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Gemcitabine for Injection

DEFINITION

Gemcitabine for Injection contains an amount of gemcitabine hydrochloride equivalent to NLT 95% and NMT 105% of the labeled amount of gemcitabine ($C_9H_{11}F_2N_3O_4$).

[**Caution—**Gemcitabine Hydrochloride is a potent cytotoxic agent. Great care should be taken to prevent inhaling particles and exposing the skin to it.]

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: 197U**

  Medium: 0.14 M phosphate buffer with a pH of 2.5 prepared as follows. Add 13.8 g of monobasic sodium phosphate and 2.5 mL of phosphoric acid to 1 L of water.

  Sample solution: 16 µg/mL of gemcitabine in *Medium*

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

ASSAY

- **Procedure**

  Mobile phase: 13.8 g of monobasic sodium phosphate and 2.5 mL of phosphoric acid in 1 L of water. [Note—The pH of this solution is 2.4–2.6.]

  System suitability solution: Transfer 10 mg of gemcitabine hydrochloride to a small vial, add 4 mL of 168 mg/mL of potassium hydroxide in methanol, cap tightly, and sonicate. Heat at 55° for 6–16 h, allow to cool, and transfer the contents to a 100-mL volumetric flask with successive washes of 1% phosphoric acid. Dilute with 1% (v/v) phosphoric acid to volume. [Note—This solution contains about 0.02 mg/mL of gemcitabine α-anomer.]

  Standard solution: 0.1 mg/mL of USP Gemcitabine Hydrochloride RS in water

  Sample solution: Equivalent to 0.1 mg/mL of gemcitabine in water from Gemcitabine for Injection prepared as follows. Reconstitute a suitable number of vials with an appropriate amount of water, based on the labeled amount of gemcitabine.

  Chromatographic system

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

  Mode: LC

  Detector: UV 275 nm

  Column: 4.6-mm × 25-cm; 5-µm packing L7

  Flow rate: 1.2 mL/min

  Injection volume: 20 µL

  System suitability

  Samples: *System suitability solution* and *Standard solution*

  [Note—The relative retention times for gemcitabine α-anomer and gemcitabine are about 0.5 and 1.0, respectively.]

  Suitability requirements

  Resolution: NLT 8.0 between gemcitabine α-anomer and gemcitabine, *System suitability solution*

  Tailing factor: NMT 1.5 for the gemcitabine peak, *System suitability solution*

  Relative standard deviation: NMT 1.0%, *Standard solution*

  Analysis

  Samples: *Standard solution* and *Sample solution*

  Calculate the percentage of the labeled amount of gemcitabine ($C_9H_{11}F_2N_3O_4$) in the portion of Gemcitabine 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 Gemcitabine Hydrochloride RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of gemcitabine, 263.20

M_{r2} = molecular weight of gemcitabine hydrochloride, 299.66

Acceptance criteria: 95%–105%

PERFORMANCE TESTS

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

IMPURITIES

Change to read:

• **Organic Impurities**

System suitability solution and **Chromatographic system:** Proceed as directed in the *Assay*.

Solution A: Use the *Mobile phase* as directed in the *Assay*.

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	97	3
8	97	3
13	50	50
20	50	50
25	97	3

Standard solution: 2 µg/mL each of USP Gemcitabine Hydrochloride RS and USP Cytosine RS in water

Sample solution: Equivalent to 2 mg/mL of gemcitabine in water prepared by reconstituting the vial with an appropriate amount of water, based on the labeled amount of gemcitabine

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 8.0 between gemcitabine α-anomer and gemcitabine, *System suitability solution*

Tailing factor: NMT 1.5 for the gemcitabine peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of cytosine, expressed as a percentage of gemcitabine hydrochloride ($C_9H_{11}F_2N_3O_4 \cdot HCl$), in the portion of Gemcitabine 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 of cytosine from the *Sample solution*

r_S = peak response of cytosine from the *Standard solution*

C_S = concentration of USP Cytosine RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of gemcitabine, 263.20

M_{r2} = molecular weight of gemcitabine hydrochloride, 299.66

Calculate the percentage of each impurity other than cytosine, expressed as a percentage of gemcitabine hydrochloride ($C_9H_{11}F_2N_3O_4 \cdot HCl$), in the portion of Gemcitabine 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 for each impurity from the *Sample solution*

r_S = peak response of gemcitabine from the *Standard solution*

C_S = concentration of USP Gemcitabine Hydrochloride RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of gemcitabine, 263.20

M_{r2} = molecular weight of gemcitabine hydrochloride, 299.66

Acceptance criteria: See *Table 2*. Disregard any impurity peaks less than 0.02%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Cytosine▲ ▲ (ERR 1-Aug-2021)	0.4	0.1
Gemcitabine α-anomer[a]	0.7	0.1
Gemcitabine	1.0	—
Any individual unspecified impurity	—	0.2
Total impurities	—	0.3

[a] 2'-Deoxy-2',2'-difluorocytidine (α-isomer).

SPECIFIC TESTS

- **Particulate Matter in Injections ⟨788⟩:** It meets the requirements for small-volume injections.
- **pH ⟨791⟩**

  Sample solution: 40 mg/mL of gemcitabine in 0.9% sodium chloride solution

  Acceptance criteria: 2.7–3.3
- **Clarity of Solution**

  Sample solution: Dissolve it in the solvent and at the concentration recommended in the labeling.

  Analysis: Determine the turbidity by ratio turbidimetry within 15 min of reconstitution, corrected for a diluent blank (see *Nephelometry and Turbidimetry ⟨855⟩*).

  Acceptance criteria: NMT 10 NTU
- **Bacterial Endotoxins Test ⟨85⟩:** It contains NMT 0.05 USP Endotoxin Unit/mg of gemcitabine.
- **Sterility Tests ⟨71⟩:** It meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined, Membrane Filtration*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve as described in *Packaging and Storage Requirements ⟨659⟩, Injection Packaging, Packaging for constitution*. Store at controlled room temperature. Do not refrigerate after reconstitution.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Cytosine RS

▲Cytosine.▲ (ERR 1-Aug-2021)

$C_4H_5N_3O$ 111.10

USP Gemcitabine Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
GEMCITABINE FOR INJECTION	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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