PEMIREX powder for concentrate for solution for infusion

Pemetrexed 100 mg

ROUTE OF ADMINISTRATION : For Intravenous use

COMPOSITION

Each vial contains

Pemetrexed Disodium 2.5 hydrate ..... 120.82 mg

(as Pemetrexed 100 mg)

Excipients with known effect: Each vial contains approximately 11mg sodium

DESCRIPTION

White to either light yellow or green-yellow, freeze-dried powder in a colorless vial.

After reconstitution, the solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8.

INDICATIONS

1) Pemetrexed in combination with cisplatin is indicated for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma.
2) 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.
3) 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.
4) 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

DOSAGE AND ADMINISTRATION

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

1. Combination use with cisplatin

The recommended dose of Pemetrexed is 500 mg/m^2 BSA administered as the completion of the pemetrexed infusion on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the completion of pemetrexed infusion on the first day of each 21-day cycle. Patients should receive hydration consistent with local practice prior to and/or after receiving cisplatin. 500

2. Single-agent use

Non-Small Cell Lung Cancer : The recommended dose of Pemetrexed is 500 mg/m^2 BAS administered as the completion of the pemetrexed infusion on the first day of each 21-day cycle.

3. Premedication regimen

1) 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 4mg of dexamethasone administered orally twice a day
2) 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 - 1,000 µg) 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.
3) Patients must also receive an intramuscular injection of vitamin B_{12} (1,000 µg) 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.

4. 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)	≥ 1500 cells/mm^3
Platelets	≥ 100,000 cells/mm^3
Creatinine Clearance	≥ 45 mL/min
The total bilirubin	≤ 1.5 times upper limit of normal
Alkaline phosphatase (AP), aspartate transaminase (AST or SGOT), alanine transaminase (ALT or SGPT)	≤ 3 times upper limit of normal ≤ 5 times upper limit of normal* (*if liver has tumor involvement)

5. 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 re-treated 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 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 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 definition of ≥ CTC Grade 2 bleeding.

If patients develop non-haematologic toxicities ≥ Grade 3 (excluding neurotoxicity), Pemetrexed 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 2.

Table 2. 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)

[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 Table for Pemetrexed (as Single Agent or in Combination) and Cisplatin - Neurotoxicity

CTC[a] 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

[a] National Cancer Institute Common Toxicity Criteria

Treatment with Pemetrexed 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 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. In clinical studies, patients with creatinine clearance of ≥ 45mL/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 45mL/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 transaminase > 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.

CONTRAINDICATIONS

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

SPECIAL WARNINGS AND PRECAUTIONS

1) 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 ≥ 1,500 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
2) 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.
3) 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
4) An insufficient number of patients has been studied with creatinine clearance of below 45mL/min. Therefore, the use of pemetrexed in patients with creatinine clearance of < 45mL/min is not recommended.
5) Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79mL/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, and aspirin (> 1.3g 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.
6) 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.
7) 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 normalised 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.
8) Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving treatment.
9) 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.
10) Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended.
11) 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.
12) 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.
13) This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'.

ADVERSE REACTIONS

<Malignant Pleural Mesothelioma>

The table below provides the frequency and severity of undesirable effects that have been reported in > 5% of 168 patients with mesothelioma who were randomised to receive cisplatin and pemetrexed, and 163 patients with mesothelioma randomised to receive single-agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B_{12}.

System organ class	Frequency	Event*	Pemetrexed/Cisplatin (N = 168)		Cisplatin (N = 163)	
			All grades toxicity (%)	Grade3-4 toxicity (%)	All grades toxicity (%)	Grade3-4 toxicity (%)
Blood and lymphatic system disorgers	Very Common	Neutrophils/ Granulocytes decreased	56.0	23.2	13.5	3.1
		Leucocytes decreased	53.0	14.9	16.6	0.6
		Haemoglobin decreased	26.2	4.2	10.4	0.0
		Platelets decreased	23.2	5.4	8.6	0.0
Metabolism and nutrition disorders	Common	Dehydration	6.5	4.2	0.6	0.6
Nervous system disorders	Very Common	Neuropathy-sensory	10.1	0.0	9.8	0.6
	Common	Taste disturbance	7.7	0.0***	6.1	0.0***
Eye disorders	Common	Conjunctivitis	5.4	0.0	0.6	0.0
Gastrointestinal disorders	Very Common	Diarrhoea	16.7	3.6	8.0	0.0
		Vomiting	56.5	10.7	49.7	4.3
		Stomatitis/	23.2	3.0	6.1	0.0

System organ class	Frequency	Event*	Pemetrexed/Cisplatin (N = 168)		Cisplatin (N = 163)	
			All grades toxicity (%)	Grade3-4 toxicity (%)	All grades toxicity (%)	Grade3-4 toxicity (%)
		Pharyngitis				
		Nausea	82.1	11.9	76.7	5.5
		Anorexia	20.2	1.2	14.1	0.6
		Constipation	11.9	0.6	7.4	0.6
	Common	Dyspepsia	5.4	0.6	0.6	0.0
Skin and subcutaneous tissue disorders	Very Common	Rash	16.1	0.6	4.9	0.0
		Alopecia	11.3	0.0***	5.5	0.0***
Renal and urinary disorders	Very Common	Creatinine Elevation	10.7	0.6	9.8	1.2
		Creatinine clearance decreased**	16.1	0.6	17.8	1.8
General disorders and administration site conditions	Very Common	Fatigue	47.6	10.1	42.3	9.2

* Refer to National Cancer Institute CTC version 2 for each grade of toxicity except the term "creatinine clearance decreased"
** Which is derived from the term "renal/genitourinary other".
***According to National Cancer Institute CTC, taste disturbance and alopecia should only be reported as Grade 1 or 2.

Frequency estimate : very common (≥1/10), common (≥1/100 and <1/10)
For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

<Locally advanced or metastatic non-small cell lung cancer after prior chemotherapy>
The table below provides the frequency and severity of undesirable effects that have been reported in > 5% of 265 patients randomly assigned to receive single-agent pemetrexed with folic acid and vitamin B12 supplementation, and 276 patients randomly assigned to receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic non-small cell lung cancer and received prior chemotherapy.

System organ class	**Frequency**	**Event***	**Pemetrexed (N = 265)**		**Docetaxel (N = 276)**	
			All grades toxicity (%)	**Grade 3-4 toxicity (%)**	**All grades toxicity (%)**	**Grade 3-4 toxicity (%)**
Blood and lymphatic system disorders	Very common	Neutrophils/ Granulocytes decreased	10.9	5.3	45.3	40.2
		Leukocytes decreased	12.1	4.2	34.1	27.2
		Haemoglobin decreased	19.2	4.2	22.1	4.3
	Common	Platelets decreased	8.3	1.9	1.1	0.4
Gastrointestinal disorders	Very common	Diarrhoea	12.8	0.4	24.3	2.5
		Vomiting	16.2	1.5	12.0	1.1
		Stomatitis/ Pharyngitis	14.7	1.1	17.4	1.1
		Nausea	30.9	2.6	16.7	1.8
		Anorexia	21.9	1.9	23.9	2.5
	Common	Constipation	5.7	0.0	4.0	0.0
Hepatobiliary disorders	Common	SGPT (ALT) elevation	7.9	1.9	1.4	0.0
		SGOT (AST) elevation	6.8	1.1	0.7	0.0
Skin and subcutaneous tissue disorders	Very common	Rash/ desquamation	14.0	0.0	6.2	0.0
	Common	Pruritus	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4**	37.7	2.2**
General disorders and administration site conditions	Very common	Fatigue	34.0	5.3	35.9	5.4
	Common	Fever	8.3	0.0	7.6	0.0

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity.
**According to National Cancer Institute CTC (v2.0; NCI 1998), alopecia should only be reported as Grade 1 or 2.

Frequency estimate : very common (≥1/10), common (≥1/100 and <1/10)
For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

<Locally advanced or metastatic non-small cell lung cancer>
The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of 839 patients with NSCLC who were randomised to receive cisplatin and pemetrexed and 830 patients with NSCLC who were randomised to receive cisplatin and gemcitabine. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B_{12}.

System organ class	Frequency	Event**	Pemetrexed/Cisplatin (N = 839)		Gemcitabine/Cisplatin (N = 830)	
			All grades toxicity (%)	Grade3-4 toxicity (%)	All grades toxicity (%)	Grade3-4 toxicity (%)
Blood and lymphatic system disorgers	Very Common	Haemoglobin decreased	33.0*	5.6*	45.7*	9.9*
		Neutrophils/ Granulocytes decreased	29.0*	15.1*	38.4*	26.7*
		Leucocytes decreased	17.8	4.8*	20.6	7.6*
		Platelets decreased	10.1*	4.1*	26.6*	12.7*
Nervous system disorders	Very Common	Neuropathy-sensory	8.5*	0.0*	12.4*	0.6*
	Common	Taste disturbance	8.1	0.0***	8.9	0.0***
Gastrointestinal disorders	Very Common	Nausea	56.1	7.2*	53.4	3.9*
		Vomiting	39.7	6.1	35.5	6.1
		Anorexia	26.6	2.4*	24.2	0.7
		Constipation	21.0	0.8	19.5	0.4
		Stomatitis/ Pharyngitis	13.5	0.8	12.4	0.1
		Diarrhoea	12.4	1.3	12.8	1.6
		without colostomy				
	Common	Dyspepsia/heartburn	5.2	0.1	5.9	0.0
Skin and subcutaneous tissue disorders	Very Common	Alopecia	11.9*	0.0***	21.4*	0.5***
	Common	Rash/desquamation	6.6	0.1	8.0	0.5
Renal and urinary disorders	Very Common	Creatinine Elevation	10.1*	0.8	6.9*	0.5
General disorders and administration site conditions	Very Common	Fatigue	42.7	6.7	44.9	4.9

* p-values < 0.05 comparing pemetrexed/cisplatin to gemcitabine/cisplatin, using Fisher Exact test.
** Refer to National Cancer Institute CTC for each Grade of Toxicity.
***According to National Cancer Institute CTC, taste disturbance and alopecia should only be reported as Grade 1 or 2.

Frequency estimate : very common (≥1/10), common (≥1/100 and <1/10)
For the purpose of this table, a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

< Locally advanced or metastatic non-small cell lung cancer after prior platinum-based chemotherapy >
The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of 800 patients randomly assigned to receive single-agent pemetrexed and 402 patients randomly assigned to receive placebo in the single-agent pemetrexed maintenance (JMEN: N= 663) and continuation pemetrexed maintenance (PARAMOUNT: N=539) studies. All patients were diagnosed with Stage IIIB or IV NSCLC and had received prior platinum-based chemotherapy. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.

System organ class	**Frequency***	**Event****	**Pemetrexed*** (N = 800)**		**Placebo*** (N = 402)**	
			All grades toxicity (%)	**Grade 3 - 4 toxicity (%)**	**All grades toxicity (%)**	**Grade 3 - 4 toxicity (%)**
Blood and lymphatic system disorders	Very common	Haemoglobin decreased	18.0	4.5	5.2	0.5
	Common	Leukocytes decreased	5.8	1.9	0.7	0.2
		Neutrophils decreased	8.4	4.4	0.2	0.0
Nervous system disorders	Common	Neuropathy-sensory	7.4	0.6	5.0	0.2
Gastrointestinal disorders	Very common	Nausea	17.3	0.8	4.0	0.2
		Anorexia	12.8	1.1	3.2	0.0
	Common	Vomiting	8.4	0.3	1.5	0.0
		Mucositis/ Stomatitis	6.8	0.8	1.7	0.0
Hepatobiliary disorders	Common	ALT (SGPT) elevation	6.5	0.1	2.2	0.0
		AST (SGOT) elevation	5.9	0.0	1.7	0.0
Skin and subcutaneous tissue disorders	Common	Rash/ desquamation	8.1	0.1	3.7	0.0
General disorders and administration site conditions	Very common	Fatigue	24.1	5.3	10.9	0.7
	Common	Pain	7.6	0.9	4.5	0.0
		Oedema	5.6	0.0	1.5	0.0
Renal Disorders	Common	Renal disorders****	7.6	0.9	1.7	0.0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Event; NCI = National Cancer Institute; SGOT = serum glutamic oxaloacetic aminotransferase; SGPT = serum glutamic pyruvic aminotransferase.
*Definition of frequency terms: Very common - ≥ 10%; Common - > 5% and < 10%. For the purpose of this table, a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.
**Refer to NCI CTCAE Criteria (Version 3.0; NCI 2003) for each grade of toxicity. The reporting rates shown are according to CTCAE version 3.0.
***Integrated adverse reactions table combines the results of the JMEN pemetrexed maintenance (N=663) and PARAMOUNT continuation pemetrexed maintenance (N=539) studies.
**** Combined term includes increased serum/blood creatinine, decreased glomerular filtration rate, renal failure and renal/genitourinary- other.

<Others>
-Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident, and transient ischaemic attack, 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.
-Pancytopenia has been uncommonly reported during clinical trials with pemetrexed.
-Cases of colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis) have been reported uncommonly in patients treated with pemetrexed.
-Cases of interstitial pneumonitis with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed.
-Uncommon cases of oedema have been reported in patients treated with pemetrexed.
-Oesophagitis/ radiation oesophagitis has been uncommonly reported.
-Sepsis, sometimes fatal, has been commonly reported.

<Post-marketing surveillance>
During post-marketing surveillance, the following adverse reactions have been reported in patients treated with pemetrexed
-Uncommon cases of acute renal failure have been reported with pemetrexed alone or in association with other chemotherapeutic agents.
-Rare cases of radiation recall have been reported in patients who have received radiotherapy previously.
-Uncommon cases of peripheral ischaemia leading sometimes to extremity necrosis have been reported.
-Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.

DRUG INTERACTIONS
1) Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by

glomerular filtration. *In vitro* studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter). 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.

2) 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.

3) 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 aspirin at higher doses (≥1.3g 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).

4) 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 doses should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration.

5) 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.

6) 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.

7) 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 anti-cancer chemotherapy require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

8) Concomitant Use Contraindicated : *Yellow fever vaccine* - Risk of fatal generalised vaccinale disease.

9) 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 those who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis).

USE IN PREGNANCY AND LACTATION

1) 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

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

3) 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.

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.

OVERDOSAGE

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.

PREPARATION AND ADMINISTRATION PRECAUTIONS

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

2) Calculate the dose and the number of vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

3) Reconstitute each vial with sodium chloride 9 mg/mL (0.9%) solution for injection, without preservative, resulting in a solution containing 25 mg/mL pemetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8. Further dilution is required.

Vial (Strength of Pemerexed)	Quantity of sodium chloride 9 mg/mL (0.9%) solution for injection	Concentration of the reconstituted solution
1 vial (100 mg)	4.2 mL	25 mg/mL
1 vial (300 mg)	12 mL	
1 vial (500 mg)	20 mL	

4) The appropriate volume of reconstituted pemetrexed solution must be further diluted to 100 mL with sodium chloride 9 mg/mL (0.9%) solution for injection, without preservative, and administered as an intravenous infusion over 10 minutes.

5) Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride- and polyolefin- lined administration sets and infusion bags.

6) Parenteral medicinal products must be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

7) Pemetrexed solutions are for single use only. Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

8) As with other potentially toxic anti-cancer 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.

SPECIAL PRECAUTIONS FOR STORAGE

1) Unopened vial: Store at room temperature not exceeding 30℃.

2) After reconstitution of the medicinal product : When prepared as directed, reconstituted and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature. 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 normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

OTHERS

1) Pharmacodynamic Properties

Pharmacotherapeutic group: 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 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.

2) 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 838mg/m^2 infused over a 10-minute period. 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. In vitro studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter).

Pemetrexed total systemic clearance is 91.8ml/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90ml/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_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

STORAGE

Preserve in hermetic containers.
Store at room temperature not exceeding 30℃.

It can be stored for 24 hours in a refrigerator (2℃~8℃) after reconstitution.

PACKAGE

1 Vial/Box

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