Profile

Peldesine is an inhibitor of the enzyme purine nucleoside phosphorylase and is reported to suppress T-cell proliferation. It has been investigated in the management of cutaneous T-cell lymphomas, and has also been tried topically in psoriasis and some T-cell mediated eye disorders.

Pemetrexed Disodium

(BANM, USAN, rINNM)

LY-231514 (pemetrexed or pemetrexed disodium); MTA; Multitargeted Antifolate; Pemetreksed Disodyum; Pemetrexed disódico; Pémétrexed Disodique; Pemetrexedum Dinatricum. Disodium *N*-{*p*-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate.

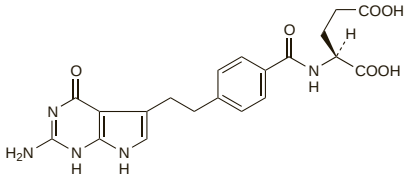
Динатрий Пеметрексед

$C_{20}H_{19}N_5Na_2O_6$ = 471.4.

CAS — 137281-23-3 (pemetrexed); 150399-23-8 (pemetrexed disodium).

ATC — L01BA04.

ATC Vet — QL01BA04.



(pemetrexed)

NOTE. In practice, pemetrexed is given as the disodium heptahydrate ($C_{20}H_{19}N_5Na_2O_6,7H_2O$ = 597.5).

Incompatibility. Licensed product information states that pemetrexed is physically incompatible with diluents containing calcium, including Ringer's solution and lactated Ringer's solution. A study[1] found pemetrexed disodium 20 mg/mL to be physically incompatible with 24 drugs resulting in precipitation or colour change during simulated Y-site administration. These drugs include amphotericin B, some cephalosporin and cephamycin antibacterials, chlorpromazine hydrochloride, ciprofloxacin, dobutamine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, gemcitabine hydrochloride, gentamicin sulfate, irinotecan hydrochloride, metronidazole, minocycline hydrochloride, mitoxantrone hydrochloride, nalbuphine hydrochloride, ondansetron hydrochloride, prochlorperazine edisilate, tobramycin sulfate, and topotecan hydrochloride.

1. Trissel LA, *et al.* Physical compatibility of pemetrexed disodium with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2004; **61:** 2289–93.

Stability. Licensed product information states that pemetrexed is chemically and physically stable, once reconstituted and diluted, for 24 hours either refrigerated at 2° to 8° or at 25°; from a microbiological point of view, solutions should be used immediately, unless prepared under controlled and validated aseptic conditions.

Pemetrexed, reconstituted in polypropylene syringes with sodium chloride 0.9% to a concentration of 25 mg/mL, was found to be both chemically and physically stable for 2 days when stored at room temperature, and for 31 days when refrigerated.[1] Although pemetrexed solutions of 2, 10, and 20 mg/mL in glucose 5% and sodium chloride 0.9% in PVC bags were chemically stable for 90 days when frozen at –20°, microparticulates formed, possibly related to the PVC containers. Pemetrexed solutions should therefore not be frozen.[2]

1. Zhang Y, Trissel LA. Physical and chemical stability of pemetrexed solutions in plastic syringes. *Ann Pharmacother* 2005; **39:** 2026–8.
2. Zhang Y, Trissel LA. Physical instability of frozen pemetrexed solutions in PVC bags. *Ann Pharmacother* 2006; **40:** 1289–92.

Adverse Effects, Treatment, and Precautions

As for Raltitrexed, p.766.

Pemetrexed may also cause fatigue, stomatitis, pharyngitis, dyspnoea, chest pain, and neuropathy. Rare cases of hepatitis, colitis, and intestinal pneumonitis have occurred; fatalities have been reported. Serious renal events, including acute renal failure, have been reported with pemetrexed when it was used either alone or with other cytotoxic drugs; most patients had underlying risk factors such as dehydration, hypertension, or diabetes. Cardiovascular events, including myocardial infarction and cerebrovascular events, have occurred rarely, usually when pemetrexed was used with other cytotoxic drugs. Cases of radiation pneumonitis and radiation recall have been reported in patients treated with radiotherapy. Hypersensitivity reactions may occur.

Complete blood cell counts should be monitored, and folate and vitamin B_{12} are given as prophylaxis against haematological and gastrointestinal toxicity during pemetrexed therapy. Pre-treatment with a corticosteroid, such as oral dexamethasone, reduces the incidence and severity of skin reactions.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

High doses of NSAIDs and aspirin may decrease pemetrexed elimination. In patients with mild to moderate renal impairment (creatinine clearance 45 to 79 mL/minute) high doses of NSAIDs and aspirin should be avoided from 2 days before until 2 days after pemetrexed use, and NSAIDs that have longer half-lives, such as piroxicam, should be avoided from 5 days before until 2 days after pemetrexed.

Analgesics. Enteric-coated *aspirin* 325 mg given orally every 6 hours for a total of 9 doses before pemetrexed, did not affect the pharmacokinetic profile of pemetrexed in an interaction study; the authors considered no dose adjustment necessary when moderate doses of aspirin were given with pemetrexed. However, this result could not be extrapolated to high-dose aspirin regimens, as the interaction might be dependent on salicylate concentrations. In contrast, oral *ibuprofen* 400 mg every 6 hours for a total of 9 doses before pemetrexed significantly reduced systemic pemetrexed clearance. Despite an increase in pemetrexed exposure, no increase in toxicity was seen. Dose adjustments were not considered necessary in patients with normal renal function (defined as creatinine clearance of 80 mL/minute or greater). However, in patients with pre-existing reduced pemetrexed clearance due to renal impairment, giving ibuprofen may result in further increases in pemetrexed exposure; the authors advised caution when using these 2 drugs together in patients with a creatinine clearance of less than 80 mL/minute.[1] For licensed drug information regarding the use of aspirin and NSAIDs with pemetrexed, see above.

1. Sweeney CJ, *et al.* Two drug interaction studies evaluating the pharmacokinetics and toxicity of pemetrexed when coadministered with aspirin or ibuprofen in patients with advanced cancer. *Clin Cancer Res* 2006; **12:** 536–42.

Pharmacokinetics

Pemetrexed has a plasma elimination half-life of 3.5 hours in patients with normal renal function. *In-vitro* data indicate that pemetrexed is about 81% bound to plasma proteins. It undergoes limited hepatic metabolism, and about 70 to 90% of a dose is eliminated unchanged in the urine within 24 hours.

Uses and Administration

Pemetrexed is primarily a thymidylate synthase inhibitor like raltitrexed (p.766), but it also inhibits other folate-dependent enzymes involved in purine synthesis such as dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. It is used as second-line monotherapy or first-line with cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer (p.668). It is also used with cisplatin in the first-line treatment of unresectable malignant pleural mesothelioma (p.669).

Pemetrexed is given as the disodium heptahydrate but doses are expressed in terms of the base: pemetrexed disodium heptahydrate 1.4 g is equivalent to about 1 g of pemetrexed. A dose of pemetrexed 500 mg/m^2 is given by intravenous infusion over 10 minutes. The dose may be repeated in 21-day cycles, and should be adjusted according to toxicity. In combination therapy, cisplatin is given about 30 minutes after the end of pemetrexed infusion.

Pre-treatment with oral dexamethasone 4 mg twice daily for 3 days is recommended, starting the day before pemetrexed. At least 5 doses of oral folic acid (350 micrograms to 1 mg) should be taken during the 7 days before the first dose of pemetrexed; dosing should continue throughout pemetrexed therapy, and for 21 days after the last pemetrexed dose. Patients should also receive an intramuscular injection of vitamin B_{12} 1 mg in the week before the first pemetrexed dose, and once every 3 cycles thereafter; subsequent injections may be given on the same day as pemetrexed.

Pemetrexed is under investigation as an antifolate antimetabolite in the treatment of colon, pancreatic, breast, and head and neck cancer.

◊ References.

1. Smit EF, *et al.* Alimta (pemetrexed disodium) as second-line treatment of non-small-cell lung cancer: a phase II study. *Ann Oncol* 2003; **14:** 455–60.
2. Vogelzang NJ, *et al.* Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; **21:** 2636–44.
3. Hanna N, *et al.* Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; **22:** 1589–97.
4. Hochster HS. The role of pemetrexed in the treatment of gastrointestinal malignancy. *Clin Colorectal Cancer* 2004; **4:** 190–5.
5. Hazarika M, *et al.* Pemetrexed in malignant pleural mesothelioma. *Clin Cancer Res* 2005; **11:** 982–92.
6. Puto K, Garey JS. Pemetrexed therapy for malignant pleural mesothelioma. *Ann Pharmacother* 2005; **39:** 678–83.
7. Rollins KD, Lindley C. Pemetrexed: a multitargeted antifolate. *Clin Ther* 2005; **27:** 1343–82.
8. Martin M. Clinical experience with pemetrexed in breast cancer. *Semin Oncol* 2006; **33** (suppl 2): S15–S18.
9. Anonymous. Can pemetrexed help in malignant mesothelioma? *Drug Ther Bull* 2006; **44:** 77–80.
10. Dundar Y, *et al.* Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. *Health Technol Assess* 2007; **11:** 1–90.
11. Green J, *et al.* Pemetrexed disodium in combination with cisplatin versus other cytotoxic agents or supportive care for the treatment of malignant pleural mesothelioma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 24/08/07).
12. Longo-Sorbello GS, *et al.* Role of pemetrexed in non-small cell lung cancer. *Cancer Invest* 2007; **25:** 59–66.

Administration in renal impairment. A pharmacokinetic study[1] found that pemetrexed clearance decreased with declining renal function. Although systemic exposure increased in these patients, this was not associated with an increase in drug-related dose-limiting toxicities for patients with a GFR of 40 mL/minute or more and receiving vitamin supplementation (folic acid and vitamin B_{12} supplementation appears to reduce toxicity without altering pemetrexed pharmacokinetics). Patients with a GFR of 80 mL/minute or more tolerated a dose of pemetrexed 600 mg/m^2, given intravenously every 3 weeks, whereas patients with a GFR of 40 to 79 mL/minute tolerated 500 mg/m^2 every 3 weeks. One patient with a GFR of 19 mL/minute died as a result of treatment-related toxicity and accrual into this group was stopped. As a result, no data were available for patients with a GFR below 40 mL/minute.

Licensed product information states that no dose adjustment is necessary in patients with a creatinine clearance (CC) of 45 mL/minute or more. Use in patients with a CC of less than 45 mL/minute is not recommended due to lack of data. Caution is advised when giving pemetrexed with NSAIDs in patients whose CC is less than 80 mL/minute (see Interactions, above).

1. Mita AC, *et al.* Phase I and pharmacokinetic study of pemetrexed administered every 3 weeks to advanced cancer patients with normal and impaired renal function. *J Clin Oncol* 2006; **24:** 552–62.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alimta; ***Austral.:*** Alimta; ***Belg.:*** Alimta; ***Canad.:*** Alimta; ***Chile:*** Alimta; Elimta†; ***Cz.:*** Alimta; ***Denm.:*** Alimta; ***Fin.:*** Alimta; ***Fr.:*** Alimta; ***Ger.:*** Alimta; ***Gr.:*** Alimta; ***Hong Kong:*** Alimta; ***Hung.:*** Alimta; ***Irl.:*** Alimta; ***Israel:*** Alimta; ***Ital.:*** Alimta; ***Malaysia:*** Alimta; ***Neth.:*** Alimta; ***Norw.:*** Alimta; ***NZ:*** Alimta; ***Pol.:*** Alimta; ***Rus.:*** Alimta (Алимта); ***Singapore:*** Alimta; ***Spain:*** Alimta; ***Swed.:*** Alimta; ***Switz.:*** Alimta; ***Thai.:*** Alimta; ***Turk.:*** Alimta; ***UK:*** Alimta; ***USA:*** Alimta.

Pemtumomab

Profile

Pemtumomab is a radiolabelled monoclonal antibody of murine origin that binds to muc-1, an epithelial cell surface protein on tumour cells. It has been investigated for the treatment of various cancers, including ovarian and gastric cancers, but results have been disappointing.