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Pemetrexed for Injection

DEFINITION

Pemetrexed for Injection is a sterile, lyophilized mixture of pemetrexed disodium and suitable added substances. It contains NLT 90.0% and NMT 110.0% of the labeled amount of pemetrexed ($C_{20}H_{21}N_5O_6$).

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

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.*
- **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**

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

Mobile phase: Acetonitrile and *Buffer* (11:89)

Standard solution: 0.14 mg/mL of USP Pemetrexed Disodium RS in water

Sample solution: Nominally equivalent to 0.1 mg/mL of pemetrexed in water, prepared from a composite of at least three vials of Pemetrexed for Injection

Chromatographic system

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

Mode: LC

Detector: UV 285 nm or diode array. [Note—Use a diode array detector to perform *Identification B*.]

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: NMT 2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of pemetrexed ($C_{20}H_{21}N_5O_6$) in the portion of Pemetrexed for Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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 = nominal concentration of pemetrexed in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of pemetrexed, 427.42

M_{r2} = molecular weight of pemetrexed disodium (anhydrous), ▲471.38▲ (ERR 1-May-2018)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Uniformity of Dosage Units ⟨905⟩, *Weight Variation*:** Meets the requirements

IMPURITIES

• **Organic Impurities**

Buffer: 0.17% (v/v) glacial acetic acid in water. Adjust with a 50% sodium hydroxide solution to a pH of 5.5.

Solution A: Acetonitrile and *Buffer* (3:97)

Solution B: Acetonitrile and *Buffer* (12.5:87.5)

Mobile phase: See *Table 1*. [Note—After each injection, re-equilibrate the chromatographic system at the initial condition for a minimum of 8 min.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
40	0	100
45	0	100
47	100	0

System suitability stock solution: 2.8 mg/mL of USP Pemetrexed Disodium RS prepared as follows. Transfer USP Pemetrexed Disodium RS to a suitable volumetric flask and add a 3% hydrogen peroxide solution equivalent to 10% of the final volume. Dilute with water to volume. Mix and heat this solution at 75° for 2–5 h and allow it to come to room temperature. [Note—The solution preparation forms ketopemetrexed, pemetrexed *R*-dimer, and pemetrexed *S*-dimer. 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 5 mL of the *System suitability stock solution* to a 50-mL volumetric flask and dilute with water to volume.

Sensitivity solution: 0.14 µg/mL of USP Pemetrexed Disodium RS in water

Sample solution: Nominally equivalent to 0.2 mg/mL of pemetrexed in water, prepared from 1 vial of Pemetrexed for Injection

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L7

Temperatures

Autosampler: 2°–8°

Column: 35°

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 0.67 and 0.71, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the pemetrexed *R*-dimer and pemetrexed *S*-dimer peaks, *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 for Injection taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

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

r_T = total peak areas from the *Sample solution*

F = relative response factor for each individual impurity (see *Table 2*)

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

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ketopemetrexed[a]	0.31	0.61	0.60
Pemetrexed	1.0	—	—
Any individual unspecified impurity	—	1.0	0.24
Total Impurities	—	—	1.30

[a] (4-{2-[(*RS*)-2-Amino-4,6-dioxo-4,5,6,7-tetrahydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]ethyl}benzoyl)-L-glutamic acid.

SPECIFIC TESTS

- **Bacterial Endotoxins Test ⟨85⟩:** NMT 0.17 USP Endotoxin Units/mg of pemetrexed
- **Sterility Tests ⟨71⟩:** Meets the requirements
- **Particulate Matter in Injections ⟨788⟩:** Meets the requirements for small-volume injections
- **pH ⟨791⟩**
  Sample: A constituted solution prepared as directed in the labeling
  Acceptance criteria: 6.6–7.8
- **Other Requirements:** Meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve as described in *Packaging and Storage Requirements ⟨659⟩, Injection Packaging, Sterile solids packaging*. Store at controlled room temperature.
- **USP Reference Standards ⟨11⟩**
  USP Endotoxin RS
  USP Pemetrexed Disodium RS

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

Topic/Question	Contact	Expert Committee
PEMETREXED FOR INJECTION	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

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