OSMOTIC PUMP MODEL 2ML1

10 µl PER HOUR, 7 DAYS

REFER TO ENCLOSED SPECIFICATIONS

STORE AT ROOM TEMPERATURE

CONTENTS:
Ten osmotic pumps
Ten silicone stoppers
One disposable filling tube
One instruction/specification sheet

CAUTION:
Not for use in humans
Not for veterinary use
For use in laboratory research
animals or in vivo

DURECT™
DURECT Corporation, Cupertino, CA 95014

LOT NO.

STANDARD MEAN VOLUME
MICROLITERS

STANDARD DEVIATION
MICROLITERS

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I. Technical Description of the ALZET Osmotic Pump Model 2ML1

A. Complete Osmotic Pump System with Flow Modulator in Place

1. Nominal Performance (at 37°C)
   - Pumping Rate: 10 µl/h (± 1.5 µl/h) 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. An apportioned 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. B. 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: 4.6 cm
      - Gauge (tube): 21
      - O.D. (tube): 0.08 cm
      - I.D. (tube): 0.05 cm
      - Weight: 0.9 g
      - Material (cap): polyethylene
      - Material (flange): styrene/ethylene/propylene
      - Material (tube): stainless steel
   - 3. Pump Body Materials
      - Outer Membrane: cellulose ester blend
      - Drug Reservoir: thermostatic hydrocarbon elastomer

II. Checklist for Satisfactory Performance of the ALZET Osmotic Pump Model 2ML1

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 vehicle solution specifications on the top of this instruction sheet.)

The vehicle-drug combination to be delivered is compatible with the interior of the experiment.

The drug to be delivered is stable in the vehicle solution at 37°C for the duration of the experiment.

When the environment in which the pump is to be used differs significantly from normal mammalian body temperature (37°C) and osmolality (330 mOsm/l), the pumping rate of ALZET pumps will be affected. (To calculate the pumping rate under specific temperature and osmolality conditions, refer to the equation in Section VI.)

ALZET Osmotic Pumps, Model 2ML1, should be removed upon completion of their delivery duration or by day 10 after implantation. After this time, due to the continued attraction of water into the pump, it may swell and leak a concentrated salt solution, resulting in local irritation around the pump. (*Refer to the equation in Section VI 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 vascular system, into the brain, or into other organ, tissue, or solution. (For instructions on how to prepare the pump for these applications, refer to Section VII.)

Verify only operation of ALZET pumps by both monitoring blood levels of drug during the course of the infusion, and determining the residual amount of solution remaining in the pump after explantation. Refer to Section VIII for further information, including an in vitro verification method.

III. Instructions for Filling ALZET Osmotic Pumps

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

Good sterile technique is used during the filling, handling and surgical implantation of osmotic pumps. (Refer to Section V for vehicle solution specifications on the top of this instruction sheet.)

When filling an ALZET pump, 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 filters. (e.g., Millex® GV, Millipore Corporate Headquarters 290 Concord Road, Billerica, MA 01821, 978-715-4321).

Prior to filling and implantation, ALZET pumps should be handled with surgical gloves. Skin oils in large quantity may interfere with the performance of a pump if they contaminate its surface. If a pump becomes contaminated, it should be wiped with an aqueous solution of 70% isopropanol immediately before use. Do not soak the pump in 70% isopropanol.

Performs the following steps when filling ALZET pumps:

Step 1. Weigh the empty pump together with its flow modulator.

Step 2. Fill the pump is accomplished with a small syringe (3 ml) and the provided blunt-tipped, 25 gauge filling tube. Use of a larger syringe leads to rapid filling which can introduce air bubbles into the reservoir. Draw the solution into the syringe, and attach the filling tube. It is essential that the syringe and attached tube be held at a 45° angle. (Refer to Section V for vehicle solution specifications on the top of this instruction sheet.)

Step 3. With the flow modulator rendered, hold the pump in an upright position and insert the filling tube through the opening at the top of the pump until it can go no further. This places the tip of the tube near the bottom of the pump reservoir.

Step 4. Incipient plunger of the syringe slowly holding the pump in an upright position. When the solution appears at the outlet, stop filling and carefully remove the tube.

Step 5. Wipe off the excess solution and insert the flow modulator until the white flange is flush with the pump. The insertion of the flow modulator will displace some of the solution from the filled pump. This overflow should be wiped off. To function properly, the flow modulator must be fully inserted into the body of the pump.

Step 6. Weigh the filled pump. The difference in the weights obtained in Steps 1 and 6 will give the net weight of the solution loaded. For most dilute aqueous solutions, the weight in milligrams (mg) is approximately the same as the volume in microliters. The fill volume should be over 90% of the Max Fill Volume indicated in the lot specifications at the top of this instruction sheet. If so, the pump is ready for use. If not, the fill should be repeated inside the pump. Evacuate the incompletely filled pump and refill (Steps 1-6).

If back pressure is encountered, the filling tube can be cocked at a slight angle during filling. The filling speed can also be widened slightly by moving the filling tube back and forth, or by inserting and removing the flow modulator several times before inserting the filling tube. If this is the case, there is no further pumping capacity. The fill volume is less than 95% of the reservoir volume indicated in the lot specifications at the top of this instruction sheet, call ALZET Technical Support for assistance at 800-692-2990 (U.S. and Canada).

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 propylene glycol. ALZET pumps are not compatible with alcoholic and aromatic 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>Table 1</th>
<th>List of Solvents Compatible With the Reservoir Material of ALZET Osmotic Pumps (for solvent compatibility with ALZET catheters, please contact Technical Support at <a href="mailto:alzet@durect.com">alzet@durect.com</a>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acids, with pH greater than 1.8</td>
<td>Benzoic acid, with less than 14</td>
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<tr>
<td>Benzoic acid, with less than 14</td>
<td>Cremophor EL, up to 25% in water</td>
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<tr>
<td>Cremophor EL, up to 25% in water</td>
<td>Culture media (1% benzyl alcohol as bacteriostatic)</td>
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<tr>
<td>Culture media (1% benzyl alcohol as bacteriostatic)</td>
<td>Cyclohexane</td>
</tr>
<tr>
<td>Cyclohexane, up to 5% in water or NaCl</td>
<td>N,N-Dimethyl formamide (DMF), up to 25% in water</td>
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<tr>
<td>N,N-Dimethyl formamide (DMF), up to 25% in water</td>
<td>DMSO, up to 50% in water or polyethylene glycol</td>
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<tr>
<td>DMSO, up to 50% in water or polyethylene glycol</td>
<td>DMSO, up to 50% in ethanol (± 15%) and water</td>
</tr>
<tr>
<td>DMSO, up to 50% in ethanol (± 15%) and water</td>
<td>Ethanol, up to 15% in water</td>
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<tr>
<td>Ethanol, up to 15% in water</td>
<td>Glucoronic acid 1-Methyl-2-Pyridone, up to 12.5% in water</td>
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<tr>
<td>1-Methyl-2-Pyridone, up to 12.5% in water</td>
<td>Polyethylene glycol 300 or 400, or neat in water</td>
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<tr>
<td>Polyethylene glycol 300 or 400, or neat in water</td>
<td>Propylene glycol, neat or in water</td>
</tr>
<tr>
<td>Propylene glycol, neat or in water</td>
<td>Ringer's solution (with or without lactate)</td>
</tr>
<tr>
<td>Ringer's solution (with or without lactate)</td>
<td>Saline, 0.9% (or other aqueous salt solution)</td>
</tr>
<tr>
<td>Saline, 0.9% (or other aqueous salt solution)</td>
<td>Serum (rat, mouse, etc.)</td>
</tr>
<tr>
<td>Serum (rat, mouse, etc.)</td>
<td>Solubil, up to 35% in water</td>
</tr>
<tr>
<td>Solubil, up to 35% in water</td>
<td>Tween 80, up to 2%</td>
</tr>
<tr>
<td>Tween 80, up to 2%</td>
<td>Water, distilled</td>
</tr>
</tbody>
</table>

Note that the solvents listed above are known to be compatible with the reservoir material of the pump. Caution must be taken to ensure the chosen solvent is biocompatible 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. This section details the compatibility with ALZET pumps. The test kit provides you with the necessary material to determine the volume including standard deviation, appear in the lot specifications section on the other side of this instruction sheet. All ALZET pumps are precision drug delivery tools. This section details the verification of the ALZET Osmotic Pump. This step is mandatory in all catheter implantation procedures. In order to test the pumping rate, DURECT recommends that the following steps be taken:

Step 1. Prepare a solution of known concentration of an indicator dissolved in isotonic saline. The amount of indicator pumped out of the pump will be the basis for the pumping rate calculation. Therefore, the indicator solution should be standardized. When using the supplied blunted-tipped filling tube and 1.0 ml syringe. Recovery of the drug solution can be enhanced by flushing the recovered volume with a fresh isotonic saline solution. The active agent in the solution which was recovered from the reservoir can then be assayed using an appropriate technique. To calculate the average pumping rate, the difference between the amount of drug initially loaded and the residual amount in the pump is divided by the elapsed time.

B. Determination of the In Vitro Pumping Rate

ALZET pumps are supplied with a specified volume pumping rate determined in the laboratory. The method DURECT uses to estimate the pumping rate of osmotic pumps is to

A. Start-Up Time

If an ALZET pump is loaded at room temperature (23°C) with a solution also at 37°C, the pumping rate will not be the same as that read from the chart for pump temperature 37°C. DURECT suggests you place the prefilled pumps in 0.9% saline for at least 1 hour to allow their temperature to equalize with the surrounding water. This procedure is mandatory when the pump is to be used with a catheter, or when viscous solutions are being delivered.

C. 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 ul as given in the specifications, and \( Q \) is pumping rate in ul/hr.

D. Predicting Pump Performance Outside Mammalian Ranges of Temperature and Osmolality

The following equation can be used to predict the pumping rate in heterothermic animals or in those whose body fluids are not isotonic with mammals:

\[ Q = \frac{0.014 (1 + 0.005 \times T)}{1 + 0.005 \times T} \]

Where \( Q \) is the predicted pumping rate at temperature \( T \) in °C, 0.005 is the temperature coefficient of the pump (ambient temperature) in °C. The ambient temperature is useful in the range of 0 to 25 °C and 4 to 42 °C. At normal mammalian osmolality of 310 mOsm/L, the osmotic pressure (\( P \)) is 7.5 atm. If the solution to be filled in the reservoir is iso-osmotic with the animal, and 1 atm is equal to 0.1013 atm, then pressures above 42°C have been found to cause fluctuating delivery rates and are not recommended. This equation is applicable only to the Model 2ML pumps. Note that as Q decreases proportionally to the environmental temperature, the pumping duration increases.

VII. Use of the ALZET Osmotic Pump With a Catheter

Via a catheter, ALZET pumps can deliver substances into the venous or arterial circulation, into the brain, or into any organ, lumen, or solid tissue. Attachment to a catheter is a common way to control the pumping rate of the pump. To operate the pump with a catheter, perform the following steps:

1. Remove the translucent end-cap from the lower connector, revealing a short, stainless steel tube protruding from the white plastic flange.

2. (a) If you are using a 2ML Osmotic Pump without a preformed lumen catheter then the tubing component for testing your agents and vehicles before use with osmotic pumps strongly recommends the use of this test kit under the following circumstances:

1. When the solvent you wish to use does not appear in Table 1.

2. When the agent is in its base form.

3. When the agent is known to bind tenaciously to various polymeric materials.

To order an ALZET Test Kit, call 877-922-5938 (toll free in the U.S. and Canada).

A solution which generates gases within the pump during use makes the pump unsuitable for use with a catheter. Performing the following steps will allow the pump to begin operating before implantation, and will minimize the chance of an occlusion or clot forming in the catheter. This step is mandatory in all catheter implantation applications. The pump and catheter can now be implanted.