

1 Oxaliplatin Injection

2 オキサリプラチン注射液

3

4 Oxaliplatin Injection is an aqueous injection.

5 It contains not less than 95.0% and not more than
6 105.0% of the labeled amount of oxaliplatin
7 ($C_8H_{14}N_2O_4Pt$: 397.29).

8 **Method of preparation** Prepare as directed under Injec-
9 tions, with Oxaliplatin.

10 **Description** Oxaliplatin Injection is a clear, colorless liq-
11 uid.

12 **Identification** To a volume of Oxaliplatin Injection, equiv-
13 alent to 5 mg of Oxaliplatin, add water to make 50 mL. De-
14 termine the absorption spectrum of this solution as directed
15 under Ultraviolet-visible Spectrophotometry <2.24>: it exhib-
16 its a maximum between 247 nm and 251 nm.

17 **pH** Being specified separately when the drug is granted ap-
18 proval based on the Law.

19 **Purity (1)** Related substances—Pipet a volume of Oxal-
20 iplatin Injection, equivalent to 50 mg of Oxaliplatin, add wa-
21 ter to make exactly 10 mL, and use this solution as the sample
22 solution. Separately, weigh accurately about 12.5 mg of Ox-
23 aliplatin Related Substance A Dinitrate for Purity RS, add 25
24 mL of methanol, shake thoroughly, and add diluted nitric acid
25 TS (1 in 200) to make exactly 100 mL. Pipet 25 mL of this
26 solution, add diluted nitric acid TS (1 in 200) to make exactly
27 100 mL, and use this solution as the standard solution. Per-
28 form the test with exactly 20 μ L each of the sample solution
29 and standard solution as directed under Liquid Chromatog-
30 raphy <2.01> according to the following conditions. Deter-
31 mine the peak areas, A_{T1} and A_S , of the related substance A in
32 each solution, the peak area, A_{T2} , of the related substance IA
33 having the relative retention time of about 1.4 to the related
34 substance A, and the peak area, A_{T3} , of each of other related
35 substances in the sample solution by the automatic integra-
36 tion method. Calculate their amounts by the following equa-
37 tions: the amounts of the related substances A and IA are not
38 more than 0.65% and not more than 0.50%, respectively, and
39 the amount of each of other related substances is not more
40 than 0.20%, and the total amount of other related substances
41 is not more than 1.00%. For the peak areas of the related sub-
42 stance IA and the other related substances in the sample so-
43 lution, multiply their correction factors, 0.40 and 0.25, re-
44 spectively.

45 Amount (%) of the related substance A
46 $=M_S \times A_{T1}/A_S \times 0.797 \times 1/20$

47 Amount (%) of the related substance IA
48 $=M_S \times A_{T2}/A_S \times 0.797 \times 1/20$

49 Amount (%) of each of other related substances

50 $=M_S \times A_{T3}/A_S \times 0.797 \times 1/20$

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

53 0.797: Conversion factor for the related substance A dini-
54 trate to related substance A

55 **Operating conditions**—

56 Detector: An ultraviolet absorption photometer (wave-
57 length: 210 nm).

58 Column: A stainless steel column 4.6 mm in inside diam-
59 eter and 75 mm in length, packed with octadecylsilanized sil-
60 ica gel for liquid chromatography. (3 μ m in particle diameter).

61 Column temperature: A constant temperature of about
62 10°C

63 Mobile phase A: Dissolve 0.55 g of sodium 1-heptane sul-
64 fonate and 1.36 g of potassium dihydrogen phosphate in 1000
65 mL of water, and adjust to pH 3.0 with phosphoric acid. To
66 810 mL of this solution add 190 mL of methanol for liquid
67 chromatography.

68 Mobile phase B: Dissolve 0.55 g of sodium 1-heptane sul-
69 fonate and 1.36 g of potassium dihydrogen phosphate in 1000
70 mL of water, and adjust to pH 3.0 with phosphoric acid. To
71 495 mL of this solution add 505 mL of methanol for liquid
72 chromatography.

73 Flowing of mobile phase: Control the gradient by mixing
74 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

75 Flow rate: 1.0 mL per minute.

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

78 **System suitability**—

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

84 System performance: Heat a solution of oxaliplatin in di-
85 luted dilute sodium hydroxide TS (1 in 20) (1 in 500) at 60°C
86 for about 2 hours, and allow to cool. To 1 mL of this solution
87 add water to make 10 mL, and use this solution as the solution
88 for system suitability test. When the procedure is run with 20
89 μ L of the solution for system suitability test under the above
90 operating conditions, the related substance A and the related
91 substance IA are eluted in this order with the resolution be-
92 tween these peaks being not less than 8, and the symmetry
93 factor of the peak of the related substance A is not more than
94 2.0.

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

99 (2) Oxalic acid—Pipet a volume of Oxaliplatin Injection,
100 equivalent to 50 mg of Oxaliplatin, add water to make exactly
101 10 mL, and use this solution as the sample solution. Sepa-
102 rately, weigh accurately about 44 mg of oxalic acid dihydrate,
103 and add water to make exactly 250 mL. Pipet 20 mL of this
104 solution, add water to make exactly 100 mL, and use this so-
105 lution as the standard solution. Perform the test with exactly
106 10 μL each of the sample solution and standard solution as
107 directed under Liquid Chromatography <2.01> according to
108 the following conditions. Determine the peak areas of oxalic
109 acid in each solution by the automatic integration method: the
110 peak area of oxalic acid obtained from the sample solution is
111 not larger than 3/5 times the peak area of oxalic acid from the
112 standard solution.

113 *Operating conditions—*

114 Detector: An ultraviolet absorption photometer (wave-
115 length: 210 nm).

116 Column: A stainless steel column 4.6 mm in inside diam-
117 eter and 25 cm in length, packed with octadecylsilanized sil-
118 ica gel for liquid chromatography (5 μm in particle diameter).

119 Column temperature: A constant temperature of about
120 40°C.

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

126 Flow rate: 2.0 mL per minute.

127 *System suitability—*

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

133 System performance: When the procedure is run with 10
134 μL of the standard solution under the above operating condi-
135 tions, the number of theoretical plates and the symmetry fac-
136 tor of the peak of oxalic acid are not less than 5000 and not
137 more than 2.0, respectively.

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

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

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

144 **Foreign insoluble matter** <6.06> Perform the test ac-
145 cording to Method 1: it meets the requirement.

146 **Insoluble particulate matter** <6.07> It meets the require-
147 ment.

148 **Sterility** <4.06> Perform the test according to the Mem-
149 brane filtration method: it meets the requirement.

150 **Assay** Pipet a volume of Oxaliplatin Injection, equivalent
151 to 10 mg of oxaliplatin ($\text{C}_8\text{H}_{14}\text{N}_2\text{O}_4\text{Pt}$), and add water to
152 make exactly 100 mL, and use this solution as the sample
153 solution. Separately, weigh accurately about 20 mg of Oxal-
154 iplatin RS (separately determine the loss on drying <2.41> un-
155 der the same conditions as Oxaliplatin), dissolve in water to
156 make exactly 200 mL, and use this solution as the standard
157 solution. Perform the test with exactly 20 μL each of the sam-
158 ple solution and standard solution as directed under Liquid
159 Chromatography <2.01> according to the following condi-
160 tions, and determine the peak areas, A_T and A_S of oxaliplatin
161 in each solution.

$$\begin{aligned} & \text{Amount (mg) of oxaliplatin (C}_8\text{H}_{14}\text{N}_2\text{O}_4\text{Pt)} \\ & = M_S \times A_T / A_S \times 1/2 \end{aligned}$$

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

164 *Operating conditions—*

165 Detector: An ultraviolet absorption photometer (wave-
166 length: 210 nm).

167 Column: A stainless steel column 4.6 mm in inside diam-
168 eter and 25 cm in length, packed with octadecylsilanized sil-
169 ica gel for liquid chromatography (5 μm in particle diameter).

170 Column temperature: A constant temperature of about
171 40°C.

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

175 Flow rate: 1.2 mL per minute.

176 *System suitability—*

177 System performance: To 1 mL of a solution of oxaliplatin
178 (1 in 500) and 1 mL of 1 mol/L sodium chloride TS add water
179 to make 10 mL. Heat this solution at 60°C for about 2 hours,
180 and allow to cool. When the procedure is run with 20 μL of
181 this solution under the above operating conditions, the reso-
182 lution between the peak having the relative retention time of
183 about 0.9 to oxaliplatin and oxaliplatin is not less than 2.0,
184 and the symmetry factor of oxaliplatin is not more than 2.0.

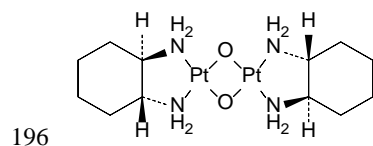
185 System repeatability: When the test is repeated 6 times
186 with 20 μL of the standard solution under the above operating
187 conditions, the relative standard deviation of the peak area of
188 oxaliplatin is not more than 1.0%.

189 **Containers and storage** Containers—Hermetic containers.

190 **Others**

191 Related substance IA:

194 (SP-4-2)-Di- μ -oxobis[(1R,2R)-cyclohexane-1,2-diamine-
195 $\kappa N, \kappa N'$]diplatinum



197 Related substance A: refer to it described in Oxaliplatin.

198 **Add the following to 9.01 Reference**

199 **Standards (1):**

200 Oxaliplatin RS

201 **Add the following to 9.41 Reagents, Test**

202 **Solutions:**

203 **Oxaliplatin** C₈H₁₄N₂O₄Pt [Same as the namesake
204 monograph]