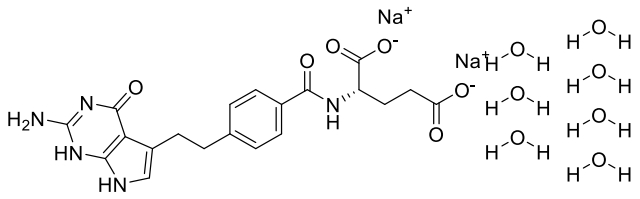
Product data sheet

MedKoo Cat#: 100710 Name: Pemetrexed disodium heptahydrate CAS#: 357166-29-1 (sodium hydrate) Chemical Formula: $C_{20}H_{33}N_5Na_2O_{13}$ Molecular Weight: 597.49	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
Pemtrexed disodium is the disodium salt of a synthetic pyrimidine-based antifolate. Pemetrexed binds to and inhibits the enzyme thymidylate synthase (TS) which catalyses the methylation of 2'-deoxyuridine-5'-monophosphate (dUMP) to 2'-deoxythymidine-5'-monophosphate (dTMP), an essential precursor in DNA synthesis.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
H2O	100.0	167.4

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.67 mL	8.37 mL	16.74 mL
5 mM	0.33 mL	1.67 mL	3.35 mL
10 mM	0.17 mL	0.84 mL	1.67 mL
50 mM	0.03 mL	0.17 mL	0.33 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Schaer DA, Geeganage S, Amaladas N, Lu ZH, Rasmussen ER, Sonyi A, Chin D, Capen A, Li Y, Meyer CM, Jones BD, Huang X, Luo S, Carpenito C, Roth KD, Nikolayev A, Tan B, Brahmachary M, Chodavarapu K, Dorsey FC, Manro JR, Doman TN, Donoho GP, Surguladze D, Hall GE, Kalos M, Novosiadly RD. The Folate Pathway Inhibitor Pemetrexed Pleiotropically Enhances Effects of Cancer Immunotherapy. Clin Cancer Res. 2019 Dec 1;25(23):7175-7188. doi: 10.1158/1078-0432.CCR-19-0433. Epub 2019 Aug 13. PMID: 31409612.
2. Okimoto T, Kotani H, Iida Y, Koyanagi A, Tanino R, Tsubata Y, Isobe T, Harada M. Pemetrexed sensitizes human lung cancer cells to cytotoxic immune cells. Cancer Sci. 2020 Jun;111(6):1910-1920. doi: 10.1111/cas.14401. Epub 2020 Apr 22. PMID: 32232903; PMCID: PMC7293070.

In vivo study

1. Schaer DA, Geeganage S, Amaladas N, Lu ZH, Rasmussen ER, Sonyi A, Chin D, Capen A, Li Y, Meyer CM, Jones BD, Huang X, Luo S, Carpenito C, Roth KD, Nikolayev A, Tan B, Brahmachary M, Chodavarapu K, Dorsey FC, Manro JR, Doman TN, Donoho GP, Surguladze D, Hall GE, Kalos M, Novosiadly RD. The Folate Pathway Inhibitor Pemetrexed Pleiotropically Enhances Effects of Cancer Immunotherapy. Clin Cancer Res. 2019 Dec 1;25(23):7175-7188. doi: 10.1158/1078-0432.CCR-19-0433. Epub 2019 Aug 13. PMID: 31409612.

2. Müller C, Schibli R, Krenning EP, de Jong M. Pemetrexed improves tumor selectivity of 111In-DTPA-folate in mice with folate receptor-positive ovarian cancer. J Nucl Med. 2008 Apr;49(4):623-9. doi: 10.2967/jnumed.107.047704. Epub 2008 Mar 14. PMID: 18344429.

7. Bioactivity

Biological target:

Pemtrexed disodium is the disodium salt of a synthetic pyrimidine-based antifolate that binds to and inhibits the enzyme thymidylate synthase (TS).

In vitro activity

In this study, the effects of PEM (pemetrexed) on the sensitivity of human NSCLC cells to two different types of cytotoxic immune cells were examined. The expression of NK receptor ligands, including MICA/B and ULBP1/2/5/6, on PC9 and A549 cells after PEM treatment were exmained. The results showed that although ULBP2/5/6 expression on both cell lines was upregulated by PEM treatment, PEM treatment significantly increased the expression of ULBP2/5/6 on PC9 cells; the increased expression of ULBP2/5/6 on A549 cells was not significant (Figure 5A and B). Because the antibody against ULBP2/5/6 was unable to discriminate among ULBP molecules, quantitative RT‐PCR (RT‐qPCR) was performed and found that PEM treatment mainly increased the mRNA expression of ULBP2/5/6 in PC9 and A549 cells (Figure 5C). In addition, given that PEM can induce senescence in lung cancer cells 13 and that NK receptor ligands on senescent cells can be targets in immunosurveillance, 20 senescence in PEM‐treated cancer cell lines was next examined. On confocal imaging, PEM treatment increased the expression of SA β‐gal (Figure 5D). In addition, PEM treatment increased the expression of p21 in A549 cells (Figure 5E) and the production of IL‐6 by PC9 cells and IL‐8 by A549 cells (Figure 5F). The production of IL‐8 by PC9 cells was slightly but significantly decreased by PEM treatment. The expression of SA β‐gal, growth arrest and production of inflammatory cytokines are features of senescent cells; these results suggest that PEM can increase the expression of NK receptor ligands, ULBP, in association with the induction of senescence, and increase the sensitivity to NK cells.

Reference: Cancer Sci. 2020 Jun;111(6):1910-1920. https://pubmed.ncbi.nlm.nih.gov/32232903/

In vivo activity

To characterize the effects of pemetrexed on intratumor immune response, initial experiments were performed in immunocompetent syngeneic mouse tumor models. To meet the research objective, the models had to meet 2 prerequisites: (i) demonstrate sensitivity to pemetrexed and (ii) responsiveness to PD(L)1 blockade. MC38 tumors were responsive to pemetrexed at 50 and 100 mg/kg (% tumor growth inhibition of 30% and 52%, respectively; Fig. 1A). Tumors collected after 14 days of pemetrexed therapy were analyzed for changes in immune cell frequencies using flow cytometry. These analyses revealed that pemetrexed increased the frequency of total intratumoral leukocytes (live CD45+cells) at both doses, with a trend towards an increased percentage of total CD3+and cycling (Ki67+) CD8+cells, particularly at 50 mg/kg (Fig. 1B–E). Molecular analysis of tumor samples using a custom-made immune profiling QuantiGene Plex (QGP) gene expression panel revealed that treatment with pemetrexed at 50 and 100 mg/kg promoted a T-cell inflamed phenotype, exemplified by upregulation of T-cell activation-associated genes including Pdcd1, Cd8b, Prf1, and Gzma (Fig. 1G). Beyond these changes, one of the genes most significantly modulated by pemetrexed treatment was Vegfc, which encodes vascular endothelial growth factor C (VEGF-C), a key regulator of lymphangiogenesis. Nos2, which encodes inducible nitric oxide synthase, is produced by myeloid-derived suppressor cells (MDSC) and DCs, was downregulated at both dose levels, suggesting that pemetrexed could potentially negatively impact myeloid cell subsets (Fig. 1G). Collectively, these results suggest that pemetrexed influences the functionality rather than frequency of myeloid cells.

Reference: Clin Cancer Res. 2019 Dec 1;25(23):7175-7188. https://pubmed.ncbi.nlm.nih.gov/31409612/