

Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-57A6B896-F4EE-4150-9979-B262DC91A91D_4_en-US
DOI: https://doi.org/10.31003/USPNF_M33315_04_01
DOI Ref: 1hg07

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Fludarabine Phosphate for Injection

DEFINITION

Fludarabine Phosphate for Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of fludarabine phosphate ($C_{10}H_{13}FN_5O_7P$).

[CAUTION—Fludarabine Phosphate is potentially cytotoxic. Great care should be taken to prevent inhaling particles and exposing the skin to it.]

IDENTIFICATION

Change to read:

- **A.** [▲ SPECTROSCOPIC IDENTIFICATION TESTS \(197\), Ultraviolet-Visible Spectroscopy: 197U](#)▲ (CN 1-MAY-2020)

Sample solution: 27 µg/mL in 0.1 M hydrochloric acid

Acceptance criteria: Meets the requirements

- **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

Solution A: 10 mM of monobasic potassium phosphate

Mobile phase: Methanol and *Solution A* (6:94)

Standard solution: 0.02 mg/mL of [USP Fludarabine Phosphate RS](#) in *Mobile phase*

Sample stock solution: 1 mg/mL of fludarabine phosphate in *Mobile phase* prepared as follows. Inject 2.0 mL of *Mobile phase* into each of five vials of Fludarabine Phosphate for Injection. Transfer the contents of the vials into a 250-mL volumetric flask, using *Mobile phase* rinses. Dilute with *Mobile phase* to volume.

Sample solution: 0.02 mg/mL of fludarabine phosphate in *Mobile phase*, from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.0 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fludarabine phosphate ($C_{10}H_{13}FN_5O_7P$) in the portion of Fludarabine Phosphate for Injection 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 Fludarabine Phosphate RS](#) in the *Standard solution* (mg/mL)

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

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

- [UNIFORMITY OF DOSAGE UNITS \(905\)](#): Meets the requirements

IMPURITIES

- **ORGANIC IMPURITIES PROCEDURE 1: EARLY-ELUTING IMPURITIES**

Mobile phase, Standard solution, and Chromatographic system: Proceed as directed in the Assay.

System suitability solution: 10 mg of Fludarabine Phosphate in 10 mL of 0.1 N hydrochloric acid. Heat the solution at 80° in a water bath for 15 min.

Sensitivity solution: 0.5 µg/mL of [USP Fludarabine Phosphate RS](#) in *Mobile phase*, from the *Standard solution*

Sample solution: Use *Sample stock solution* as directed in the Assay.

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between the iso-ara-guanine monophosphate and isoguanine peaks, *System suitability solution*

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

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each early-eluting impurity in the portion of Fludarabine Phosphate for Injection taken:

$$\text{Result} = (r_U/r_S) \times (1/F_1) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of fludarabine phosphate from the *Sample solution*

F_1 = relative response factor for each individual impurity (see [Table 1](#))

Acceptance criteria: See [Table 1](#).

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Iso-ara-guanine-monophosphate	0.26	0.25	1.0
Isoguanine	0.34	0.40	0.2
3',5'-Diphosphate analog ^a	0.42	—	—
Any other individual degradation product	<1.0	1.0	0.2
Fludarabine phosphate	1.0	—	—

^a This is a process impurity and controlled in the drug substance monograph.

• ORGANIC IMPURITIES PROCEDURE 2: LATE-ELUTING IMPURITIES

Solvent A: 10 mM monobasic potassium phosphate

Mobile phase: Methanol and *Solvent A* (1:4)

Standard solution and Chromatographic system: Proceed as directed in the Assay.

Sensitivity solution and Sample solution: Prepare as directed in *Organic Impurities Procedure 1: Early-Eluting Impurities*.

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

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

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each late-eluting impurity in the portion of Fludarabine Phosphate for Injection taken:

$$\text{Result} = (r_U/r_S) \times (1/F_2) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of fludarabine phosphate from the *Sample solution*