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

Pemetrexed Kabi 25 mg/ml concentrate for solution for infusion

DESCRIPTION:

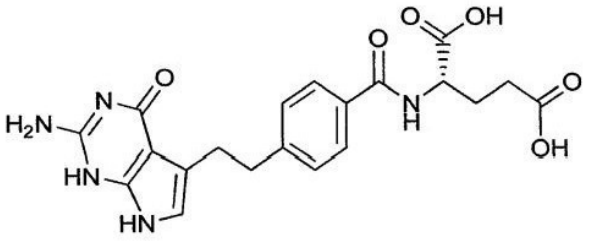
Pemetrexed Kabi 25 mg/ml concentrate for solution for infusion is a colorless to slightly yellowish or yellow greenish solution, containing Pemetrexed as active substance, Hydroxypropylbetadex (Ph. Eur.) as stabilizing agent, trometamol (Ph. Eur.) as pH adjuster and buffering agent and hydrochloric acid (Ph. Eur.) as pH adjuster, water for injections (Ph. Eur.) as vehicle and nitrogen (Ph. Eur.) as processing aid. Pemetrexed Injection is diluted with 5% Glucose intravenous infusion or with sodium chloride 9 mg/ml (0.9 %) solution for injection. After dilution, the solution is colourless and free from visible particles.

COMPOSITION:

Each mL contains:	
Pemetrexed diacid	25 mg
Hydroxypropylbetadex	241 mg
Trometamol	15 mg
Trometamol	q.s.
Hydrochloric acid, concentrated	q.s.
Water for Injections	q.s. to 1 ml

CHEMICAL STRUCTURE:

Pemetrexed diacid has the chemical name N-{4-[2-(2-amino-4-oxo-4,7-dihydro-1H- pyrrolo[2,3-d] pyrimidin-5-yl)ethyl] benzoyl}-L-glutamic acid. It is a white to either light yellow or greenish yellow colored powder with a molecular formula of $C_{20}H_{21}N_5O_6$ and a molecular weight of 427.41. The structural formula is as follows:



PHARMACOLOGY:

Mechanism of action:

Pharmacotherapeutic group: antineoplastic agents, folic acid analogues, ATC code: L01BA04

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 multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the *de novo* biosynthesis of thymidine and purine nucleotides. 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.

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Pharmacokinetics:
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/min^2 infused over a 10-minute period.

Distribution
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.

Biotransformation
Pemetrexed undergoes limited hepatic metabolism.

Elimination
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 %.

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.

Linearity/non-linearity
Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

INDICATIONS:

Malignant pleural mesothelioma
Pemetrexed Kabi in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer
Pemetrexed Kabi 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 Kabi 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 Kabi 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.

Pemetrexed in combination with pembrolizumab and platinum chemotherapy, is indicated for the first line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.

CONTRAINDICATIONS:

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

ADVERSE 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.

Nephrogenic diabetes insipidus and renal tubular necrosis have been reported in post marketing setting with an unknown frequency.

Tabulated list of adverse reactions

The table 1 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 available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Frequencies of all grades adverse drug events regardless of causality from the pivotal registration studies: JMEI (pemetrexed vs docetaxel), JMDB (pemetrexed and cisplatin versus gemcitabine and cisplatin, JMCH (pemetrexed 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
Infectionsand 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		
ImmuneSystem disorders		Hypersensitivity		Anaphylactic shock		
Metabolism and nutrition disorders		Dehydration				

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System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare	Not known
Nervoussystem 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		Cardiacfailure Arrhythmia	Angina Myocardial infarction Coronary artery disease Arrhythmia supraventricular			
Vascular disorders			Peripheral ischaemia[c]			
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism Interstitial pneumonitis[bd]			
Gastrointestinal disorders	Stomatitis Anorexia Vomiting Diarrhoea Nausea	Dyspepsia Constipation Abdominal pain	Rectal haemorrhage Gastrointestinal haemorrhage Intestinal perforation Oesophagitis Colitis[e]			
Hepatobiliary disorders		Aalanine aminotransferase increased Aspartate aminotransferase increased		Hepatitis		

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System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare	Not known
Skin and subcutaneous tissuedisorders	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] Pseudocellulitis Dermatitis Eczema Prurigo	
Renal and urinary disorders	Creatinine clearance decreased Blood creatinine increased[e]	Renal failure Glomerular filtration rate decreased				Nephrogenic diabetes insipidus Renal tubular necrosis
General disorders	Fatigue	Pyrexia, Pain				
administration siteconditions		Oedema Chest pain Mucosal inflammation				
Investigations		Gammaglutamyl transferase increased				
Injury, poisoning and procedural complications			Radiation oesophagitis Radiation pneumonitis	Recall phenomenon		

[a]with and without neutropenia [b]in some cases fatal

[c]sometimes leading to extremity necrosis [d]with respiratory insufficiency

[e]seen only in combination with cisplatin [f]mainly of the lower limbs

DRUG INTERACTIONS:

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic medicinal product (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.

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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 medicinal products 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 medicinal product (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 reactions. 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 medicinal product metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Interactions common to all cytotoxics
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).

PRECAUTIONS AND WARNINGS:
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^3 and platelet count returns to ≥ 100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum 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-

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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 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 phase 2 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.

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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 radio sensitising agents.

Cases of radiation recall have been reported in patients who received radiotherapy weeks or Font years previously.

FERTILITY, PREGNANCY AND LACTATION:

Women of childbearing potential/ 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 breast-feeding 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.

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.

DOSAGE AND ADMINISTRATION:
Pemetrexed Kabi must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy. The Pemetrexed Kabi solution must be prepared according to the instructions provided in section Method of Administration.

Posology

Pemetrexed Kabi in combination with cisplatin
The recommended dose of Pemetrexed Kabi 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 cisplatin package insert for more information).

Pemetrexed Kabi as single agent
In patients treated for non-small cell lung cancer after prior chemotherapy, the recommended dose

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of Pemetrexed Kabi is 500 mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Pemetrexed Kabi in combination with pembrolizumab
The recommended dose of pemetrexed when administered with pembrolizumab and platinum chemotherapy forthe initial treatment of metastatic non-squamous NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes administered after pembrolizumab and prior to carboplatin or cisplatin on Day 1 of each 21-day cycle for 4 cycles. Following completion of platinum-based therapy, treatment with pemetrexed with or without pembrolizumab is administered until disease progression or unacceptable toxicity (see also pembrolizumab product insert for specific dosing advice).

Pre-medication regimen
Corticosteroids: 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 (see section Warnings)

Vitamin Supplementation: 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 B12 (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 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 $\geq$ 1500 cells/mm^3 and platelets should be $\geq$ 100,000 cells/mm^3.

Creatinine clearance should be $\geq$ 45 ml/min.

The total bilirubin should be $\leq$ 1.5 times upper limit of normal. Alkaline phosphatase (AP), aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) should be $\leq$ 3 times upper limit of normal. Alkaline phosphatase, AST and ALT $\leq$ 5 times upper limit of normal is acceptable if liver has tumour involvement.

Dose Reduction Recommendations
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 2, 3 and 4, which are applicable for Pemetrexed Kabi used as a single agent or in combination with cisplatin.

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Table 2 - Dose modification table for pemetrexed (as single agent or in combination) and cisplatin - Haematologic 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), Pemetrexed Kabi should be withheld until resolution to less than or equal to the patient's pre- therapy value. Treatment should be resumed according to the guidelines in Table 3.

Table 3 - Dose modification table for pemetrexed (as single agent or in combination) and cisplatin-Non-haematologic 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 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 Pemetrexed Kabi and cisplatin is documented in Table 4. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 4 - Dose modification table 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 v2.0; NCI 1998)

Discontinuation Recommendation:
Treatment with Pemetrexed Kabi 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
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.

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

Patients with renal impairment
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. (see section Warnings)

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.

Instruction for Use

Pemetrexed Kabi is for intravenous use. Pemetrexed Kabi should be administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

- Use aseptic technique during the dilution of pemetrexed for intravenous infusion administration.
- Calculate the dose and the number of Pemetrexed Kabi vials needed.
- The appropriate volume of Pemetrexed Kabi must be diluted to 100 ml with sodium chloride 9 mg/ml (0.9 %) solution for injection or 5% glucose intravenous infusion and administered as an intravenous infusion over 10minutes.
- Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags.
- Parenteral medicinal products must be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.
- Pemetrexed solutions are for single use only. Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

Preparation and administration precautions:
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.

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.

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STORAGE:
Unopened vial: Store below 25°C. Keep the vial in the outer carton in order to protect from light.

Diluted solutions:
Chemical and physical in-use stability of diluted solution was demonstrated for 24 hours at 2°C to 8°C and 6 hours at below 25°C. When prepared as directed, infusion solutions of Pemetrexed Kabi contain no antimicrobial preservatives. From a microbiological point of view, 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 not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

INCOMPATIBILITIES:
Pemetrexed Kabi contains trometamol as an excipient. Trometamol is incompatible with cisplatin resulting in degradation of cisplatin. This medicinal product must not be mixed with other medicinal products. Intravenous lines should be flushed after administration of Pemetrexed Kabi. Pemetrexed is physically incompatible with diluents containing calcium, including Lactate Ringer's Injection and Ringer's Injection, and therefore these should not be used.

In the absence of other compatibility studies this medicinal product must not be mixed with other medicinal products.

SHELF LIFE:

Unopened vial: 2 years.

Diluted solution: Chemical and physical in-use stability of diluted solution was demonstrated for 24 hours at 2°C to 8°C and 6 hours at below 25°C. When prepared as directed, infusion solutions of Pemetrexed Kabi contains no antimicrobial preservatives. From a microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

PRESENTATION:

100 mg/4 ml
Filled in 6ml Type I, tubular, clear, colourless glass vial, with 20 mm grey flurotec chlorobutyl/bromobutyl rubber stopper and sealed with green flip-off aluminium seal, containing 4 ml concentrate. Each vial is unit packed in carton and one package insert is inserted.

500 mg/20 ml
Filled in 30ml Type I, tubular, clear, colourless glass vial, with 20 mm grey flurotec chlorobutyl/bromobutyl rubber stopper and sealed with blue flip-off aluminium seal, containing 20 ml concentrate. Each vial is unit packed in carton and one package insert is inserted.

1,000 mg/40 ml
Filled in 50ml Type I, tubular, clear, colourless glass vial, with 20 mm grey flurotec chlorobutyl/bromobutyl rubber stopper and sealed with red flip-off aluminium seal, containing 40 ml concentrate. Each vial is unit packed in carton and one package insert is inserted.

Not all pack sizes may be marketed.

Product Registration Holder/Importer
Fresenius Kabi Malaysia Sdn Bhd
3-1 & 3-2, Axis Technology Centre, Lot 13, Jalan 51A/225
46100 Petaling Jaya Selangor, Malaysia

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MANUFACTURER INFORMATION:

Manufactured in India by:
Fresenius Kabi Oncology Limited
Village- Kishanpura,
Baddi,
Tehsil-Nalagarh,
Distt. Solan,
Himachal Pradesh, IN -174101

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