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Gadodiamide Injection

DEFINITION

Gadodiamide Injection is a sterile solution of Gadodiamide in Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of gadodiamide ($C_{16}H_{26}GdN_5O_8$). It may contain stabilizers and buffers. Gadodiamide Injection intended for intravascular use contains no antimicrobial agents.

IDENTIFICATION

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

  Wavelength range: 240–300 nm

  Solution: 57 mg/mL of gadodiamide in water

- **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: Dissolve 14 mL of triethylamine and 5.7 mL of glacial acetic acid in 1 L of water.

  Mobile phase: Transfer 50 mL of *Solution A* to a 1-L volumetric flask. Add 900 mL of water. Adjust with 1 N acetic acid or 1 N sodium hydroxide to a pH between 6.5 and 7.0. Dilute with water to volume.

  Postcolumn reagent: Dissolve 325 mg of urea in a solution of 60 mg of arsenazo III acid in 550 mL of water previously acidified with 3.2 mL of nitric acid. Pass the solution through a filter of 0.45-µm pore size, wash the filter with 400 mL of water, and dilute with water to 1000 mL.

  Standard solution: 0.18 mg/mL of USP Gadodiamide RS

  Sample solution: Equivalent to a nominal concentration of 0.18 mg/mL of gadodiamide from Injection

  Chromatographic system

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

  Mode: LC

  Detector: Vis 658 nm

  Column: 4.6-mm × 25-cm; 5-µm base-deactivated packing L1. [Note—A second pump mixes the *Mobile phase* with the *Postcolumn reagent* prior to detection via a T-junction.]

  Column temperature: 20°–35° (system maintained at constant temperature)

  Flow rate: 1.5 mL/min

  Injection volume: 10 µL

  System suitability

  Sample: *Standard solution*

  Suitability requirements

  Relative standard deviation: NMT 2.5%

  Analysis

  Samples: *Standard solution* and *Sample solution*

  Calculate the percentage of gadodiamide ($C_{16}H_{26}GdN_5O_8$) in the portion of Injection taken:

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

  r_U = peak response of gadodiamide from the *Sample solution*

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

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

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

  Acceptance criteria: 90.0%–110.0%

IMPURITIES

- **Organic Impurities**

  Solution A, Mobile phase, and **Chromatographic system:** Prepare as directed in the *Assay*.

Postcolumn reagent: Dissolve 120 mg of arsenazo III acid in 400 mL of water previously acidified with 6.3 mL of nitric acid. Add 650 mg of urea, and mix to dissolve. Pass the solution through a filter of 0.45-µm pore size, washing the filter with 600 mL of water. Dilute with water to 1000 mL.

System suitability solution: 10 µg/mL of USP Gadodiamide Related Compound A RS, 10 µg/mL of USP Gadodiamide Related Compound B RS, and 2 mg/mL of USP Gadodiamide RS in an aqueous solution

Sample solution: Equivalent to a nominal concentration of 2 mg/mL of gadodiamide from Injection

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.0 between the gadodiamide and gadodiamide related compound A peaks; NLT 1.5 between gadodiamide related compound A and gadodiamide related compound B peaks

Relative standard deviation: NMT 10%

[NOTE—The tail of the gadodiamide peak may contain a small shoulder due to an isomer. The area of the shoulder should be included in the gadodiamide peak area.]

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the volume of Injection taken:

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

r_U = peak response of each impurity

r_T = sum of all peaks having a percentage greater than 0.10%

Acceptance criteria: See *Table 1*.

Table 1

Name	Acceptance Criteria, NMT (%)
Gadodiamide related compound A	2.0
Gadodiamide related compound B	2.0
Any other individual impurity	0.2
Total impurities (sum of all impurities other than gadodiamide related compounds A and B)	0.5

SPECIFIC TESTS

Change to read:

• ▲Osmolality and Osmolarity ⟨785⟩

Osmolality: ▲(Official 1-Aug-2022) 650–1000 mOsmol/kg

• pH ⟨791⟩**:** 5.5–7.0

• Bacterial Endotoxins Test ⟨85⟩**:** NMT 0.029 USP Endotoxin Unit/mg of gadodiamide

• Injections and Implanted Drug Products ⟨1⟩**:** Meets the requirements

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in single-dose or multiple-dose plastic or Type I glass containers. Store at controlled room temperature, protected from light. Do not freeze.

• **Labeling:** Label containers of Injection to direct the user to discard any unused portion. Label it to state its routes of administration. Label it to indicate “serious injury can occur if given by intrathecal route.”

• **USP Reference Standards ⟨11⟩**

USP Gadodiamide RS

USP Gadodiamide Related Compound A RS

Gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide.

$C_{15}H_{22}GdN_4NaO_9$ 582.60

USP Gadodiamide Related Compound B RS

Gadolinium disodium diethylenetriamine pentaacetic acid.

$C_{14}H_{18}GdN_3Na_2O_{10}$ 591.54

Topic/Question	Contact	Expert Committee
GADODIAMIDE INJECTION	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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