Oxaliplatin for Injection

DEFINITION

Change to read:

Oxaliplatin for Injection is a sterile, lyophilized mixture of Oxaliplatin and Lactose Monohydrate. It contains NLT •90.0%• (RB 1-Oct-2010) and NMT •110.0%• (RB 1-Oct-2010) of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$).

IDENTIFICATION

- 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**

[NOTE—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Use polypropylene HPLC autosampler vials.]

Acidified water: Adjust water with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Acidified water* (1:99)

System suitability solution: 0.1 mg/mL each of USP Oxaliplatin RS and USP Oxaliplatin System Suitability RS in water. [NOTE—USP Oxaliplatin System Suitability RS is compound [*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: Constitute a suitable number of vials of Oxaliplatin for Injection with the appropriate amount of water to obtain a solution having a known concentration of about 0.1 mg/mL of oxaliplatin, based on the label claim.

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 size: 20 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for USP Oxaliplatin System Suitability RS and oxaliplatin are about 0.9 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.0 between the peaks of USP Oxaliplatin System Suitability RS and oxaliplatin, *System suitability solution*
Tailing factor: NMT 2.0 for the oxaliplatin peak, *System suitability solution*
Relative standard deviation: NMT 1.0%, *Standard solution*

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 Oxaliplatin for 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%• (RB 1-Oct-2010)

PERFORMANCE TESTS
- **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** Meets the requirements

IMPURITIES

Change to read:

- **LIMIT OF OXALIC ACID**

[NOTE—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Use polypropylene HPLC autosampler vials.]

Buffer: Add 1.36 g of potassium dihydrogen phosphate to 10 mL of 10% tetrabutylammonium hydroxide in water, and dilute with water to 1000 mL. Adjust with phosphoric acid to a pH of 6.0.

Mobile phase: Acetonitrile and *Buffer* (1:4)

Standard stock solution: 0.06 mg/mL of USP Oxaliplatin Related Compound A RS in water. [NOTE—USP Oxaliplatin Related Compound A RS is available as oxalic acid dihydrate.]

Standard solution: 15 µg/mL of USP Oxaliplatin Related Compound A RS in water, from the *Standard stock solution*

System suitability stock solution: 0.05 mg/mL of sodium nitrate in water

System suitability solution: 1.0 µg/mL of sodium nitrate and 15 µg/mL of oxaliplatin related compound A in water, from the *System suitability stock solution* and *Standard stock solution*, respectively

Sensitivity solution: Make a 1 to 10 dilution of the *Standard solution* in water

Sample solution: 2.0 mg/mL of oxaliplatin in water from Oxaliplatin for Injection

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 205 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 2 mL/min
Injection size: 20 µL

System suitability
Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*
[NOTE—The relative retention times for sodium nitrate and oxalic acid are about 0.6 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.0 between oxalic acid and sodium nitrate, *System suitability solution*
Relative standard deviation: NMT 3.0% for the oxalic acid peak, *Standard solution*
Sensitivity: The signal-to-noise ratio of the peak at approximately the same retention time as that in the *Standard solution* is NLT 10, *Sensitivity solution*.

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of oxalic acid in the portion of Oxaliplatin for 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 = concentration of oxaliplatin in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of anhydrous oxalic acid, 90.03
M_{r2} = molecular weight of USP Oxaliplatin Related Compound A RS, 126.07

Acceptance criteria: NMT ●0.5%● (RB 1-Oct-2010)

Change to read:

- **LIMIT OF (*SP*-4-2)-DIAQUA[(1*R*,2*R*)-CYCLOHEXANE-1,2-DIAMINE-*N*,*N*′]PLATINUM**

[NOTE—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Use polypropylene HPLC autosampler vials.]

Buffer: Dissolve 1.36 g of potassium dihydrogen phosphate and 1 g of sodium 1-heptanesufonate in 1 L of water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (1:4)

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. [NOTE—Sonicate if necessary.] 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 diaquodiaminocyclohexaneplatinum dimer and (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum.]

Standard solution: Transfer USP Oxaliplatin Related Compound B RS to a suitable volumetric flask, add 25% of the final volume of methanol, and sonicate for approximately 30 min to dissolve. Allow to cool if necessary, and dilute with water to volume to obtain a solution having a known concentration of about 0.0125 mg/mL. [NOTE—When preparing the solution, USP Oxaliplatin Related Compound B RS is converted to (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum.]

Sample solution: Use the *Sample solution* from the test for *Limit of Oxalic Acid*.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 2 mL/min
Injection size: 20 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum and diaquodiaminocyclohexaneplatinum dimer are about 1.0 and 1.5, respectively.]
Suitability requirements
Resolution: NLT 2.0 between (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum and diaquodiaminocyclohexaneplatinum dimer, *System suitability solution*
Relative standard deviation: NMT 3.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum in the portion of Oxaliplatin for 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 (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum 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 USP Oxaliplatin Related Compound B RS, 433.28

Acceptance criteria: NMT ●0.5%● (RB 1-Oct-2010)

Change to read:

- **LIMIT OF RELATED COMPOUND C AND UNSPECIFIED IMPURITIES**

[NOTE—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Use polypropylene HPLC autosampler vials.]

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard stock solution: 0.1 mg/mL each of USP Oxaliplatin RS and USP Oxaliplatin Related Compound C RS in water

Standard solution: 0.01 mg/mL each of USP Oxaliplatin RS and USP Oxaliplatin Related Compound C RS in water, from the *Standard stock solution*

System suitability stock solution: Dissolve USP Oxaliplatin System Suitability RS in methanol, and sonicate for approximately 10 min to obtain a solution having a concentration of 0.1 mg/mL.

System suitability solution: Transfer 10 mL each of the *Standard stock solution* and the *System suitability stock solution* into a 100-mL volumetric flask, and dilute with water to volume.

Sample solution: Use the *Sample solution* from the test for *Limit of Oxalic Acid*.

System suitability
Samples: *Standard solution* and *System suitability solution*
Suitability requirements
Resolution: NLT 2.0 between [*SP*-4-2-(1*R*-*trans*)]-(1,2-cyclohexanediamine-*N*,*N*′) dichloridoplatinum(II) and oxaliplatin, *System suitability solution*
Tailing factor: NMT 2.0 for the oxaliplatin peak, *System suitability solution*
Relative standard deviation: NMT 3.0% each for the oxaliplatin and oxaliplatin related compound C peaks, *Standard solution*.

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of oxaliplatin related compound C in the portion of Oxaliplatin for Injection taken:

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

r_U = peak response of oxaliplatin related compound C from the *Sample solution*

r_S = peak response of oxaliplatin related compound C from the *Standard solution*
C_S = concentration of USP Oxaliplatin Related Compound C RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of oxaliplatin in the *Sample solution* (mg/mL)

Calculate the percentage of each unspecified impurity in the portion of Oxaliplatin for Injection taken:

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

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of oxaliplatin 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: See *Table 1*.

[NOTE—*Total impurities* includes oxalic acid, (*SP*-4-2)-diaqua [(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum, oxaliplatin related compound C, and total unspecified impurities.]

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Oxaliplatin related compound C[a]	0.6	•0.3•(RB 1-Oct-2010)
[*SP*-4-2-(1*R-trans*)]-(1,2-Cyclohexanediamine-*N*,*N*′) dichloridoplatinum(II)[b]	0.8	—
Oxaliplatin	1.0	—
Any individual unspecified impurity	—	•0.2•(RB 1-Oct-2010)
		•(RB 1-Oct-2010)
Total impurities	—	•1.5•(RB 1-Oct-2010)

[a] [1*R-trans*-(1,2-Cyclohexanediamine-*N*,*N*′)]-*trans*-dihydroxido-[oxalato(2-)-*O*,*O*′]platinum(IV).
[b] The relative retention time of [*SP*-4-2-(1*R-trans*)]-(1,2-cyclohexanediamine-*N*,*N*′) dichloridoplatinum(II) has been included for system suitability purposes only.

SPECIFIC TESTS

Change to read:

- **pH** ⟨**791**⟩**:** 4.0–•7.0•(RB 1-Oct-2010) using a polymer combination electrode, determined in a solution constituted as directed in the labeling
- **PARTICULATE MATTER IN INJECTIONS** ⟨**788**⟩**:** It meets the requirements for small-volume injections.
- **CONSTITUTED SOLUTION:** At the time of use, it meets the requirements under *Injections* ⟨1⟩*, Constituted Solutions*.
- **BACTERIAL ENDOTOXINS TEST** ⟨**85**⟩**:** NMT 1.0 USP Endotoxin Unit/mg of oxaliplatin
- **STERILITY TESTS** ⟨**71**⟩**:** Meets the requirements

Change to read:

- **WATER DETERMINATION,** *Method 1*⟨**921**⟩**:** NMT •4.0%• (RB 1-Oct-2010)
- **OTHER REQUIREMENTS:** It meets the requirements under *Injections* ⟨1⟩.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in *Containers for Sterile Solids* as described under *Injections* ⟨1⟩. Store at controlled room temperature.
- **LABELING:** Label it to indicate that it is to be diluted with a suitable parenteral vehicle prior to intravenous infusion.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Endotoxin RS
  USP Oxaliplatin RS
  [*SP*-4-2-(1*R-trans*)]-(1,2-Cyclohexanediamine-*N*,*N*′) [ethanedioato(2-)-*O*,*O*′]platinum.
  $C_8H_{14}N_2O_4Pt$ 397.29
  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 Related Compound C RS
  [1*R-trans*-(1,2-Cyclohexanediamine-*N*,*N*′)]-*trans*-dihydroxido-[oxalato(2-)-*O*,*O*′]platinum(IV).
  $C_8H_{16}N_2O_6Pt$ 431.30
  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