Oxaliplatin Injection

オキサリプラチン注射液

Oxaliplatin Injection is an aqueous injection.

It contains not less than 95.0% and not more than 105.0% of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$: 397.29).

Method of preparation Prepare as directed under Injections, with Oxaliplatin.

Description Oxaliplatin Injection is a clear, colorless liquid.

Identification To a volume of Oxaliplatin Injection, equivalent to 5 mg of Oxaliplatin, add water to make 50 mL. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*: it exhibits a maximum between 247 nm and 251 nm.

pH Being specified separately when the drug is granted approval based on the Law.

Purity (1) Related substances—Pipet a volume of Oxaliplatin Injection, equivalent to 50 mg of Oxaliplatin, add water to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 12.5 mg of Oxaliplatin Related Substance A Dinitrate for Purity RS, add 25 mL of methanol, shake thoroughly, and add diluted nitric acid TS (1 in 200) to make exactly 100 mL. Pipet 25 mL of this solution, add diluted nitric acid TS (1 in 200) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine the peak areas, A_{T1} and A_S, of the related substance A in each solution, the peak area, A_{T2}, of the related substance IA having the relative retention time of about 1.4 to the related substance A, and the peak area, A_{T3}, of each of other related substances in the sample solution by the automatic integration method. Calculate their amounts by the following equations: the amounts of the related substances A and IA are not more than 0.65% and not more than 0.50%, respectively, and the amount of each of other related substances is not more than 0.20%, and the total amount of other related substances is not more than 1.00%. For the peak areas of the related substance IA and the other related substances in the sample solution, multiply their correction factors, 0.40 and 0.25, respectively.

Amount (%) of the related substance A
$= M_S \times A_{T1} / A_S \times 0.797 \times 1/20$

Amount (%) of the related substance IA
$= M_S \times A_{T2} / A_S \times 0.797 \times 1/20$

Amount (%) of each of other related substances
$= M_S \times A_{T3} / A_S \times 0.797 \times 1/20$

M_S: Amount (mg) of Oxaliplatin Related Substance A Dinitrate for Purity RS taken

0.797: Conversion factor for the related substance A dinitrate to related substance A

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 75 mm in length, packed with octadecylsilanized silica gel for liquid chromatography. (3 μm in particle diameter).

Column temperature: A constant temperature of about 10°C

Mobile phase A: Dissolve 0.55 g of sodium 1-heptane sulfonate and 1.36 g of potassium dihydrogen phosphate in 1000 mL of water, and adjust to pH 3.0 with phosphoric acid. To 810 mL of this solution add 190 mL of methanol for liquid chromatography.

Mobile phase B: Dissolve 0.55 g of sodium 1-heptane sulfonate and 1.36 g of potassium dihydrogen phosphate in 1000 mL of water, and adjust to pH3.0 with phosphoric acid. To 495 mL of this solution add 505 mL of methanol for liquid chromatography.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 － 0.1	100	0
0.1 － 45.1	100 → 0	0 → 100

Flow rate: 1.0 mL per minute.

Time span of measurement: For 45 minutes after injection of the sample solution.

System suitability—

Test for required detectability: Pipet 1 mL of the standard solution, add water to make exactly 10 mL. Confirm that the peak area of the related substance A obtained with 20 μL of this solution is equivalent to 8 to 12% of that with 20 μL of the standard solution.

System performance: Heat a solution of oxaliplatin in diluted dilute sodium hydroxide TS (1 in 20) (1 in 500) at 60°C for about 2 hours, and allow to cool. To 1 mL of this solution add water to make 10 mL, and use this solution as the solution for system suitability test. When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the related substance A and the related substance IA are eluted in this order with the resolution between these peaks being not less than 8, and the symmetry factor of the peak of the related substance A is not more than 2.0.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of the related substance A is not more than 2.0%.

(2) Oxalic acid—Pipet a volume of Oxaliplatin Injection, equivalent to 50 mg of Oxaliplatin, add water to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 44 mg of oxalic acid dihydrate, and add water to make exactly 250 mL. Pipet 20 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine the peak areas of oxalic acid in each solution by the automatic integration method: the peak area of oxalic acid obtained from the sample solution is not larger than 3/5 times the peak area of oxalic acid from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: Dissolve 2.6 mL of 40% tetrabutylammonium hydroxide TS and 1.36 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust to pH 6.0 with phosphoric acid. To 800 mL of this solution add 200 mL of acetonitrile for liquid chromatography.

Flow rate: 2.0 mL per minute.

System suitability—

Test for required detectability: Pipet 1 mL of the standard solution, add water to make exactly 10 mL. Confirm that the peak area of oxalic acid obtained with 10 μL of this solution is equivalent to 8 to 12% of that with 10 μL of the standard solution.

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of oxalic acid are not less than 5000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of oxalic acid is not more than 2.0%.

Bacterial endotoxins *<4.01>* Less than 2.67 EU/mg.

Extractable volume *<6.05>* It meets the requirement.

Foreign insoluble matter *<6.06>* Perform the test according to Method 1: it meets the requirement.

Insoluble particulate matter *<6.07>* It meets the requirement.

Sterility *<4.06>* Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Pipet a volume of Oxaliplatin Injection, equivalent to 10 mg of oxaliplatin ($C_8H_{14}N_2O_4Pt$), and add water to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of Oxaliplatin RS (separately determine the loss on drying *<2.41>* under the same conditions as Oxaliplatin), dissolve in water to make exactly 200 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, A_T and A_S of oxaliplatin in each solution.

$$\text{Amount (mg) of oxaliplatin } (C_8H_{14}N_2O_4Pt) = M_S \times A_T / A_S \times 1/2$$

M_S: Amount (mg) of Oxaliplatin RS taken, calculated on the dried basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: Adjust the pH of 1000 mL of water to 3.0 with phosphoric acid. To 990 mL of this solution add 10 mL of acetonitrile for liquid chromatography.

Flow rate: 1.2 mL per minute.

System suitability—

System performance: To 1 mL of a solution of oxaliplatin (1 in 500) and 1 mL of 1 mol/L sodium chloride TS add water to make 10 mL. Heat this solution at 60°C for about 2 hours, and allow to cool. When the procedure is run with 20 μL of this solution under the above operating conditions, the resolution between the peak having the relative retention time of about 0.9 to oxaliplatin and oxaliplatin is not less than 2.0, and the symmetry factor of oxaliplatin is not more than 2.0.

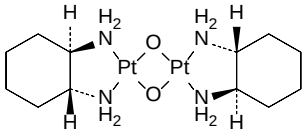
System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of oxaliplatin is not more than 1.0%.

Containers and storage Containers—Hermetic containers.

Others

Related substance IA:

(*SP*-4-2)-Di-μ-oxobis[(1*R*,2R)-cyclohexane-1,2-diamine-κ*N*,κ*N*']diplatinum



Related substance A: refer to it described in Oxaliplatin.

Add the following to 9.01 Reference Standards (1):

Oxaliplatin RS

Add the following to 9.41 Reagents, Test Solutions:

Oxaliplatin $C_8H_{14}N_2O_4Pt$ [Same as the namesake monograph]