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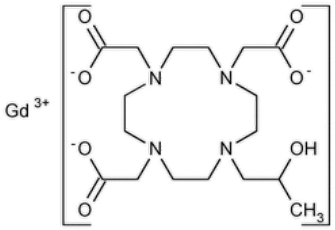
Gadoteridol

Change to read:



$C_{17}H_{29}GdN_4O_7$ ▲558.69▲ (CN 1-Aug-2024)

Gadolinium, [10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)-N^1,N^4,N^7,N^{10},O^1,O^4,O^7,O^{10}]-.

(±)-[10-(2-Hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)]gadolinium CAS RN®: 120066-54-8; UNII: 0199MV609F.

» Gadoteridol contains not less than 97.0 percent and not more than 101.0 percent of $C_{17}H_{29}GdN_4O_7$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

Change to read:

USP Reference standards ⟨11⟩—

USP Gadoteridol RS

USP Gadoteridol Related Compound A RS

▲2,2',2"-(10-(2-Hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid.▲ (CN 1-Aug-2024)

$C_{17}H_{32}N_4O_7$ 404.46

USP Gadoteridol Related Compound B RS

▲Gadolinium(III) 2,2',2"-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate dihydrate.

$C_{14}H_{23}GdN_4O_6 \cdot 2H_2O$ 536.64▲ (CN 1-Aug-2024)

USP Gadoteridol Related Compound C RS

▲2,2'-(11-Oxo-1,4,7,10-tetraazabicyclo[8.2.2]tetradecane-4,7-diyl)diacetic acid.

$C_{14}H_{24}N_4O_5$ 328.37▲ (CN 1-Aug-2024)

Identification—

A: *Spectroscopic Identification Tests* ⟨197⟩, *Infrared Spectroscopy: 197K*

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

Solution: 10 mg per mL.

Medium: water.

Water Determination, *Method I* ⟨921⟩: not more than 15%.

Limit of gadoteridol related compound A—

Buffer solution—Dissolve 0.60 g of tromethamine and 3.72 g of edetate disodium in 3 L of water, adjust with 5 N sodium hydroxide to a pH of 7.0, dilute with water to 4 L, and mix. Filter, and chill between 5° and 8°.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution,* acetonitrile, and tetrahydrofuran (98.8:1.0:0.2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Cupric acetate solution—Transfer 3.99 g of cupric acetate and 12.11 g of tromethamine to a 2-L volumetric flask, dissolve in 1500 mL of water, adjust with glacial acetic acid to a pH of 7.0, dilute with water to volume, and mix. Filter, and chill between 5° and 8°.

Standard stock solution—Dissolve an accurately weighed quantity of USP Gadoteridol Related Compound A RS in *Buffer solution*, and dilute quantitatively and stepwise with *Buffer solution* to obtain a solution having a known concentration of about 6 µg per mL.

Standard solution—Just prior to injection onto the column, dilute 1.0 mL of the *Standard stock solution* with 1.0 mL of *Cupric acetate solution* to obtain a solution having a known concentration of about 3 µg of USP Gadoteridol Related Compound A RS per mL. [Note—The copper–gadoteridol related compound A complex is stable for at least 2 hours, if maintained at about 5°.]

Test solution—Transfer about 30 mg of Gadoteridol, accurately weighed, to a test tube, add 1.0 mL of *Buffer solution*, and mix on a vortex mixer to dissolve. Add 1.0 mL of *Cupric acetate solution*, and mix. Immediately inject the solution into the chromatograph. [Note—The copper–gadoteridol related compound A complex is stable for at least 2 hours, if maintained at about 5°.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.0-mm × 15-cm column that contains packing L47. The flow rate is about 2 mL per minute. Chromatograph the *Standard solution*, and record the peak

responses as directed for *Procedure:* the relative retention times are about 1.0 for gadoteridol related compound A and 2.0 for copper-edetate; the resolution, *R,* between gadoteridol related compound A and copper-edetate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of gadoteridol related compound A in the portion of Gadoteridol taken by the formula:

$$100(C/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Gadoteridol Related Compound A RS in the *Standard stock solution; W* is the weight, in mg, of Gadoteridol taken to prepare the *Test solution;* and r_U and r_S are the gadoteridol related compound A peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.01% is found, calculated on the anhydrous basis.

Limit of free gadolinium (III)—

Buffer solution, *Mobile phase*, *Diluent*, *Standard stock solution 1*, *Standard stock solution 2*, *Standard solution*, and *Chromatographic system*—Proceed as directed for *Chromatographic purity*, *Test 1*.

Test solution—Transfer about 60 mg of Gadoteridol, accurately weighed, to a vial, add 2.0 mL of *Diluent*, and mix. Immediately place the vial in a bath maintained at about 5°.

Procedure—Proceed as directed for *Procedure* under *Chromatographic purity*, *Test 1*. Calculate the percentage of free gadolinium (III) in the portion of Gadoteridol taken by the formula:

$$200(157.25/334.38)(C/W)(r_U/r_S)$$

in which 157.25 is the molecular weight of gadolinium and 334.38 is the molecular weight of gadolinium acetate; C is the concentration, in mg per mL, of gadolinium acetate, calculated on the anhydrous basis, in the *Standard solution; W* is the weight, in mg, of Gadoteridol taken to prepare the *Test solution;* and r_U and r_S are the free gadolinium (III) peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.01% is found.

Limit of regioisomer—Using the chromatogram of the *Assay preparation* as obtained in the *Assay*, calculate the percentage of regioisomer peak at a relative retention time of about 1.2 in relation to that of the gadoteridol peak by the formula:

$$100r_R/(r_R + r_G)$$

in which r_R and r_G are the regioisomer and gadoteridol peak responses, respectively, in the *Assay preparation:* not more than 2.5% is found.

Chromatographic purity—

TEST 1: GADOLINIUM-CONTAINING IMPURITIES—

Buffer solution—Dissolve 10.2 g of monobasic potassium phosphate, 0.165 g of dibasic potassium phosphate, and 1.76 g of edetate disodium in 3000 mL of water, and filter.

Mobile phase—Prepare a degassed mixture of *Buffer solution* and acetonitrile (98:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Transfer 3.40 g of monobasic potassium phosphate, 4.21 g of dibasic potassium phosphate, and 0.584 g of edetate disodium to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Standard stock solution 1—Quantitatively dissolve an accurately weighed quantity of gadolinium (Gd III) acetate in water to obtain a solution having a concentration of about 0.4 mg per mL.

Standard stock solution 2—Prepare a solution of USP Gadoteridol Related Compound B RS in water to obtain a solution having a known concentration of about 0.6 mg per mL.

Standard solution—Transfer 1.0 mL of *Standard stock solution 1* and 2.0 mL of *Standard stock solution 2* to a 10-mL volumetric flask, and dilute with *Diluent* to volume. Transfer 1.0 mL of this solution to a vial, add 3.0 mL of *Diluent*, and mix.

Test solution—Transfer about 60 mg of Gadoteridol, accurately weighed, to a vial, add 2.0 mL of *Diluent*, and mix. Immediately place the vial in a bath maintained at about 5°.

Chromatographic system (see *Chromatography* ⟨621⟩)— The liquid chromatograph is equipped with a fluorometric detector operating at an excitation wavelength of 275 nm and an emission wavelength of 314 nm, and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for free gadolinium (III), 1.6 for 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid gadolinium sodium salt (gadoteridol related compound D), and 2.2 for gadoteridol related compound B; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Allow the *Test solution* to elute for not less than 1.3 times the retention time of the gadoteridol peak. Calculate the percentage of gadoteridol related compound D in the portion of Gadoteridol taken by the formula:

$$200(C/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Gadoteridol Related Compound B RS, calculated on the anhydrous basis, in the *Standard solution; W* is the weight, in mg, of Gadoteridol taken to prepare the *Test solution;* and r_U and r_S are the gadoteridol related

compound D peak responses obtained from the *Test solution* and the *Standard solution*, respectively. Calculate the percentage of gadoteridol related compound B in the portion of Gadoteridol taken by the formula:

$$200(C/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Gadoteridol Related Compound B RS, calculated on the anhydrous basis, in the *Standard solution*; W is the weight, in mg, of Gadoteridol taken to prepare the *Test solution;* and r_U and r_S are the gadoteridol related compound B peak responses obtained from the *Test solution* and *Standard solution*, respectively. Calculate the percentage of any other impurity in the portion of Gadoteridol taken by the formula:

$$200(C/W)(r_i/r_S)$$

in which r_i is the peak response of any other impurity obtained from the *Test solution;* and r_S is the peak response for gadoteridol related compound B obtained from the *Standard solution:* not more than 0.1% of any individual impurity is found, and not more than 0.3% of gadolinium-containing impurities is found.

Test 2 (nongadolinium-containing impurities)—

50 mM Ammonium phosphate buffer—Dissolve 17.25 g of monobasic ammonium phosphate in 3000 mL of water, and filter.

pH 5.0 Buffer—Transfer 2000 mL of *50 mM Ammonium phosphate buffer* to a 2-L beaker, and adjust with ammonium hydroxide to a pH of 5.0.

pH 7.0 Buffer—Transfer 1000 mL of *50 mM Ammonium phosphate buffer* to a 1-L beaker, and adjust with ammonium hydroxide to a pH of 7.0.

Mobile phase—Prepare a filtered and degassed mixture of *pH 5.0 buffer* and acetonitrile (87:13). Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Standard solution—Dissolve an accurately weighed quantity of USP Gadoteridol Related Compound C RS in *pH 7.0 Buffer* to obtain a solution having a known concentration of about 5 µg per mL.

System suitability solution—Prepare a solution in *pH 7.0 buffer* containing about 2 mg of USP Gadoteridol RS and 0.002 mg of USP Gadoteridol Related Compound C RS per mL.

Test solution—Transfer about 50 mg of Gadoteridol to a 25-mL volumetric flask, dissolve in and dilute with *pH 7.0 Buffer* to volume, and mix.

Chromatographic system (see Chromatography ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L18. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution*, and record the responses as directed for *Procedure:* the relative retention times are about 1.0 for gadoteridol, 1.2 for 1,4,7,10-tetraaza-1,4,7-tris-(carboxymethyl)-11-oxo-bicyclo [8.2.2] tetradecanium chloride (gadoteridol related compound F), 1.5 for 1,4,7,10-tetraaza-13-oxo-bicyclo [8.2.1] tridecane-4,7-diacetic acid (gadoteridol related compound E), and 1.7 for gadoteridol related compound C; and the resolution, R, between gadoteridol and gadoteridol related compound C is not less than 5. Chromatograph the *Standard solution* as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Allow the *Test solution* to elute for not less than twice the retention time of the gadoteridol peak. Calculate the percentage of gadoteridol related compound C in the portion of Gadoteridol taken by the formula:

$$2.5(C/W)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Gadoteridol Related Compound C RS in the *Standard solution*; W is the weight, in mg, of Gadoteridol taken to prepare the *Test solution;* and r_U and r_S are the peak responses for gadoteridol related compound C obtained from the *Test solution* and *Standard solution*, respectively. Calculate the percentages of gadoteridol related compound F and gadoteridol related compound E in the portion of Gadoteridol taken by the formula:

$$2.5(1/F)(C/W)(r_i/r_S)$$

in which F is the relative response factor for gadoteridol related compound F (0.68) or for gadoteridol related compound E (1.7); r_i is the peak response for gadoteridol related compound E or gadoteridol related compound F in the *Test solution;* and C, W, and r_S are as defined above. Calculate the percentage of any other impurity in the portion of Gadoteridol taken by the formula:

$$2.5(C/W)(r_i/r_S)$$

in which r_i is the response of any other impurity in the chromatogram of the *Test solution;* and C, W, and r_S are as defined above: not more than 0.1% of any other impurity is found, and the total of nongadolinium-containing impurities is not more than 0.3%, calculated on the anhydrous basis.

Other requirements—Where the label states that Gadoteridol is sterile, it meets the requirements for *Sterility Tests ⟨71⟩* and *Bacterial endotoxins* under *Gadoteridol Injection*. Where the label states that Gadoteridol must be subjected to further processing during the preparation of injectable dosage form, it meets the requirements for *Bacterial endotoxins* under *Gadoteridol Injection*.

Assay—

Buffer solution—Dissolve 10.2 g of monobasic potassium phosphate and 0.165 g of dibasic potassium phosphate in 3 L of water, and filter.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (98:2). Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Standard preparation—Dissolve an accurately weighed quantity of USP Gadoteridol RS in *Buffer solution* to obtain a solution having a known concentration of about 0.6 mg per mL.

Assay preparation—Transfer about 60 mg of Gadoteridol, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Buffer solution* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a fluorometric detector operating at an excitation wavelength of 275 nm and an emission wavelength of 314 nm, and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the gadoteridol peak and the peak with a relative retention time of about 1.2 is not less than 1.2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{17}H_{29}GdN_4O_7$ in the portion of Gadoteridol taken by the formula:

$$100C(r_U/r_S)$$

in which C is the concentration of USP Gadoteridol RS, in mg per mL, in the *Standard preparation;* and r_U and r_S are the gadoteridol peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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

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

Chromatographic Database Information: Chromatographic Database

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