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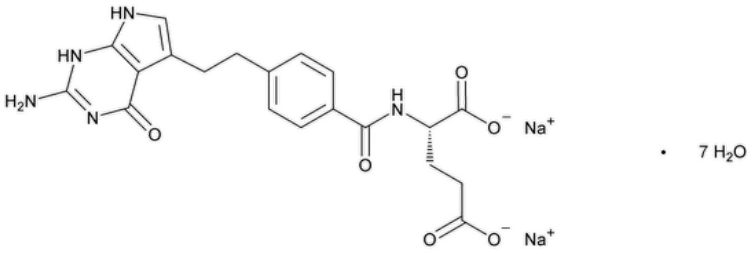
Pemetrexed Disodium

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-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate;

Disodium *N*-{*p*-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate heptahydrate CAS RN®: 357166-29-1; ▲UNII: 9T47E4OM16.▲ (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.

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

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[NOTE—The relative retention times for the pemetrexed *R*-dimer and pemetrexed *S*-dimer peaks are 0.87 and 0.88, respectively.]

Suitability requirements

Peak-to-valley ratio: The ratio of the height of the pemetrexed *R*-dimer peak to the height of the valley between the pemetrexed *R*-dimer and pemetrexed *S*-dimer is NLT 1.5, *System suitability solution*.

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Pemetrexed Disodium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak area of each impurity from the *Sample solution*

r_T = total peak areas from the *Sample solution*

Acceptance criteria: See *Table 2*. Disregard any peak less than 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
N-Methyl pemetrexed[a]	0.82	0.15
Pemetrexed glutamide[b]	0.90	0.15
Pemetrexed	1.0	—
Any individual unspecified impurity	—	0.10
Total impurities	—	0.60

[a] {4-[2-(2-Amino-1-methyl-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid.

[b] {4-[2-(2-Amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-4-L-glutamyl-L-glutamic acid.

• **ENANTIOMERIC PURITY**

Buffer: Dissolve 8 g of anhydrous beta cyclodextrin in 1 L of water. Add 15 mL of triethylamine to this solution and mix. Add about 6 mL of phosphoric acid and adjust with additional phosphoric acid to a pH of 6.0.

Mobile phase: Acetonitrile and *Buffer* (5:95)

Standard solution: 0.24 mg/mL of USP Pemetrexed Disodium RS in water

Sensitivity solution: 0.12 µg/mL of USP Pemetrexed Disodium RS in water from the *Standard solution*

Sample solution: 0.24 mg/mL of Pemetrexed Disodium in water

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 2°–8°

Column: 40°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

[NOTE—USP Pemetrexed Disodium RS contains a small amount of pemetrexed enantiomer disodium (disodium *N*-{*p*-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-D-glutamate). The relative retention times for pemetrexed enantiomer and pemetrexed are about 0.94 and 1.0, respectively.]

Suitability requirements

Peak-to-valley ratio: The ratio of the height of the pemetrexed enantiomer peak to the height of the valley between the pemetrexed enantiomer and pemetrexed is NLT 5.0, *Standard solution*

Signal-to-noise ratio: NLT 10 for the pemetrexed peak, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of pemetrexed enantiomer in the portion of Pemetrexed Disodium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak area of pemetrexed enantiomer from the *Sample solution*

r_T = total peak areas of pemetrexed enantiomer and pemetrexed from the *Sample solution*

Acceptance criteria: NMT 0.3%

SPECIFIC TESTS

Change to read:

• **WATER DETERMINATION** ⟨921⟩, *Method I*, *Method Ia* or *Method Ic*:

▲**For heptahydrate form:**▲ (RB 7-Aug-2024) 19.5%–22.1%

▲**For hemipentahydrate form:** 8.0%–10.5%▲ (RB 7-Aug-2024)

• **pH** ⟨791⟩

Sample: 56 mg/mL in water

Acceptance criteria: 7.5–8.4

• **BACTERIAL ENDOTOXINS TEST** ⟨85⟩**:** It contains less than 0.17 USP Endotoxin Units/mg of pemetrexed.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature.

Add the following:

▲• **LABELING:** Label to indicate where it is hemipentahydrate form.▲ (RB 7-Aug-2024)

Change to read:

• **USP REFERENCE STANDARDS** ⟨11⟩

▲▲ (RB 7-Aug-2024)

USP Pemetrexed Disodium RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
PEMETREXED DISODIUM	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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