexed.
From literatures reported: The pharmacokinetics of pemetrexed administered as a single agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed is primarily eliminated unchanged in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. 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 clearance decreases, and exposure (AUC) increases, as renal function decreases. 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. 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.
Special Populations
From literatures reported: The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in single group studies.
Geriatric—No obviously changes of age on the pharmacokinetics of pemetrexed was observed over a range of 26 to 80 years.
Pediatric—Pediatric patients were not include in clinical trials.
Gender—The pharmacokinetics of pemetrexed were not different in male and female patients.
Race—The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. There had a test on the pharmacokinetics of Japanese patients. Through there is no statistics control report on the pharmacokinetic parameters between the West and the Japanese, it still shows that the absolute dose parameters of the two is basically similar, and no significant clinical differences.
Hepatic Insufficiency—There was no effect of elevated AST (SGOT), ALT (SGTP), or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted (see Hepatic Insufficiency under **【Precaution】**).
Renal Insufficiency—Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed in the presence of cisplatin decreases as renal function decreases, with 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 (see**【Dosage and Administration】** and Warnings under**【Precaution】**).
【Storage】 Preserve in tightly closed containers, stored in a dry place, protected from light.
【Package】 1 vail/pack.
【Expiry date】24 months
【Registration Certificate No.】NDC. H20123010
【Manufacturer】
Name: Shanghai Chemo Wanbang Biobpharma Co., Ltd
Address: No. 1098, Yuegong Road, Jinshan Industrial Zone, Shanghai, P.R. China
Zip code: 201506
Telephone: 021-60128558
Fax: 021-60128578