Pemetrexed Disodium

Type of Posting	Notice of Intent to Revise
Posting Date	29-Jan-2021
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 3

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 3 Expert Committee intends to revise the Pemetrexed Disodium monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the following sections:

1. *Chemical Information*: include hemipentahydrate form.
2. *Water Determination*: include the limit of the hemipentahydrate form.
3. *Labeling*: include the hemipentahydrate form.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

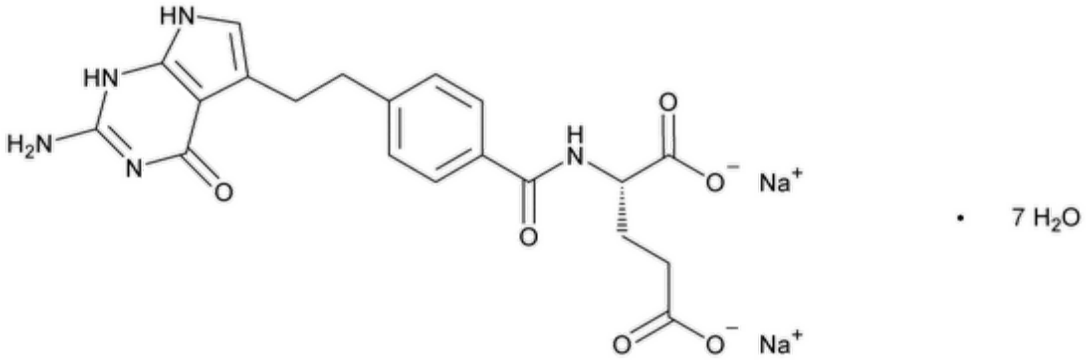
Should you have any questions, please contact Devarshi Narendra Thaker, Scientific Liaison (404-448-8945 or devarshinarendra.t@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Pemetrexed Disodium

Change to read:



Click image to enlarge

$C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$ 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 [357166-29-1]; ▲UNII: 9T47E4OM16. ▲ (TBD)

$C_{20}H_{19}N_5Na_2O_6$ 471.38
Anhydrous [150399-23-8]; ▲UNII: 2PKU919BA9. ▲ (TBD)

$C_{20}H_{21}N_5O_6$ 427.42
Pemetrexed (free acid) [137281-23-3]; ▲UNII: 04Q9AIZ7NO.

$C_{20}H_{19}N_5Na_2O_6 \cdot 2.5\ H_2O$ 516.42
Hemipentahydrate [357166-30-4]; UNII: F4GSH45R4C. ▲ (TBD)

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:▲ (TBD) 19.5%–22.1%

▲For hemipentahydrate form: 8.0%–10.5%▲ (TBD)

- **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.▲ (TBD)

Change to read:

- **USP Reference Standards** ⟨11⟩

▲▲ (TBD)

USP Pemetrexed Disodium RS

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Not Applicable

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