**Pemetrexed:**

**Class**:

- Antineoplastic Agent, Antimetabolite (Antifolate)

**Indications**:

- Treatment of unresectable malignant pleural mesothelioma (in combination with cisplatin);
- treatment of locally advanced or metastatic **non**squamous nonsmall cell lung cancer (NSCLC; as initial treatment in combination with cisplatin, as single-agent maintenance treatment after 4 cycles of initial platinum-based double therapy, and single-agent treatment after prior chemotherapy)

**Note:** Not indicated for the treatment of **squamous** cell NSCLC

**Unlabeled use :**

- Treatment of bladder cancer (metastatic),
- cervical cancer (recurrent or metastatic),
- ovarian cancer (recurrent or persistent),
- thymic malignancies;
- treatment of malignant pleural mesothelioma (either as a single agent or in combination with carboplatin)

**Available dosage form in the hospital**:

25 mg / ml infusion / 20 ml

**Trade Names:**

Alimta , Jepale , Jie Baili

**Dosage:**

Details concerning dosing in combination regimens should also be consulted. **Note:** Start vitamin supplements 1 week before initial pemetrexed dose: Folic acid 400-1000 mcg daily orally (begin 7 days prior to treatment initiation; continue daily during treatment and for 21 days after last pemetrexed dose) and vitamin $B_{12}$ 1000 mcg I.M. 7 days prior to treatment initiation and then every 3 cycles. Give dexamethasone 4 mg orally twice daily for 3 days, beginning the day before treatment to minimize cutaneous reactions. New treatment cycles should not begin unless ANC $\geq$1500/$mm^3$, platelets $\geq$100,000/$mm^3$, and $Cl_{cr}$ $\geq$45 mL/minute.

-**Malignant pleural mesothelioma:** I.V.: 500 mg/$m^2$ on day 1 of each 21-day cycle (in combination with cisplatin) **or** (unlabeled) in combination with carboplatin (Castagneto, 2008; Ceresoli, 2006) **or** (unlabeled) as single-agent therapy (Jassem, 2008; Taylor, 2008)

-**Nonsmall cell lung cancer:** I.V:

-*Initial treatment:* 500 mg/$m^2$ on day 1 of each 21-day cycle (in combination with cisplatin)

-*Maintenance or second-line treatment:* 500 mg/$m^2$ on day 1 of each 21-day cycle (as a single-agent)

-**Bladder cancer (unlabeled use):** I.V.: 500 mg/$m^2$ on day 1 of each 21-day cycle (Sweeney, 2006)

-**Cervical cancer, persistent or recurrent (unlabeled use):** I.V.: 500 mg/$m^2$ on day 1 of each 21-day cycle until disease progression or unacceptable toxicity occurs (Lorusso, 2010) **or** 900 mg/$m^2$ on day 1 of each 21-day cycle (Miller, 2008)

-**Ovarian cancer, platinum-resistant (unlabeled use):** I.V.: 500 mg/$m^2$ on day 1 of each 21-day cycle (Vergote, 2009)

**-Thymic malignancies, metastatic (unlabeled use):** I.V.: 500 mg/m$^2$ on day 1 of each 21-day cycle for 6 cycles or until disease progression or unacceptable toxicity occurs (Loehrer, 2006)

**Geriatric**

Refer to adult dosing.

**Renal Impairment**:

-Renal function may be estimated using the Cockcroft-Gault formula (using actual body weight) or glomerular filtration rate (GFR) measured by Tc99m-DPTA serum clearance.

- $Cl_{cr}$ ≥45 mL/minute: No dosage adjustment necessary.
- $Cl_{cr}$ <45 mL/minute: Use not recommended (an insufficient number of patients have been studied for dosage recommendations).

-*Concomitant NSAID use with renal dysfunction:*

- $Cl_{cr}$ ≥80 mL/minute: No dosage adjustment necessary.
- $Cl_{cr}$ 45 to 79 mL/minute and NSAIDs with short half-lives (eg, ibuprofen, indomethacin, ketoprofen, ketorolac): Avoid NSAID for 2 days before, the day of, and for 2 days following a dose of pemetrexed.
- Any creatinine clearance and NSAIDs with long half-lives (eg, nabumetone, naproxen, oxaprozin, piroxicam): Avoid NSAID for 5 days before, the day of, and 2 days following a dose of pemetrexed.

**Hepatic Impairment:**

Grade 3 (5.1-20 times ULN) **or** 4 (>20 times ULN) transaminase elevation during treatment: Reduce pemetrexed dose to 75% of previous dose (and cisplatin).

**Obesity**

*ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer:* Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

**Dosing: Adjustment for Toxicity**

*1.Toxicity:* Discontinue if patient develops grade 3 or 4 toxicity after two dose reductions or immediately if grade 3 or 4 neurotoxicity develops

*2.Hematologic toxicity:* Upon recovery, reinitiate therapy

- Nadir ANC <500/mm$^3$ and nadir platelets ≥50,000/mm$^3$: Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)
- Nadir platelets <50,000/mm$^3$ **without bleeding** (regardless of nadir ANC): Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)
- Nadir platelets <50,000/mm$^3$ **with bleeding** (regardless of nadir ANC): Reduce dose to 50% of previous dose of pemetrexed (and cisplatin)

*3.Nonhematologic toxicity ≥grade 3 (excluding neurotoxicity):* Withhold treatment until recovery to baseline; upon recovery, reinitiate therapy as follows:

- Grade 3 or 4 toxicity (excluding mucositis): Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)
- Grade 3 or 4 diarrhea or any diarrhea requiring hospitalization: Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

- Grade 3 or 4 mucositis: Reduce pemetrexed dose to 50% of previous dose (continue cisplatin at 100% of previous dose)

*4.Neurotoxicity:*

- Grade 0-1: Continue pemetrexed at 100% of previous dose (and cisplatin)
- Grade 2: Continue pemetrexed at 100% of previous dose; reduce cisplatin dose to 50% of previous dose

**Common side effect:**

Central nervous system: Fatigue (18% to 34%; dose-limiting)

Dermatologic: Rash/desquamation (10% to 14%)

Gastrointestinal: Nausea (12% to 31%), anorexia (19% to 22%), vomiting (6% to 16%), stomatitis (5% to 15%), diarrhea (5% to 13%)

Hematologic: Anemia (15% to 19%; grades 3/4: 3% to 5%), leukopenia (6% to 12%; grades 3/4: 2% to 4%), neutropenia (6% to 11%; grades 3/4: 3% to 5%; dose-limiting; nadir: 8-10 days; recovery: 4-8 days after nadir)

Respiratory: Pharyngitis (15%)

**Pregnancy Risk Factor: D**