Good sterile technique is used during the filling, handling and surgical implantation of the pump. (Refer to Section VI for the equation to calculate the exact delivery duration and maximum explanation date for this lot of osmotic pumps.)

Via a catheter, ALZET pumps can be used to deliver substances into the ventricular space, into the brain, or into other body tissues or solid tissue. (For instructions on how to prepare the pump for these applications, refer to Section VII.)

The function of ALZET pumps can be verified by monitoring blood levels of drug during the course of the experiment, by determining the residual amount of solution remaining in the pump at the end of the experiment, or by testing in vivo. (Refer to Section VII for a description of these verification techniques.)

### III. Instructions for Filling ALZET Osmotic Pumps

It is essential that each pump is filled completely with solution and that correct filling is verified by the method detailed below. Air bubbles trapped in the pump reservoir or in the flow moderator will insert the flow moderator into the pump may result in unpredictable pumping rate fluctuations. Solutions should be at room temperature during filling.

DURECT recommends that good sterile technique be used during the filling and handling of ALZET pumps and during the surgical implantation procedure. If sterility of your solution is a concern, fill the pumps through a 0.22 µm syringe-end filter (e.g., Millipore® GV, Millipore Corporation Headquarters 290 Concord Road, Billerica, MA 01821; 978-715-4321).

DURECT recommends filling or refilling ALZET pumps with solutions by water-soluble glass, skin oils in large quantity may interfere with the performance of a pump if the pump becomes contaminated. Solutions should be at room temperature during filling.

DURECT recommends that good sterile technique be used during the filling and handling of ALZET pumps during the surgical implantation procedure. If sterility of your solution is a concern, fill the pumps through a 0.22 µm syringe-end filter (e.g., Millipore® GV, Millipore Corporation Headquarters 290 Concord Road, Billerica, MA 01821; 978-715-4321). Solutions should be at room temperature during filling.

DURECT recommends filling or refilling ALZET pumps with solutions by water-soluble glass, skin oils in large quantity may interfere with the performance of a pump if the pump becomes contaminated. Solutions should be at room temperature during filling.

#### 1. Technical Description of the ALZET Osmotic Pump Model 2ML1

A. Complete Osmotic Pump System with Flow Moderator in Place

1. **Nominal Performance (at 37°C)**
   - **Pumping Rate**: 10 µl/hr (± 1.5 µl/hr)
   - **Duration**: 7 days
   - **Reservoir Volume**: 2000 µl (2 ml)

   The nominal performance is a target for all pumps manufactured. Individual lots of pumps may vary from this target within limits. The actual pumping rate and fill volume of this particular lot (derived by statistical testing) are listed with the lot specifications on the top of this instruction sheet.

2. **Dimensions, overall**
   - **Length**: 5.1 cm
   - **Diameter**: 1.4 cm
   - **Weight (empty)**: 5.1 g
   - **Total Displaced Volume**: 6.5 ml

3. **Components**
   - **1. Filling Tube**
     - **Length (tube only)**: 3.8 cm
     - **Gauge (tube only)**: 20
     - **O.D. (tube)**: 0.05 cm
     - **I.D. (tube)**: 0.03 cm
   - **2. Flow Moderator**
     - **Length (overall)**: 4.6 cm
     - **Gauge**: 21
     - **O.D. (tube)**: 0.08 cm
     - **I.D. (tube)**: 0.05 cm
     - **Weight (overall)**: 0.9 g
     - **Material (cap)**: polyethylene
     - **Material (flange)**: styrene butadiene rubber
     - **Material (tube)**: stainless steel
   - **3. Pump Body Materials**
     - **Outer Membrane**: cellulose ester blend
     - **Drug Reservoir**: thermoplastic hydrocarbon elastomer

#### II. Checklist for Satisfactory Performance of the ALZET Osmotic Pump

- A partially or completely discharged ALZET pump cannot be refilled or reused.
- All ALZET pumps are filled completely and all fill volumes have been recorded. (Refer to Section III for filling technique.)
- The vehicle-drug combination to be delivered is compatible with the interior of the pump. (Refer to Section IV for vehicle compatibility guidelines.)
- The drug to be delivered is stable in the vehicle solution at 37°C for the duration of the experiment.
- The mass rate of drug delivery is calculated using the following equation:
  \[ \text{Delivery Rate} = \frac{k \times Q}{1 + k \times Q}, \]

  where:
  - **k**: A constant determined by the drug and vehicle (determined by the pump manufacturer).

  The drug to be delivered is stable in the vehicle solution at 37°C for at least 4 to 6 hours (preferably overnight). (Refer to Section VI part B for complete instructions.)

### IV. Solvent and Agent Compatibility With ALZET Osmotic Pumps

The pumps are compatible with aqueous solutions, dilute acids and bases, dilute or low concentrations of DMSO and alcohol, and up to 100% propylene glycol and polyethylene glycol. ALZET pumps are not compatible with aromatic and hydrocarbons, such as heptane, toluene, and natural oils. Contact with such substances can result in a pump malfunction. Table 1 provides examples of commonly used solvents known to be compatible with the pump.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Compatibility with ALZET Pumps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Yes</td>
</tr>
<tr>
<td>70% isopropanol</td>
<td>Yes</td>
</tr>
<tr>
<td>70% isopropanol</td>
<td>No</td>
</tr>
<tr>
<td>75% EtOH</td>
<td>No</td>
</tr>
<tr>
<td>85% EtOH</td>
<td>No</td>
</tr>
<tr>
<td>95% EtOH</td>
<td>No</td>
</tr>
</tbody>
</table>

**Acids, with pH greater than 1.8**

- **Bases, up to pH of 14**
  - Cremophor EL, up to 25% in water
  - Culture media (1% benzyl alcohol as bacteriostatic)
  - Cycloexetrin
  - Dextrose, up to 5%, in water or NaCl
  - N,N-Dimethyl formamide (DMF), up to 25% in water
  - Propylene glycol, neat or in water
  - Glycerin
  - Ethanol, up to 15% in water

**Bases, with pH less than 14**

- Acids, with pH greater than 1.8
  - Cremophor EL, up to 25% in water
  - Culture media (1% benzyl alcohol as bacteriostatic)
  - Cycloexetrin
  - Dextrose, up to 5%, in water or NaCl
  - N,N-Dimethyl formamide (DMF), up to 25% in water
  - Propylene glycol, neat or in water
  - Glycerin
  - Ethanol, up to 15% in water

**Solvents**

- Acids, with pH greater than 1.8
- Bases, up to pH of 14
- Water

**Propylene glycol, neat or in water**

- Glycerin
- Ethanol, up to 15% in water

**Glycerin**

- Ethanol, up to 15% in water

**Ethanol, up to 15% in water**

- Water

**Solvent**

- Acids, with pH greater than 1.8
- Bases, up to pH of 14
- Water

**Propylene glycol, neat or in water**

- Glycerin
- Ethanol, up to 15% in water

**Glycerin**

- Ethanol, up to 15% in water

**Ethanol, up to 15% in water**

- Water

**Notes:**

- The solvents listed above are known to be compatible with the reservoir material of the pump. Caution must be taken to ensure the solvent is non-toxic and non-biodegradable with tissues and fluids at the site of administration.
If the solvent you wish to use is not listed in Table 1, an ALZAID® chemical test kit is available to you. To order an ALZAID test kit, call 800-692-2990 (U.S. and Canada) or 415-972-2344 (outside the U.S. and Canada).  

**V. Implantation of the ALZET Osmotic Pump in Vivo**

The ALZET osmotic pump can be implanted subcutaneously in an animal that weighs 200 to 400 g. For subcutaneous placement, a small incision is made in the skin between the scapulae. Using a hemostat, a small pocket is formed by spreading the skin at the proposed incision site and connecting the pockets formed on either side of the incision. With the pocket formed, the catheter is inserted into the pocket with the flow moderator pointing away from the incision. The skin incision can be closed with wound clips or sutures. For infraplacement placement, make a small midline incision in the skin below the rib cage of an animal weighing at least 300 g. Another small incision is made in the abdomen just lateral to the midline directly below the midline incision. This pump is inserted, flow moderator first, into the peritoneal cavity. The muscle incision is closed with sutures, and then the skin incision can be closed with either wound clips or sutures. The catheter does not alter the pumping rate of the pump. To operate the pump with a catheter, or to deliver a substance into the brain, or into any organ, lumen, or solid tissue. Attachment to a catheter can now be removed.

NOTE: The weight of a partially emptied or discharged pump cannot be used to determine the quantity of drug delivered because the pump imbibes water during operation. Likewise, opening a open spent is not a reliable means for verifying pump performance.

**VI. Operation of the ALZET Osmotic Pump**

ALZET pumps are precision drug administration tools. This section details the actual pumping rate and fill volume specifications for the lot of Model 2ML1 pumps tested. The following section discusses the classic technique known as the 'flow start-up transient,' the Model 2ML1 pumps infuse at a constant rate that lies within a predictable range until all but about 5% of the reservoir contents have been delivered; then the rate falls rapidly to zero.

The method DURECT uses to estimate the pumping rate of osmotic pumps is to measure their pumping rate in vitro and in vivo. This in vitro method gives a good measure of reproducibility – over time within pumps and between lots of pumps – and allows an estimate of rate to be expected in homoeothermic animals for which 0.9% saline is isotonic. For example, in rats and mice the pumping rate of subcutaneously or intraperitoneally implanted osmotic pumps can be measured in vitro (data available from DURECT upon request).

**A. Start-Up Time**

In an ALZET pump is loaded at room temperature (20°C) with a solution also at room temperature. The pumping rate will not be known for about several hours. To obtain a more immediate pumping, DURECT suggests you place the preinfused pumps in 0.9% saline for at least one hour to ensure an optimum overnight onset of subcutaneous implantation. This procedure is mandatory when the pump is to be used with a catheter, or when viscosus solutions are being delivered.

**B. Determination of Pumping Duration**

The duration of pumping can be computed from the following equation:

\[
D = \left(\frac{V}{Q}\right) (0.95)
\]

In this equation, D is duration in hours, V is the pump’s reservoir volume in µl as given in the specifications, and Q is pumping rate in µl/hr.

**C. Determination of Pumps Temperature**

The reservoir volume of ALZET osmotic pumps is slightly larger than that required for continuous delivery. During the complete 7 days, the pumping duration some of the drug solution will remain in the pump. This solution can be aspirated from the pump using the supplied blunt-tipped filling tube and a syringe. To determine if the drug solution can be enhanced by flushing the reservoir with additional solvent. The active agent in the solution which was recovered from the resin can then be assayed using an appropriate technique. To determine the average pumping rate, the difference between the amount of drug delivered divided by the net residual amount in the pump is divided by the elapsed time.

**D. Determination of the In Vitro Pumping Rate**

ALZET pumps are supplied with a specified volume pumping rate determined in isotonic saline at 37°C (±0.5°C). In the event that you find it necessary to test a pumping rate, DURECT recommends that the following steps be taken

**Step 1.** Prepare a solution of known concentration of an inhibitor dissolved in isotonic saline. The amount of inhibitor pumped out of the pump will be the basis for your calculation of the baseline delivery. Therefore, the time interval for this test should be compatible with the pump and be easy to analyze in isotonic saline. (One such indicator is FOAC 41 blue dye, available from Senscol Colors, 2026 Baldwin St., St. Louis, MO 63106, 1-800-325-8110 x7475, catalog #5601.)

**Step 2.** Fill the ALZET pump with the indicator solution according to Section III.

**Step 3.** Place the ALZET pump into a 10 ml test tube prefilled with 7 ml of isotonic saline and pre incubated at 37°C (±0.5°C). Cap the tube to prevent evaporation.

**Step 4.** Record the start time of the incubation.

**Step 5.** Transfer the ALZET pump to a new test tube filled with 7 ml of isotonic saline and pre incubated at 37°C (±0.5°C). Cap the tube to prevent evaporation.

**Step 6.** Repeat Step 5 for 7 days.

**Step 7.** Score the pump for the concentration of indicator in each test tube against a standard of known concentration to determine the amount of indicator pumped during each time interval. From this amount and the concentration of the indicator, you can compute the pumping rate of ALZET pumps. This technique can be used, the recommended wavelength for spectrophotometric analysis is 630 nm.

**IX. Additional Technical Information About ALZET Osmotic Pumps**

A wealth of information on ALZET osmotic pumps and their uses is available through ALZET Technical Support. Through this complimentary service you can receive:

- A Technical Information Manual
- A video of commonly used surgical implantation procedures
- Custom searches of the ALZET osmotic pump bibliography of products
- Presentation materials for authors presenting their work
- Information about ALZET Brain Infusion Kits, ALZET Catheters and other products

To obtain any of these materials, or if you desire additional information, contact ALZET Technical Support:

**ALZET Technical Support**
DURECT Corporation
P.O. Box 530
Cupertino, CA 95015-0530

800-692-2990 (U.S. and Canada) 808-367-4038 (Outside the U.S.) 888-146-1406 (Facsimile) alzetinfo@alzet.com  www.alzet.com

**Warranty**

If you purchase a 12 months from date of shipment, DURECT warrants that the ALZET® Osmotic Pump (“Product”) is free from defects in materials and workmanship, and will, on average, deliver its contents at the rate and within the parameters described in the literature accompanying the product, unless otherwise excluded herein, for a period of five years from the delivery date. This warranty is in lieu of all other warranties, expressed or implied, including warranties of merchantability and fitness for a particular purpose. **EXCEPT AS SET FORTH ABOVE, DURECT DISCLAIMS ALL OTHER WARRANTY TO THE MAXIMUM EXTENT PERMITTED BY LAW. THIS WARRANTY IS IN LIEU OF ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE.**

This warranty shall not apply to the repair or replacement of any defective or damaged goods. This warranty shall not be applicable to any special, incidental, indirect or consequential damages, however caused, on any theory of liability, DURECT’S LIABILITY WITH RESPECT TO THE PRODUCT SHALL IN NO EVENT EXCEED THE AMOUNT PAID BY THE CUSTOMER FOR THE PURCHASE 0.01 µm. Recovery of the drug solution,

**Disclaimer**

DURECT Corporation
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