Cisplatin
AHFS 10:00

Products
Cisplatin is available as a sterile aqueous injection containing cisplatin 1 mg/mL and sodium chloride 9 mg/mL, with hydrochloric acid and/or sodium hydroxide to adjust the pH. This aqueous solution is available in 50-mL (50-mg), 100-mL (100-mg), and 200-mL (200-mg) vials. From 15 to 120 minutes and continuous infusion over 1 to 5 days. Intra-arterial infusion and intraperitoneal instillation have been used.4

pH
From 3.5 to 4.5.1(1/08)

Osmolality
The aqueous injection has an osmolality of about 285 mOsm/kg.4

Sodium Content
Each 10 mg of cisplatin contains 1.54 mEq of sodium.846 869

Administration
Cisplatin is administered by intravenous infusion with a regimen of hydration (with or without mannitol and/or furosemide) prior to therapy. One regimen consists of 1 to 2 L of fluid given over 8 to 12 hours prior to cisplatin administration. In addition, adequate hydration and urinary output must be maintained for 24 hours after therapy. The official labeling recommends diluting the cisplatin dose in 2 L of compatible infusion solution containing mannitol 37.5 g and infusing over 6 to 8 hours.1(1/08) 4 Other dilutions and rates of administration have been used, including intravenous infusions over periods from 15 to 120 minutes and continuous infusion over 1 to 5 days. Intra-arterial infusion and intraperitoneal instillation have been used.4

Because of an interaction occurring between cisplatin and the metal aluminum, only administration equipment such as needles, syringes, catheters, and sets that contain no aluminum should be used for this drug. Aluminum in contact with cisplatin solution will result in a replacement oxidation–reduction reaction, forcing platinum from the cisplatin molecule out of solution and appearing as a black or brown precipitate. Other metal components such as stainless steel needles and plated brass hubs do not elicit an observable reaction within 24 hours.1(1/08) 4

Stability
Intact vials of the clear, colorless aqueous injection should be stored between 20 and 25°C and protected from light; they should not be refrigerated.1(1/08) 4 After initial vial entry, the aqueous cisplatin injection in amber vials is stable for 28 days if it is protected from light or for 7 days if it is exposed to fluorescent room light.1(1/08) 4

Concern has been expressed that storage of cisplatin solutions for several weeks might result in substantial amounts of the toxic mono- and di-aquo species.1199 However, the solution's chloride content, rather than extended storage time periods, appears to determine the extent of aquated product formation. (See Effect of Chloride Ion below.)

Kristjansson et al. evaluated the long-term stability of cisplatin 1 mg/mL in an aqueous solution containing sodium chloride 9 mg/mL and mannitol 10 mg/mL in glass vials. After 22 months at 5°C, the 4% loss of cisplatin could be explained as the expected equilibrium between cisplatin and its aquated products. Furthermore, a precipitate formed and required sonication at 40°C for about 20 to 30 minutes to redissolve. Storage of the cisplatin solution at 40°C for 10 months resulted in no physical change. After an additional 1 year at 5°C, these samples exhibited an average 15% loss, which the authors concluded was not the result of the formation of aquated species or the toxic and inactive oligomeric species. These proposed degradation products were not present in the 40°C sample.1246

Theuer et al. reported little or no loss of cisplatin potency, after 27 days at room temperature with protection from light, from a solution of cisplatin 500 mcg/mL in sodium chloride 0.9% at pH 4.75 and 3.25.1605

Cisplatin may react with sodium thiosulfate, sodium metabisulfite, and sodium bisulfite in solution, rapidly and completely inactivating the cisplatin.4 1089 1175

Cisplatin 1 mg/mL did not support the growth of several microorganisms and may impart an antimicrobial effect at this concentration. Loss of viability was observed for Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Pseudomonas cepacia, Candida albicans, and Aspergillus niger.1187

pH Effects
The pH of maximum stability is 3.5 to 5.5. Alkaline media should be avoided because of increased hydrolysis.1379

In the dark at pH 6.3, cisplatin (Bristol) 1 mg/mL in sodium chloride 0.9% reached the maximum amount of decomposition product permitted in the USP in 34 days. Half of that amount was formed in 96 days at pH 4.3.1647

Cisplatin degradation results in ammonia formation, which increases the solution pH. Thus, the initial cisplatin degradation rate may be slow but increases with time.1647

Temperature Effects
It is recommended that cisplatin not be refrigerated because of the formation of a crystalline precipitate.1(1/08) 4 633 636 1246 In a study of cisplatin at concentrations of 0.4 to 1 mg/mL in sodium chloride 0.9%, it was found that at 0.6 mg/mL or greater a precipitate formed on refrigeration at 2 to 6°C. At 1 mg/mL, the precipitation was noted in 1 hour. However, the 0.6-mg/mL solution did not have a precipitate until after 48 hours under refrigeration. The 0.5-mg/mL and lower solutions did not precipitate for up to 72 hours at 2 to 6°C. In solutions where precipitate did form, redissolution occurred very slowly with warming back to
room temperature. Sonication at 40°C has been used to redisolve the precipitate in about 20 to 30 minutes. The warming of precipitated cisplatin solutions to effect redissolution is not recommended, however. Solutions containing a precipitate should not be used.

**Freezing Solutions**

Cisplatin (Bristol) 50 and 200 mg/L in dextrose 5% in sodium chloride 0.45% in polyvinyl chloride (PVC) bags and admixed with either mannitol 18.75 g/L or magnesium sulfate 1 or 2 g/L is reportedly stable for 30 days when frozen at −15°C followed by an additional 48 hours at 25°C.

**Light Effects**

Although changes in the UV spectra of cisplatin solutions on exposure to intense light have long been recognized, their significance was questioned. It was reported that exposure to normal laboratory light for 72 hours had no significant effect on cisplatin’s stability.

More recently, however, Zieske et al. reported substantial cisplatin decomposition after exposure to typical laboratory light, a mixture of incandescent and fluorescent illumination. As much as 12% degraded to trichloroammineplatinate (II) after 25 hours. Cisplatin was most sensitive to light in the UV to blue region and had little sensitivity to yellow or red light. It was protected from light-induced degradation by low-actinic amber glass flasks but not by PVC bags, clear glass vials, or polyethylene syringes. The authors concluded that exposure to moderately intense white light for more than 1 hour should be avoided.

The manufacturer recommends that a cisplatin solution removed from its amber vial be protected from light if it is not used within 6 hours. Even in the amber vial, the cisplatin solution should be discarded after 7 days if exposed to fluorescent room light.

**Chloride Ion Effects**

The stability of cisplatin in solution is dependent on the chloride ion concentration present. Cisplatin is stable in solutions containing an adequate amount of chloride ion but is incompatible in solutions having a low chloride content.

In solutions with an inadequate chloride content, one or both chloride ions in the cisplatin molecule are displaced by water, forming mono- and di-aquo species. The minimum acceptable chloride ion concentration is about 0.040 mol/L, the equivalent of about 0.2% sodium chloride.

At a cisplatin concentration of 200 mg/L in sodium chloride 0.9% with the pH adjusted to 4, about 3% decomposition occurs in less than 1 hour at room temperature. An equilibrium is then reached, with the cisplatin remaining stable thereafter. At lesser concentrations of chloride ion, greater decomposition of cisplatin occurs. In sodium chloride 0.45 and 0.2%, approximately 4 and 7% decomposition occurred at equilibrium, respectively. In very low chloride-containing solutions, most of the drug may be decomposed. The decomposition appears to be reversible, with cisplatin being reformed in the presence of high chloride concentrations.

In another study, the stability of cisplatin 50 and 500 mg/L was evaluated in aqueous solutions containing sodium chloride 0.9, 0.45, and 0.1% and also in water over 24 hours at 25°C exposed to light. Approximately 2 and 4% of the cisplatin were lost in the sodium chloride 0.9 and 0.45% solutions, respectively. In the 0.1% solution, about 4 to 10% decomposition occurred in 4 to 6 hours, increasing to approximately 11 to 15% at both 12 and 24 hours. In aqueous solution with no chloride content, cisplatin decomposed rapidly, with about a 30 to 35% loss in 4 hours increasing to a 70 to 80% loss in 24 hours.

**Ambulatory Pumps**

Cisplatin (David Bull) reconstituted to concentrations of 1 and 1.6 mg/mL with sterile water for injection was evaluated for stability for 14 days protected from light in Pharmacia Deltec medication cassettes at 24 and 37°C. The 1.6-mg/mL concentration developed a yellow crystalline precipitate rendering it unfit for use. For the 1-mg/mL concentration, little change in cisplatin concentration was found, but water loss due to evaporation was found to be about 1% at 24°C and 3% at 37°C in 14 days.

**Filtration**

Cisplatin 10 to 300 mcg/mL exhibited no loss due to sorption to cellulose nitrate/cellulose acetate ester (Millex OR) or Teflon (Millex FG) filters.

**Compatibility Information**

**Solution Compatibility**

<table>
<thead>
<tr>
<th>Test Soln Name</th>
<th>Mfr</th>
<th>Conc/L or %</th>
<th>Remarks</th>
<th>Ref</th>
<th>CI</th>
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</thead>
<tbody>
<tr>
<td>Dextrose 5% in sodium chloride 0.225%</td>
<td>AB*</td>
<td>NCI</td>
<td>300 mg</td>
<td>3% loss in 23 hr at 25°C under fluorescent light</td>
<td>1087</td>
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<td>BV</td>
<td>50 and 500 mg</td>
<td>Less than 10% loss in 24 hr at room temperature</td>
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<td>C</td>
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<tr>
<td>Dextrose 5% in sodium chloride 0.45%</td>
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<td>2% loss in 23 hr at 25°C under fluorescent light</td>
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<td>BV</td>
<td>50 and 500 mg</td>
<td>Less than 10% loss in 24 hr at room temperature</td>
<td>234</td>
<td>C</td>
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<tr>
<td>Dextrose 5% in sodium chloride 0.9%</td>
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<td></td>
<td>500 mg</td>
<td>2% loss in 24 hr at 25°C</td>
<td>635</td>
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