Cisplatin Injection

General Notices

Details for the public consultation of this monograph are as follows:

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<thead>
<tr>
<th>EAG/Panel/Working Party</th>
<th>Medicinal Chemicals 1</th>
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<tbody>
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<td>Deadline for Comment</td>
<td>30th September 2019</td>
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<td>Target Publication Date (subject to change)</td>
<td>BP 2021</td>
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<td>Notes:</td>
<td>Revised monograph</td>
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<td>Limit amended for trichloroammineplatinate from 1.5% to 3.0%</td>
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Action and use

Platinum-containing cytotoxic.

DEFINITION

Cisplatin Injection is a sterile solution of Cisplatin. It is either supplied as a ready-to-use solution or it is prepared by dissolving Cisplatin for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

When supplied as a ready-to-use solution, the injection complies with the following requirements.

CHARACTERISTICS

A clear, colourless to pale yellow solution.

Content of cisplatin, C12H6N2Pt

90.0 to 105.0% of the stated amount.

With the exception of identification test A, carry out the following procedures protected from light.

IDENTIFICATION

A. The light absorption, Appendix II B, in the range 230 to 350 nm of a solution diluted, if necessary, to contain 0.1% w/v of Cisplatin exhibits a maximum at 300 nm.
B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 6.5, Appendix V L.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions in a 0.9% w/v solution of sodium chloride. Prepare the solutions immediately before use and protect from light.

(1) Use the injection diluted, if necessary, to produce a solution containing 0.05% w/v of Cisplatin.
(2) Dilute 1 volume of solution (1) to 100 volumes with a 0.9% w/v solution of sodium chloride and dilute 1 volume of the resulting solution to 5 volumes.
(3) Dissolve sufficient potassium trichloroammineplatinate BPCRS (cisplatin impurity B) in a 0.9% w/v solution of sodium chloride to produce a solution containing 0.00075% w/v of trichloroammineplatinate.
(4) 0.001% w/v of transplatin BPCRS (cisplatin impurity A) in a 0.9% w/v solution of sodium chloride.
(5) 0.001% w/v each of transplatin BPCRS, potassium trichloroammineplatinate BPCRS and cisplatin BPCRS in a 0.9% w/v solution of sodium chloride.
(6) 0.9% w/v solution of sodium chloride (blank solution).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with base-deactivated octylsilyl silica gel for chromatography (4 µm) (Superspher RPB is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 7 times the retention time of cisplatin.

MOBILE PHASE

Dissolve 1.08 g of sodium octanesulfonate, 1.70 g of tetrabutylammonium hydrogen sulfate and 2.72 g of potassium dihydrogen orthophosphate in water and dilute to 950 mL with the same solvent. Adjust to a pH of 5.9 with 1M sodium hydroxide and dilute to 1000 mL with water.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to cisplatin (retention time about 4 minutes) are: impurity A, about 0.6; impurity B, about 0.7 and cisplatin aquo complex, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5):

the resolution between the peaks corresponding to transplatin (impurity A) and trichloroammineplatinate (impurity B) is at least 2.5;
the \textit{resolution} between the peaks corresponding to the displacement peak and transplatin are well separated.

**LIMITS**

Use the chromatogram obtained with the blank solution (6) to identify the displacement peak (the last eluting peak in the group of injection peaks) and use the chromatogram obtained with solution (1) to identify cisplatin aquo complex.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to trichloroammineplatinate is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3.0%);
- the area of any peak corresponding to transplatin is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2.0%);
- the area of any other \textit{secondary peak} is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the sum of the areas of any other \textit{secondary peaks} is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard the displacement peak, any peak due to the cisplatin aquo complex and any peak less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

**ASSAY**

Carry out the method for \textit{liquid chromatography}, Appendix III D, using the following solutions.

1. Use the injection being examined diluted, if necessary, with a 0.9% w/v solution of \textit{sodium chloride} to produce a solution containing 0.1% w/v of Cisplatin.
2. 0.1% w/v of \textit{cisplatin BPCRS} in a 0.9% w/v solution of \textit{sodium chloride}.
3. 0.05% w/v of \textit{cisplatin BPCRS} and 0.005% w/v of \textit{transplatin BPCRS} in a 0.9% w/v solution of \textit{sodium chloride}; shake for 30 minutes to effect dissolution of the transplatin.

**CHROMATOGRAPHIC CONDITIONS**

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with particles of silica the surface of which has been modified by chemically bonded amine groups (10 µm) (Lichrosorb NH₂ is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

**MOBILE PHASE**

10 volumes of \textit{water} and 90 volumes of \textit{acetonitrile}.

**SYSTEM SUITABILITY**

The test is not valid unless, in the chromatogram obtained with solution (3), the \textit{resolution} between the peaks due to transplatin and cisplatin is at least 3.5.

**DETERMINATION OF CONTENT**

Calculate the content of Cl₂H₆N₂Pt in the injection using the declared content of Cl₂H₆N₂Pt in \textit{cisplatin BPCRS}. 
STORAGE

When supplied as a ready-to-use solution, Cisplatin Injection should be protected from light. It should not be refrigerated.

CISPLATIN FOR INJECTION

DEFINITION

Cisplatin for Injection is a sterile material consisting of Cisplatin with Mannitol and Sodium Chloride. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of cisplatin, $\text{Cl}_2\text{H}_6\text{N}_2\text{Pt}$

95.0 to 105.0% of the stated amount.

With the exception of identification test A, carry out the procedures protected from light.

IDENTIFICATION

A. The light absorption, Appendix II B, in the range 230 to 350 nm of a solution containing 0.1% w/v of Cisplatin in 0.1M hydrochloric acid exhibits a maximum only at 300 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of a solution containing 0.1% w/v of Cisplatin, 3.5 to 6.5, Appendix V L.

Related substances

Complies with the test described for the ready-to-use solution above but preparing solution (1) in the following manner.

Dissolve the contents of a sealed container in sufficient of a 0.9% w/v solution of sodium chloride to produce a solution containing 0.05% w/v of Cisplatin.

Uniformity of content

Sealed containers containing the equivalent of 100 mg or less of anhydrous cisplatin comply with the requirements stated under Parenteral Preparations, Powders for Injections. Use the individual results obtained in the Assay.

ASSAY
Carry out the method described for the ready-to-use formulation above. For solution (1) dissolve the contents of a sealed container in sufficient of a 0.9% w/v solution of sodium chloride solution to produce a solution containing 0.1% w/v of Cisplatin.

Calculate the content of Cl₂H₆N₂Pt in the sealed container using the declared content of Cl₂H₆N₂Pt in cisplatin BPCRS. Repeat the procedure with a further nine sealed containers. Calculate the average content of Cl₂H₆N₂Pt per container from the 10 individual results thus obtained.

**STORAGE**

The sealed container should be protected from light. It should not be refrigerated.

**IMPURITIES**

The impurities limited by the requirements of this monograph include impurities A and B listed under Cisplatin.