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Cisplatin for Injection

DEFINITION

Cisplatin for Injection is a sterile, lyophilized mixture of Cisplatin, Mannitol, and Sodium Chloride. It contains NLT 90.0% and NMT 110.0% of the labeled amount of cisplatin ($Cl_2H_6N_2Pt$).

[**Caution—**Cisplatin is potentially cytotoxic. Great care should be taken in handling the powder and preparing solutions.]

IDENTIFICATION

Delete the following:

▲• **A. Thin-Layer Chromatography**

Solution A: 5.6 g of stannous chloride in 10 mL of hydrochloric acid. Stir for 5 min. [Note—It is not necessary that all of the solids dissolve.]

Solution B: 0.2 g of potassium iodide in 90 mL of water

Standard solution: 1.0 mg/mL of USP Cisplatin RS, 9 mg/mL of sodium chloride, and 10 mg/mL of D-mannitol in water

Sample solution: Nominally equivalent to 1.0 mg/mL of cisplatin by dissolving the contents of 1 container of Cisplatin for Injection in water, based on the label claim

Chromatographic system

(See *Chromatography ⟨621⟩, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 5 µL

Developing solvent system: Acetone and 1 N nitric acid (9:1)

Spray reagent A: Mix *Solution A* and *Solution B* together. Disregard any precipitate that is formed. Store in the dark. [Note—The solution is usable for at least 1 week.]

Spray reagent B: 20 mg/mL of potassium iodide in water

Analysis

Samples: *Standard solution* and *Sample solution*

Develop with *Developing solvent system*, in a suitable chromatographic chamber containing a filter paper lining and equilibrated for 30 min with the *Developing solvent system*, for a distance of about 8 cm from the origin, followed by air drying. Complete the drying by heating in a forced-air oven at about 100° for 1 min. Spray with *Spray reagent A*, heat in an oven at about 100° for 5 min, cool, and spray with *Spray reagent B* to bring out the full color of the spots.

Acceptance criteria: The principal spot from the *Sample solution* corresponds in appearance and R_F value to that produced by the *Standard solution*.▲ (USP 1-Dec-2021)

Add the following:

▲• **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Dec-2021)

• **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

Change to read:

• **Procedure**

Mobile phase: Ethyl acetate, methanol, dimethylformamide, and degassed water (25:16:5:5)

Standard solution: 1 mg/mL of USP Cisplatin RS in dimethylformamide. Use within 1 h.

Sample solution: Nominally 1.0 mg/mL of cisplatin in dimethylformamide, prepared as follows. Quantitatively dissolve 1 container of Cisplatin for Injection in dimethylformamide by sonicating for 5 min. Pass 5 mL of this solution through a suitable filter and collect the filtrate after discarding the first milliliters of the filtrate. Use within 1 h.

Chromatographic system

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

Mode: LC

Detector: UV 310 nm. ▲For *Identification A*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-Dec-2021)

Column: 4.0-mm × 30-cm; packing L8

Flow rate: 2.0 mL/min

Injection volume: 40 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 cisplatin ($Cl_2H_6N_2Pt$) in the portion of Cisplatin for Injection taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

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

IMPURITIES

Change to read:

• **Limit of ▲Aminotrichloroplatinum▲** (USP 1-Dec-2021)

Mobile phase: 0.4 g/L of ammonium sulfate in water. Adjust with 6 N ammonium hydroxide to a pH of 5.9.

Standard solution: 6 µg/mL of USP Potassium Trichloroammineplatinate RS in saline TS. Protect the solution from light. Use the solution within 4 h.

Sample solution: Nominally 0.5 mg/mL of cisplatin, prepared as follows. Quantitatively dissolve the contents of 1 container of Cisplatin for Injection in water. Protect the solution from light. Use the solution within 4 h.

Chromatographic system

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

Mode: LC

Detector: UV 209 nm

Column: 4.6-mm × 25-cm; packing L14

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for saline and ▲aminotrichloroplatinum▲ (USP 1-Dec-2021) are about 0.4 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between saline and ▲aminotrichloroplatinum▲ (USP 1-Dec-2021)

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲aminotrichloroplatinum▲ (USP 1-Dec-2021) in the portion of Cisplatin for Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak area of ▲aminotrichloroplatinum▲ (USP 1-Dec-2021) from the *Sample solution*

r_S = peak area of ▲aminotrichloroplatinum▲ (USP 1-Dec-2021) from the *Standard solution*

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

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

M_{r1} = molecular weight of ▲aminotrichloroplatinum, 318.47▲ (USP 1-Dec-2021)

M_{r2} = molecular weight of potassium trichloroammineplatinate, ▲357.56▲ (USP 1-Dec-2021)

Acceptance criteria: NMT 1.0%

Change to read:

• **Limit of Transplatin**

Mobile phase: 0.18 M monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.2.

Standard stock solution A: 0.05 mg/mL of USP Transplatin RS in saline TS. Dissolve by stirring by mechanical means for 30 min.

Standard stock solution B: Transfer 5 mL of *Standard stock solution A* to a 25-mL volumetric flask containing 12 mg of USP Cisplatin RS. Dilute with saline TS to volume, and stir by mechanical means for 30 min to dissolve.

System suitability stock solution: 0.05 mg/mL of USP Cisplatin RS in saline TS. Dissolve by stirring by mechanical means for 30 min.

System suitability solution: Transfer 10 mL each of *System suitability stock solution* and *Standard stock solution A* to a 50-mL volumetric flask. Add 5.0 mL of a 5 mg/mL solution of thiourea prepared fresh daily and 5.0 mL of 1 N hydrochloric acid, and dilute with saline TS to volume. Place 10 mL of this solution in a suitable serum vial, seal with a polytef-lined closure, and heat in a heating block at 60 ± 0.5° for 60 min. Remove and cool to room temperature.

Standard solution: Transfer 10 mL of *Standard stock solution B* to a 50-mL volumetric flask. Add 5.0 mL of a 5 mg/mL solution of thiourea prepared fresh daily and 5.0 mL of 1 N hydrochloric acid, and dilute with saline TS to volume. Place 10 mL of this solution in a suitable serum vial, seal with a polytef-lined closure, and heat in a heating block at 60 ± 0.5° for 60 min. Remove and cool to room temperature.

Sample stock solution: Nominally 0.5 mg/mL of cisplatin, prepared as follows. Dissolve the contents of 1 container of Cisplatin for Injection in water.

Sample solution: Transfer 10 mL of *Sample stock solution* to a 50-mL volumetric flask. Add 5.0 mL of a 5 mg/mL solution of thiourea prepared fresh daily and 5.0 mL of 1 N hydrochloric acid, and dilute with saline TS to volume. Place 10 mL of this solution in a suitable serum vial, seal with a polytef-lined closure, and heat in a heating block at 60 ± 0.5° for 60 min. Remove and cool to room temperature.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; packing L9

Column temperature: 45°

Flow rate: 2.0 mL/min

Injection volume: 20 µL

[Note—Condition the *Column* by pumping the *Mobile phase* at a flow rate of 2.0 mL/min for 30 min, then at 0.5 mL/min for 30 min, and then again at 2.0 mL/min for 30 min.]

System suitability

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

[Note—The retention time for derivatized transplatin is between 5.0 and 9.0 min; if it is not, modify the *Mobile phase* as necessary and recondition the *Column*. The relative retention times for derivatized cisplatin and derivatized transplatin are about 1.0 and 1.3, respectively.]

Suitability requirements

Resolution: NLT 1.7 between derivatized cisplatin and derivatized transplatin▲▲ (USP 1-Dec-2021), *System suitability solution*

Relative standard deviation: NMT 4.0% for derivatized transplatin▲▲ (USP 1-Dec-2021), *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of transplatin in the portion of Cisplatin for Injection taken:

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

r_U = peak area of derivatized transplatin from the *Sample solution*

r_S = peak area of derivatized transplatin from the *Standard solution*

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

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

Acceptance criteria: NMT 2.0%

SPECIFIC TESTS

• **pH** ⟨791⟩

Sample: Constituted as directed in the labeling, using Sterile Water for Injection

Acceptance criteria: 3.5–6.2

Change to read:

• **Bacterial Endotoxins Test** ⟨85⟩**:** ▲Meets the requirements▲ (USP 1-Dec-2021)

Change to read:

• **Sterility Tests** ⟨71⟩▲▲ (USP 1-Dec-2021) **:** Meets the requirements

• **Water Determination** ⟨921⟩, *Method I*

Sample: 1 container of Cisplatin for Injection

Extraction solvent: Anhydrous formamide

Analysis: Introduce 50 mL of *Extraction solvent* into the titration vessel, and titrate with the *Reagent* to the electrometric endpoint. Use the formamide thus dried to rinse a suitable glass syringe equipped with a 22-gauge needle, about 8 cm long. Add the rinse back to the titration vessel, and, if necessary, again titrate the vessel contents. Via the syringe, withdraw 5 mL of the formamide thus titrated, and, through the closure of the container, expel the contents into the container. Shake the container to obtain a solution. With the same syringe, withdraw all of the contents of the container, and transfer to the titration vessel. Titrate to the endpoint, adjusting the feeding speed control to the lowest setting, to avoid over-titration.

Acceptance criteria: NMT 2.0%

• **Constituted Solutions:** At the time of use, it meets the requirements for *Injections and Implanted Drug Products* ⟨1⟩*, Product Quality Tests Common to Parenteral Dosage Forms, Specific Tests, Completeness and clarity of solutions*.

• **Other Requirements:** It meets the requirements for *Labeling* ⟨7⟩*, Labels and Labeling for Injectable Products*.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve as described in *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging, Packaging for Constitution*. Protect from light.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Cisplatin RS		
USP Potassium Trichloroammineplatinate RS	Cl_3H_3KNPt	▲357.56▲ (USP 1-Dec-2021)
USP Transplatin RS	▲$Cl_2H_6N_2Pt$	300.05▲ (USP 1-Dec-2021)

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

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

Chromatographic Database Information: Chromatographic Database

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