

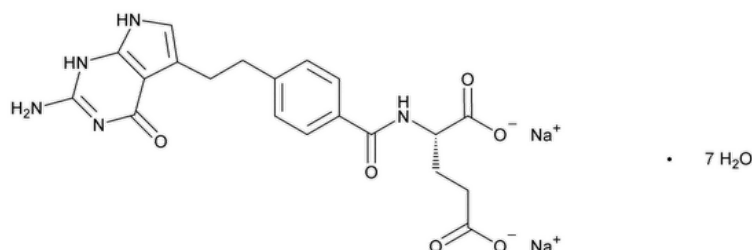
Status: Currently Official on 16-Feb-2025
 Official Date: Official as of 07-Aug-2024
 Document Type: USP Monographs
 DocId: GUID-74EEB2EB-AE83-4A3B-BDAE-40BDB0493B7B_7_en-US
 DOI: https://doi.org/10.31003/USPNF_M1125_07_01
 DOI Ref: 5gd7o

© 2025 USPC
 Do not distribute

Pemetrexed Disodium

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-pemetrexed-disodium-20240830.

Change to read:



$C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$ 597.49

L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate;

Disodium N-[p-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamate heptahydrate CAS RN[®]: 357166-29-1;

▲UNII: 9T47E40M16.▲ (RB 7-Aug-2024)

$C_{20}H_{19}N_5Na_2O_6$ 471.38

Anhydrous CAS RN[®]: 150399-23-8; ▲UNII: 2PKU919BA9.▲ (RB 7-Aug-2024)

$C_{20}H_{21}N_5O_6$ 427.42

Pemetrexed (free acid) CAS RN[®]: 137281-23-3; ▲UNII: 04Q9AIZ7NO.

$C_{20}H_{19}N_5Na_2O_6 \cdot 2.5H_2O$ 516.42

Hemipentahydrate CAS RN[®]: 357166-30-4; UNII: F4GSH45R4C.▲ (RB 7-Aug-2024)

DEFINITION

Pemetrexed Disodium contains NLT 97.5% and NMT 102.0% of pemetrexed disodium ($C_{20}H_{19}N_5Na_2O_6$), calculated on the anhydrous and solvent-free basis.

[CAUTION—Handle pemetrexed disodium with great care as it alters genetic material and may be irritating to the eyes and skin.]

IDENTIFICATION

- **A. SPECTROSCOPIC IDENTIFICATION TESTS (197), Infrared Spectroscopy:** 197A or 197K
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Enantiomeric Purity* test.
- **C. IDENTIFICATION TESTS—GENERAL (191), Chemical Identification Tests, Sodium**

ASSAY

PROCEDURE

Buffer: 0.17% (v/v) [glacial acetic acid](#) in [water](#). Adjust with a 50% [sodium hydroxide](#) solution to a pH of 5.3 ± 0.1 .

Mobile phase: [Acetonitrile](#) and *Buffer* (11:89)

Standard solution: 0.15 mg/mL of [USP Pemetrexed Disodium RS](#) in [water](#)

Sample solution: 0.15 mg/mL of Pemetrexed Disodium in [water](#)

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 285 nm

Column: 4.6-mm × 7.5-cm; 3.5-μm packing [L7](#)

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–1.5

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of pemetrexed disodium ($C_{20}H_{19}N_5Na_2O_6$) in the portion of Pemetrexed Disodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of [USP Pemetrexed Disodium RS](#) in the *Standard solution* (mg/mL)

C_U = concentration of Pemetrexed Disodium in the *Sample solution* (mg/mL)

Acceptance criteria: 97.5%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• ORGANIC IMPURITIES

Buffer: 1.45 g/L of [ammonium formate](#) in [water](#). Adjust with [formic acid](#) to a pH of 3.5 ± 0.1 .

Solution A: [Acetonitrile](#) and *Buffer* (5:95)

Solution B: [Acetonitrile](#) and *Buffer* (30:70)

Mobile phase: See [Table 1](#). [NOTE—After each injection, re-equilibrate the chromatographic system at the initial condition for a minimum of 13 min.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
45	0	100
47	100	0

System suitability stock solution: Prepare 3 mg/mL of [USP Pemetrexed Disodium RS](#) in [0.1 N sodium hydroxide](#). Heat this solution at 70° for 40 min.

[NOTE—The preparation degrades pemetrexed and generates the pemetrexed *R*-dimer and pemetrexed *S*-dimer as follows:

Pemetrexed *R*-dimer: (2*S*,2'*S*)-2,2'-{[(*R*)-2,2'-Diamino-4,4',6-trioxo-1,4,4',6,7,7'-hexahydro-1'*H*,5*H*-5,6'-bipyrrolo[2,3-*d*]pyrimidine-5,5'-diyl]bis(ethylenebenzene-4,1-diylcarbonylimino)}diglutamic acid.

Pemetrexed *S*-dimer: (2*S*,2'*S*)-2,2'-{[(*S*)-2,2'-Diamino-4,4',6-trioxo-1,4,4',6,7,7'-hexahydro-1'*H*,5*H*-5,6'-bipyrrolo[2,3-*d*]pyrimidine-5,5'-diyl]bis(ethylenebenzene-4,1-diylcarbonylimino)}diglutamic acid.]

System suitability solution: Transfer 1 mL of the *System suitability stock solution* to a 10-mL volumetric flask and dilute with [water](#) to volume.

Sensitivity solution: 0.1 µg/mL of [USP Pemetrexed Disodium RS](#) in [water](#)

Sample solution: 0.2 mg/mL of Pemetrexed Disodium in [water](#). Do not sonicate.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing [L7](#)

Autosampler temperature: 2°–8°

Flow rate: 1 mL/min