Oxaliplatin Injection

DEFINITION

Oxaliplatin Injection is a sterile solution of Oxaliplatin in Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION** ⟨**197U**⟩
  Sample solution: 100 µg/mL
  Medium: 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

[NOTE—All HPLC autosampler vials should be made of polypropylene.]

- **PROCEDURE**
  Acidified water: Adjust with phosphoric acid to a pH of 3.0.
  Mobile phase: Acetonitrile and *Acidified water* (1:99)
  System suitability solution: 0.1 mg/mL of USP Oxaliplatin RS and 0.1 mg/mL of USP Oxaliplatin System Suitability RS in water. [NOTE—USP Oxaliplatin System Suitability RS is [*SP*-4-2-(1*R*-*trans*)]-(1,2-cyclohexanediamine-*N*,*N*′) dichloridoplatinum(II).]
  Standard solution: 0.1 mg/mL of USP Oxaliplatin RS in water
  Sample solution: 0.1 mg/mL of oxaliplatin in water, from the combined contents of NLT three vials of Injection
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 210 nm
  Column: 4.6-mm × 25-cm; 5-µm packing L1
  Column temperature: 40°
  Flow rate: 1.2 mL/min
  Injection volume: 20 µL
  System suitability
  Sample: *System suitability solution*
  [NOTE—The relative retention times for USP Oxaliplatin System Suitability RS and oxaliplatin are 0.9 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 2.0 between USP Oxaliplatin System Suitability RS and oxaliplatin
  Tailing factor: NMT 2.0 for the oxaliplatin peak
  Relative standard deviation: NMT 1.0% for the oxaliplatin peak
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$) in the portion of 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 Oxaliplatin RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of oxaliplatin in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

Change to read:

- **LIMIT OF OXALIC ACID**
  [NOTE—All HPLC autosampler vials should be made of polypropylene.]
  Solution A: Dissolve 1.36 g of monobasic potassium phosphate in 10 mL of 10% tetrabutylammonium hydroxide, dilute with water to 1 L, and adjust with phosphoric acid to a pH of 6.0.
  Mobile phase: Acetonitrile and *Solution A* (1:4)
  Standard solution: 35 µg/mL of USP Oxaliplatin Related Compound A RS in water. [NOTE—USP Oxaliplatin Related Compound A RS is available as dihydrate oxalic acid.]
  System suitability solution: 0.1 mg/mL of succinic acid in the *Standard solution*
  Sensitivity solution: 3.5 µg/mL of USP Oxaliplatin Related Compound A RS in water from the *Standard solution*
  Sample solution: Combined contents of NLT three vials of Injection
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 210 nm
  Column: 4.6-mm × 25-cm; 5-µm packing L1
  Column temperature: 40°
  Flow rate: 2 mL/min
  Injection volume: 10 µL
  System suitability
  Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*
  [NOTE—The relative retention times for succinic acid and oxalic acid are 0.8 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 2.0 between succinic acid and oxalic acid, *System suitability solution*
  Tailing factor: 0.5–2.0 for the oxalic acid peak, *System suitability solution*
  Signal-to-noise ratio: NLT 10, *Sensitivity solution*
  Relative standard deviation: NMT 3.0%, *Standard solution*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of each impurity in the portion of Injection taken:

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

r_U = peak response of oxalic acid from the *Sample solution*
r_S = peak response of oxalic acid from the *Standard solution*
C_S = concentration of USP Oxaliplatin Related Compound A RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of oxaliplatin in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of anhydrous oxalic acid, 90.03
M_{r2} = molecular weight of oxaliplatin related compound A, 126.07

  Acceptance criteria: NMT 0.6%
- **LIMIT OF (*SP*-4-2)-DIAQUA[(1*R*,2*R*)-CYCLOHEXANE-1,2-DIAMINE-*N*,*N*′]PLATINUM AND UNSPECIFIED IMPURITIES**
  [NOTE—All HPLC autosampler vials should be made of polypropylene.]

Solution A: Dissolve 1.36 g of monobasic potassium phosphate and 0.55 g of sodium heptanesulfonate in 1 L of water. Adjust with phosphoric acid to a pH of 3.0.
Solution B: Methanol and *Solution A* (19:81)
Solution C: Methanol and *Solution A* (50.5: 49.5)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	100	0
45.0	0	100
45.5	100	0
53.0	100	0

System suitability solution: 2 mg/mL of USP Oxaliplatin RS in 0.005 M sodium hydroxide. Allow this solution to stand at room temperature for at least 5 days. Transfer 5 mL of this solution into a 50-mL volumetric flask, and dilute with water to volume. [NOTE—The preparation of the *System suitability solution* forms (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum and diaquodiaminocyclohexaneplatinum dimer.]
Standard stock solution: Transfer a weighed quantity of USP Oxaliplatin Related Compound B RS into a suitable volumetric flask, add a volume of methanol equivalent to about 25% of the final volume, and sonicate for approximately 2 min to disperse the solids. Add a volume of 0.01 M nitric acid equivalent to about 65% of the final volume, and sonicate for approximately 30 min to dissolve. Allow to cool if necessary, and dilute with 0.01 M nitric acid to volume to obtain a solution with a concentration of 0.125 mg/mL.
Standard solution: 31.25 µg/mL of USP Oxaliplatin Related Compound B RS in 0.01 M nitric acid, from the *Standard stock solution*. [NOTE—USP Oxaliplatin Related Compound B RS is converted to (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum in the *Standard solution* preparation.]
Sample solution: Combined contents of NLT three vials of Injection
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 7.5-cm; 3-µm packing L1
Column temperature: 10°
Flow rate: 1 mL/min
Injection volume: 20 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 8.0 between the peaks of (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum and diaquodiaminocyclohexaneplatinum dimer, *System suitability solution*
Tailing factor: NMT 2.0 for the (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum peak, *System suitability solution*
Relative standard deviation: NMT 3.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum from the *Standard solution*
C_S = concentration of USP Oxaliplatin Related Compound B RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of oxaliplatin in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum, 345.30
M_{r2} = molecular weight of oxaliplatin related compound B, 433.28
F = relative response factor for each individual impurity (see *Table 2*)

Acceptance criteria
Individual impurities: See *Table 2*.
Total impurities: NMT 2.45%, from *Limit of oxalic acid* and *Limit of (SP-4-2)-Diaqua[(1R,2R)-cyclohexane-1,2-diamine-N,N′]platinum and Unspecified Impurities*

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
(*SP*-4-2)-Diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum	1.0	1.0	0.65
Diaquodiaminocyclohexaneplatinum dimer[a]	1.4	2.5	0.50
Any individual unspecified impurity	—	4.0	●0.2● (RB 1-Oct-2012)

[a] (*SP*-4-2)-Di-µ-oxobis[(1*R*,2*R*)-cyclohexane-1,2-diamine-k*N*,k*N*′]diplatinum.

SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** It contains NMT 1.0 USP Endotoxin Units/mg of oxaliplatin.
- **STERILITY TESTS ⟨71⟩:** It meets the requirements when tested as directed for *Membrane Filtration* in the *Test for Sterility of the Product to Be Examined*.
- **pH ⟨791⟩:** 4.0–7.0 using a polymer combination electrode
- **PARTICULATE MATTER IN INJECTIONS ⟨788⟩:** It meets the requirements for small-volume injections.
- **OTHER REQUIREMENTS:** It meets the requirements in *Injections* ⟨1⟩.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass, protected from light. Store at controlled room temperature. Do not freeze.
- **LABELING:** Label it to indicate that it is to be diluted with a 5% dextrose solution. Oxaliplatin Injection must not be diluted in sodium chloride solutions or in chloride-containing solutions.
- **USP REFERENCE STANDARDS ⟨11⟩**
  USP Endotoxin RS
  USP Oxaliplatin RS
  USP Oxaliplatin Related Compound A RS
  Oxalic acid dihydrate.

$C_2H_2O_4 \cdot 2H_2O$ 126.07

USP Oxaliplatin Related Compound B RS
[*SP*-4-2-(1*R*-*trans*)]-(1,2-Cyclohexanediamine-*N,N'*)
dinitratoplatinum(II).
$C_6H_{14}N_4O_6Pt$ 433.28

USP Oxaliplatin System Suitability RS
[*SP*-4-2-(1*R*-*trans*)]-(1,2-Cyclohexanediamine-*N,N'*)
dichloridoplatinum(II).
$C_6H_{14}Cl_2N_2Pt$ 380.17