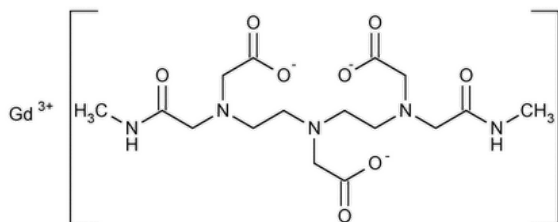


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# Gadodiamide



$C_{16}H_{26}GdN_5O_8$  573.66

[5,8-Bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato(3-)]gadolinium.

[N,N-Bis[2-[(carboxymethyl)](methylcarbamoyl)methyl]-amino]ethyl]glycinato(3-)]gadolinium CAS RN®: 131410-48-5; UNII: 84F6U3J2R6.

» Gadodiamide contains not less than 97.0 percent and not more than 103.0 percent of  $C_{16}H_{26}GdN_5O_8$ , calculated on the anhydrous basis.

**Packaging and storage**—Preserve in tight containers, and store at controlled room temperature.

## 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

## Clarity of solution—

### Reference solution—

REFERENCE SOLUTION A— Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours. [CAUTION—Hydrazine sulfate is highly toxic. Avoid skin contact.]

REFERENCE SOLUTION B— Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25 mL of water, and mix to dissolve.

PRIMARY OPALESCENT MIXTURE— To the flask containing *Reference solution B*, add 25.0 mL of *Reference solution A*, mix, and allow to stand for 24 hours. [NOTE—The suspension is stable for 2 months. Mix before use, and do not use if it adheres to the container.]

OPALESCENCE STANDARD— Dilute 15.0 mL of the *Primary opalescent mixture* with water to 1000.0 mL, and mix. This standard must be freshly prepared.

PROCEDURE— Transfer 10.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 40 mL of this solution (*Reference solution*) to a 50-mL color comparison tube.

**Test solution**—Transfer an accurately weighed quantity of Gadodiamide, equivalent to about 15 g of anhydrous gadodiamide, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 40 mL of this solution to a 50-mL color comparison tube.

**Blank**—Transfer 40 mL of water to a 50-mL color comparison tube.

**Procedure**—Five minutes after preparation of the *Reference solution*, view the *Reference solution*, the *Test solution*, and the *Blank* against a black background: the *Test solution* is not more opalescent than the *Reference solution*. [NOTE—If the *Test solution* is more opalescent than the *Reference solution*, heat the *Test solution* to 60° to 70° for 2 to 3 minutes, cool to room temperature, and view again.]

## Identification—

### Change to read:

**A:** ▲ [Spectroscopic Identification Tests \(197\)](#), [Infrared Spectroscopy: 197K](#) ▲ (CN 1-May-2020) ·

**B:** It exhibits the maximum absorption at the relevant wavelength specified when tested as directed under the test for *Content of gadolinium*.

**MICROBIAL ENUMERATION TESTS (61)** and **TESTS FOR SPECIFIED MICROORGANISMS (62)**—The total aerobic microbial count is not more than 500 cfu per g. The total combined molds and yeasts count is not more than 50 cfu per g.

**BACTERIAL ENDOTOXINS TEST (85)**—It contains not more than 3.5 USP Endotoxin Units per g.

**WATER DETERMINATION, Method I (921)**: between 3.0% and 14.0%.

## Limit of free gadolinium (III)—

**Arsenazo III indicator**—Transfer 150 mg of arsenazo III disodium to a 100-mL volumetric flask, dilute with water to volume, and mix.

**MES buffer**—Transfer 48.8 g of 2-(N-morpholino)ethanesulfonic acid (MES) to a 250-mL volumetric flask. Add 180 mL of water and 25 mL of 2 N sodium hydroxide, and mix. Adjust with 2 N sodium hydroxide to a pH of 6.0, dilute with water to volume, and mix.

**Edetate disodium titrant**—Pipet 100 mL of 0.02 M edetate disodium VS into a 1000-mL volumetric flask, dilute with water to volume, and mix.

**Test solution**—Transfer about 1 g of Gadodiamide, accurately weighed, to a 125-mL conical flask, add 25 mL of *MES buffer* and 0.1 mL of *Arsenazo III indicator*, and mix. A turquoise color indicates the presence of excess gadolinium.

**Procedure**—Titrate the *Test solution* with *Edetate disodium titrant* to a violet-pink endpoint. Each mL of *Edetate disodium titrant* is equivalent to 0.3145 mg of excess gadolinium: not more than 0.3% of free gadolinium is found, calculated on the anhydrous basis.

#### Limit of free diethylenetriamine pentaacetic acid bismethylamide—

**Arsenazo III indicator and MES buffer**—Proceed as directed for *Limit of free gadolinium (III)*.

**0.002 M gadolinium (III) titrant**—Transfer 18.6 g of gadolinium chloride to a 1000-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix. Pipet 10 mL of this solution into a conical flask, and add 25 mL of *MES buffer* and 0.1 mL of *Arsenazo III indicator*. Titrate with 0.02 M edetate disodium VS to a violet-pink endpoint, and determine the molarity. Pipet 40 mL of this solution into a 1000-mL volumetric flask, dilute with water to volume, and mix.

**Blank solution**—Transfer 25 mL of *MES buffer* and 0.1 mL of *Arsenazo III indicator* into a suitable flask, and mix.

**Test solution**—Transfer about 1 g of Gadodiamide, accurately weighed, to a 125-mL conical flask. Add 25 mL of *MES buffer* and 0.1 mL of *Arsenazo III indicator*, and mix. A violet-pink color indicates the presence of excess diethylenetriamine pentaacetic acid bismethylamide.

**Procedure**—Concomitantly titrate the *Blank solution* and the *Test solution* with 0.002 M gadolinium (III) titrant to a turquoise endpoint. Calculate the percentage of free diethylenetriamine pentaacetic acid bismethylamide in the portion of Gadodiamide taken by the formula:

$$100(V_U - V_B)M_T(419.43)/W$$

in which  $V_U$  is the volume of gadolinium (III) in the *Test solution*;  $V_B$  is the volume of gadolinium (III) in the *Blank solution*;  $M_T$  is the molarity of the 0.002 M gadolinium (III) titrant; 419.43 is the molecular weight of diethylenetriamine pentaacetic acid bismethylamide; and  $W$  is the weight, in mg, of Gadodiamide taken to prepare the *Test solution*: not more than 0.7% of diethylenetriamine pentaacetic acid bismethylamide is found, calculated on the anhydrous basis.

#### Limit of methylamine—

**Borate buffer**—Transfer 12.4 g of boric acid to a 500-mL volumetric flask, and suspend it in 300 mL of water. Add 100 mL of 1 N potassium hydroxide, and mix. Adjust with 1 N potassium hydroxide to a pH of 10.0, dilute with water to volume, and mix. Store in a closed plastic container.

**OPA reagent**—Transfer 100 mg of o-phthalaldehyde to an amber bottle, add 3 mL of methanol, and mix. Add 220 mL of *Borate buffer* and 0.1 mL of mercaptoethanol, and mix. [NOTE—This solution must be freshly prepared.]

**Standard solutions**—Transfer about 110 mg of methylamine hydrochloride, accurately weighed, to a 500-mL volumetric flask, and dilute with water to volume to obtain a solution having a concentration of about 100 µg of methylamine per mL. Pipet 1, 5, 10, and 20 mL of this solution into separate 100-mL volumetric flasks, dilute the contents of each flask with water to volume, and mix.

**Test solution**—Transfer about 1.5 g of Gadodiamide, accurately weighed, to a 10-mL volumetric flask, dilute with water to volume, and mix.

**Procedure**—Proceed as follows for each of the *Standard solutions*. Add 3.0 mL of *OPA reagent*, mix, and within 1 minute measure the absorbance at 335 nm. Compare to a blank consisting of 3.0 mL of water and 3.0 mL of *OPA reagent*. Plot a calibration curve of absorbance versus standard concentration, in µg of methylamine per mL. Mix 3.0 mL of the *Test solution* with 3.0 mL of *OPA reagent*, and proceed as directed above. [NOTE—If the absorbance obtained with the *Test solution* exceeds the absorbance of the highest *Standard solution*, perform an additional quantitative dilution of the *Test solution*, and repeat the analysis.] Determine the concentration, in µg per mL, of methylamine in the *Test solution* by interpolation from the calibration curve. Calculate the amount of methylamine in the portion of Gadodiamide taken: not more than 0.05% of methylamine is found.

#### Limit of acetone, ethyl alcohol, and isopropyl alcohol—

**Internal standard solution**—Transfer about 500 mg of methyl ethyl ketone to a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix.

**Stock solution**—Transfer about 1000 mg each of acetone, ethyl alcohol, and isopropyl alcohol, accurately weighed, to a 100-mL volumetric flask, dilute with water to volume, and mix.

**Diluted stock solution A**—Pipet 5 mL of the *Stock solution* into a 100-mL volumetric flask, dilute with water to volume, and mix.

**Diluted stock solution B**—Pipet 10 mL of the *Stock solution* into a 100-mL volumetric flask, dilute with water to volume, and mix.

**System suitability solution**—Pipet 10 mL of the *Internal standard solution* and 15 mL of *Diluted stock solution A* into a 100-mL volumetric flask, dilute with water to volume, and mix.

**Test solution 1**—Pipet 10 mL of the *Internal standard solution* into a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 7.0 mL of this solution to a 10-mL gas chromatographic headspace vial, add about 1300 mg of Gadodiamide, accurately weighed, and cap immediately. Swirl to dissolve.

**Test solution 2**—Pipet 10 mL of the *Internal standard solution* and 2.5 mL of *Diluted stock solution A* into a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 7.0 mL of this solution to a 10-mL gas chromatographic headspace vial, add about 1300 mg of Gadodiamide, accurately weighed, and cap immediately. Swirl to dissolve.

**Test solution 3**—Pipet 10 mL of the *Internal standard solution* and 15 mL of *Diluted stock solution A* into a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 7.0 mL of this solution to a 10-mL gas chromatographic headspace vial, add about 1300 mg of Gadodiamide, accurately weighed, and cap immediately. Swirl to dissolve.