Lorazepam
AHFS 28:24.08

Products
Lorazepam is available in 2- and 4-mg/mL solutions in 1-mL single-use vials and 10-mL multidose vials. Both concentrations are also available in 1-mL disposable syringe cartridges. Each mL of lorazepam injection solution also contains 0.18 mL of polyethylene glycol 400 and 2% benzyl alcohol in propylene glycol.

For intramuscular use, lorazepam may be injected undiluted. For intravenous use, however, lorazepam must be diluted immediately prior to injection with an equal volume of a compatible diluent (e.g., sterile water for injection, dextrose 5%).

To dilute the dose in a syringe cartridge, all of the air should first be eliminated and the proper volume of a compatible diluent (e.g., sterile water for injection, dextrose 5%) should then be aspirated. The plunger should then be pulled back slightly to provide some mixing space and the syringe cartridge should be repeatedly and gently inverted to mix the contents. A similar procedure should be followed for diluting a dose withdrawn from a vial, taking care to repeatedly and gently invert the container until a homogeneous solution results. To avoid air entrapment, neither the syringe cartridge nor the container should be shaken vigorously.

Trade Name(s)
Ativan

Administration
Lorazepam may be administered by deep intramuscular injection; alternatively, the drug may be administered by intravenous injection, when diluted immediately prior to use with an equal volume of a compatible diluent (e.g., sterile water for injection, dextrose 5%). The volume of the diluent to be added should not exceed the volume of the drug. Intravenous injection should be made slowly (i.e., at a rate not exceeding 2 mg/min), with frequent aspiration, directly into a vein or into the tubing of a running intravenous infusion.

Lorazepam also has been administered by continuous intravenous infusion.

Care should be taken to ensure that intra-arterial administration or perivascular extravasation do not occur.

Stability
Intact vials and syringe cartridges of lorazepam should be refrigerated and stored in the original carton to protect from light. One manufacturer had previously stated that the product could be stored for up to 2 weeks at room temperature and other manufacturers had acknowledged that both physical and chemical stability were acceptable for 60 to 90 days at room temperature; however, these recommendations for extended room temperature stability are no longer supported by manufacturers.

Lorazepam injection solution should be visually inspected for discoloration and particulate matter; if discolored or if a precipitate is present, the solution should not be used.

Precipitation
The choice of commercial lorazepam concentration to use in the preparation of dilutions is a critical factor in the physical stability of the dilutions. Both the 2- and 4-mg/mL concentrations utilize the same concentrations of solubilizing solvents. On admixture, the solvents that keep the aqueous insoluble lorazepam in solution are diluted twice as much using the 4-mg/mL concentration than if the 2-mg/mL were used, resulting in different precipitation potentials for the same concentration of lorazepam. Care should be taken to ensure that the compounding procedure that is to be used for lorazepam admixtures has been demonstrated to result in solutions in which the lorazepam remains soluble.

Lorazepam concentrations up to 0.08 mg/mL have been reported to be physically stable, while occasional precipitate formation in admixtures of lorazepam 0.1 to 0.2 mg/mL has been reported. The precipitate has been observed in both containers and in administration set tubing. In one case, a visible precipitate formed in a lorazepam 0.5-mg/mL admixture in sodium chloride 0.9% in a glass bottle. However, a 0.5-mg/mL concentration may remain in solution longer if prepared from the 2-mg/mL concentration, yielding a higher concentration of organic solvents in the final admixture. Concentrations of 1 and 2 mg/mL have been reported to be physically stable for up to 24 hours, as well as concentrations below 0.08 mg/mL. Concentrations in the middle range of 0.08 to 1 mg/mL may be problematic. In one report, use of lorazepam 2 mg/mL to prepare lorazepam 1-mg/mL admixtures in dextrose 5% or sodium chloride 0.9% was acceptable, but use of the lorazepam 4-mg/mL concentration to prepare the same solutions resulted in almost immediate precipitation.

Lorazepam solubility in common infusion solutions has been reported (Table 1). Solubility of lorazepam in sodium chloride 0.9% is approximately half that found in the other tested solutions. This result was attributed to the pH of the sodium chloride 0.9% solution (pH 6.3) being essentially the same as the isoelectric point of lorazepam (pH 6.4), where aqueous solubility would be the lowest. Dextrose 5% was the best diluent for lorazepam in this study.
Table 1. Lorazepam equilibrium solubility

<table>
<thead>
<tr>
<th>Solution</th>
<th>Lorazepam Solubility (mg/mL)</th>
<th>Solution pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deionized water</td>
<td>0.054</td>
<td>7.09</td>
</tr>
<tr>
<td>Dextrose 5%</td>
<td>0.062</td>
<td>4.41</td>
</tr>
<tr>
<td>Ringer’s injection, lactated</td>
<td>0.055</td>
<td>7.21</td>
</tr>
<tr>
<td>Sodium chloride 0.9%</td>
<td>0.027</td>
<td>6.30</td>
</tr>
</tbody>
</table>

**Bacteriostatic Water**

Dilution of lorazepam (Wyeth) to 1 mg/mL with bacteriostatic water for injection (bacteriostat unspecified), packaged in glass vials, resulted in lorazepam losses. Losses of about 10% at 4°C and 12% at 22°C occurred in 7 days. Drug precipitated in varying periods after the first week of storage.

**Syringes**

Lorazepam (Wyeth) 2 mg/mL was packaged as 3 mL in 10-mL polypropylene infusion pump syringes (Pharmacia Deltec). About 12 to 14% loss occurred in 3 days and 25% loss occurred in 10 days at 5 and 30°C. The authors recommended against storing lorazepam in the syringes for these time periods.

Lorazepam (Wyeth) 1 mg/mL, prepared from the 2-mg/mL commercial concentration and diluted in dextrose 5% or in sodium chloride 0.9%, was filled as 40 mL in 60-mL polypropylene syringes (Becton Dickinson). The filled syringes were stored at 22°C for 28 hours. Visual inspection found that the solutions remained physically stable, and less than 3% drug loss occurred in this time period.

The physical and chemical stability of lorazepam (Wyeth-Ayerst) 0.2, 0.5, and 1 mg/mL in dextrose 5% and in sodium chloride 0.9% was evaluated when packaged in polypropylene syringes. When prepared using lorazepam 2 mg/mL, the solutions were found to be physically stable over 24 hours and chemically stable for 48 hours at room temperature. When prepared using lorazepam 4 mg/mL, the solutions consistently precipitated.

Lorazepam (Pfizer) 4 mg/24 mL in sodium chloride 0.9% in a 30-mL polypropylene syringe (BD) was physically stable for 48 hours at room temperature.

**Sorption**

Lorazepam (Wyeth) 2- and 4-mg/mL concentrations were diluted 1:1 using dextrose 5%, sodium chloride 0.9%, and water for injection. A 2-mL sample of each dilution was injected into the Y-sites of administration sets from 5 different manufacturers through which dextrose 5%, sodium chloride 0.9%, Ringer’s injection, or Ringer’s injection, lactated was flowing at rates of 30 and 125 mL/hr. No differences were found among the various infusion sets, infusion solutions, or flow rates. All effluent solutions were visually acceptable and had no loss of lorazepam.

In another study, lorazepam (Wyeth) 2 mg/50 mL in dextrose 5% was delivered at rates of 600, 200, and 100 mL/hr using an infusion controller fitted with 180 or 350 cm of polyvinyl chloride (PVC) tubing. Lorazepam loss due to sorption was greater with the longer tubing and at slower rates. Losses ranged from a high of 5% (350 cm, 100 mL/hr) to a low of 0.7% (180 cm, 600 mL/hr).

In static sorption studies, lorazepam (Wyeth) 2 mg/50 mL in dextrose 5% was filled into PVC containers in the following amounts: 50 mL into 50-mL bags, 100 mL into 50-mL bags, and 100 mL into 250-mL bags. The bags were stored at 23°C. A rapid initial loss of lorazepam occurred (about 3.9 to 5.8% in the first hour) followed by a slower, approximately constant loss after 8 hours. Cumulative losses of 6 to 8% occurred in about 5 hours in the smaller bags with smaller bag surface area to volume ratios. The solution in the larger bags exhibited over a 10% loss in 2 hours.

**Plasticizer Leaching**

Lorazepam (Wyeth-Ayerst) 0.1 mg/mL in dextrose 5% did not leach diethylhexyl phthalate (DEHP) plasticizer from 50-mL PVC bags in 24 hours at 24°C.

**Compatibility Information**

**Solution Compatibility**

<table>
<thead>
<tr>
<th>Test Soln Name</th>
<th>Mfr</th>
<th>Mfr</th>
<th>Conc/L or %</th>
<th>Remarks</th>
<th>Ref</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose 5%</td>
<td>BA</td>
<td>WY</td>
<td>0.1 g</td>
<td>Sorption losses of 11% in 8 hr and 27% in 24 hr at 37°C, 8% in 8 hr and 17% in 24 hr at 24°C, and 3% in 24 hr and 8% in 7 days at 4°C</td>
<td>1684</td>
<td>I</td>
</tr>
<tr>
<td>Dextrose 5%</td>
<td>MG</td>
<td>WY</td>
<td>0.1 g</td>
<td>3% loss in 24 hr and 9% in 72 hr at 37°C, little or no loss in 24 hr and 5% in 7 days at 24°C, and no loss in 7 days at 4°C and −20°C</td>
<td>1684</td>
<td>C</td>
</tr>
<tr>
<td>Dextrose 5%</td>
<td>AB</td>
<td>WY</td>
<td>0.16, 0.24, 0.5 g</td>
<td>About 10 to 20% loss due to sorption throughout 24-hr delivery at 24°C under fluorescent light</td>
<td>1858</td>
<td>I</td>
</tr>
<tr>
<td>Dextrose 5%</td>
<td>BA</td>
<td>WY</td>
<td>0.08 g</td>
<td>10 to 17% loss due to sorption in 4 hr at 4°C. 17% loss in 1 hr, increasing to over 30% in 24 hr at 21°C</td>
<td>1873</td>
<td>I</td>
</tr>
<tr>
<td>Dextrose 5%</td>
<td>BA</td>
<td>WY</td>
<td>0.5 g</td>
<td>About 14% loss due to sorption in 4 hr at 21°C</td>
<td>1873</td>
<td>I</td>
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</tbody>
</table>