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alzet®

MICRO-OSMOTIC PUMP MODEL 1004

0.11 µl PER HOUR, 28 DAYS

REFER TO ENCLOSED SPECIFICATIONS

STORE AT ROOM TEMPERATURE

CONTENTS:
Ten micro-osmotic pumps
Ten flow moderators
One disposable filling tube
One instruction/specification sheet

CAUTION:
Not for use in humans
Not for veterinary use
For use only in laboratory research animals or for tests *in vitro*

DURECT™ DURECT Corporation, Cupertino, CA 95014

LOT NO.

MEAN PUMPING RATE MICROLITERS/HR.

STANDARD DEVIATION MICROLITERS/HR.

MEAN FILL VOLUME MICROLITERS

STANDARD DEVIATION MICROLITERS

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ALZET® MICRO-OSMOTIC PUMP MODEL 1004 INSTRUCTION AND SPECIFICATION SHEET

DURECT Corporation manufactures a miniature implantable pump for use in laboratory animals. The ALZET Micro-Osmotic Pump Model 1004 delivers solutions continuously for 28 days without the need for external connections or frequent handling of animals.

This product is for use in experimental animals only. It is not to be placed into animals used for food or food products, or in humans.

ALZET pumps have been exposed to a sterilizing dose of radiation from a ^{60}Co source.

I. Technical Description of the ALZET Micro-Osmotic Pump Model 1004

A. Complete Micro-Osmotic Pump System with Flow Moderator In Place

1. Nominal Performance (at 37°C)

Pumping Rate	0.11 µl/hr
Duration	28 days
Reservoir Volume	100 µl

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. **Always use actual pumping rate and fill volume information specific to each lot of pumps when making dose calculations.**

2. Dimensions, overall

Length	1.5 cm
Diameter	0.6 cm
Weight (empty)	0.4 g
Total Displaced Volume	0.5 ml

B. Components

1. Filling Tube

Length (tube only)	1.1 cm
Gauge (tube only)	27
O.D. (tube)	0.04 cm
I.D. (tube)	0.02 cm

2. Flow Moderator

Length (overall)	1.3 cm
Gauge (tube)	21
O.D. (tube)	0.08 cm
I.D. (tube)	0.05 cm
Weight (overall)	0.05 g
Material (flange)	styrene acrylonitrile
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 Micro-Osmotic Pump

❒ Use the mean pumping rate and fill volume information specific to this lot of pumps when making dose calculations.

❒ 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 correct 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 soluble in the vehicle solution at 37°C for the duration of the experiment.

❒ 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 infusion is calculated using the following equation:

$$k_o = Q \cdot C_d$$

Here k_o is the mass delivery rate (µg/hr), Q is the volume delivery rate (µl/hr) of the vehicle solution from the pump, and C_d is the concentration (µg/µl) of the agent in the vehicle.

❒ Good sterile technique is used during the filling, handling and surgical implantation of micro-osmotic pumps (refer to Section III for filling procedure and Section V for implantation procedure). ALZET pumps have been exposed to a sterilizing dose of radiation from a ^{60}Co source.

❒ **If you desire the pump to start immediately, are working with a viscous solution, or if you wish to attach a catheter, incubate the pre-filled pump in sterile saline at 37°C for at least 48 hours.** (Refer to Section VI part B for complete instructions.)

❒ When the environment in which the pump is to be used differs significantly from normal mammalian body temperature (37°C) and osmolality (310 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 part D.)

❒ **ALZET Micro-Osmotic Pumps, Model 1004, should be removed upon completion of their delivery duration or by day 42* after implantation.** After this time, due to continued attraction of water into the pump, it may swell and leak a concentrated salt solution, resulting in local irritation around the pump. (*This explantation date is calculated based on nominal duration. Refer to the equation in Section VI part C, and the actual release rate and fill volume specifications to calculate the exact delivery duration and maximum explantation date for this lot of micro-osmotic pumps.)

❒ Via a catheter, ALZET pumps can be used to deliver substances into the venous or arterial circulation, into the brain, or into any organ, lumen, or solid tissue. (For instructions on how to prepare the pump for these applications, refer to Section VII.)

❒ Verify correct 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 Micro-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 failure to 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., Sterile Millex® Syringe Filters - EMD Millipore Headquarters 290, Concord Road, Billerica, MA 01821, 978-715-4321).

During 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 accumulate on its surface. If a pump becomes contaminated, its surface may be wiped with an aqueous solution of 70% isopropanol immediately before use. **Do not soak the pump in 70% isopropanol.**

Perform the following steps when filling ALZET pumps:

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

Step 2. Filling the pump is accomplished with a small syringe (1.0 ml) and the provided blunt-tipped, 27 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 free of air bubbles.

Step 3. With the flow moderator removed, 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. Push the 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. (Rapid filling can introduce air bubbles into the reservoir.)

Step 5. Wipe off the excess solution and insert the flow moderator until the white flange is flush with the top of the pump. The insertion of the flow moderator will displace some of the solution from the filled pump. This overflow should be wiped off. To function properly, the flow moderator 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 (µl). The fill volume should be over 90% of the reservoir volume specified on the top of this instruction sheet. If so, the filled pump is now ready for use. If not, there may be some air trapped inside the pump. Evacuate the incompletely filled pump and refill (Steps 1-6).

If back pressure is encountered, the filling tube can be tilted at a slight angle during filling. The filling aperture can also be widened slightly by moving the filling tube back and forth, or by inserting and removing the flow moderator several times before inserting the filling tube.

If, after a second filling, the fill volume is less than 90% 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 Micro 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 and polyethylene glycol. ALZET pumps are not compatible with aliphatic 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 some commonly used solvents known to be compatible with the pumps.

TABLE 1

List of Solvents Compatible with the Reservoir Material of ALZET Micro-Osmotic Pumps

(for solvent compatibility with ALZET Catheters, please contact ALZET Technical Support at alzet@durect.com)

Acids, with pH greater than 1.8
Bases, with pH less than 14
Cremophor EL, up to 25% in water
Culture media (1% benzyl alcohol as bacteriostatic)
Cyclodextrins
Dextrose, up to 5%, in water or NaCl
N,N-Dimethyl formamide (DMF), up to 25% in water
DMSO, up to 50% in water or polyethylene glycol
DMSO, up to 50% in ethanol (≤15%) and water
Ethanol, up to 15% in water
Glycerol
1-Methyl-2-Pyrrolidone, up to 12.5% in water
Phosphate buffer
Polyethylene glycol 300 or 400, neat or in water
Propylene glycol, neat or in water
Ringer's solution (with or without lactate)
Saline, 0.9% (or other aqueous salt solution)
Serum (rat, mouse, etc.)
Solutol, up to 30% in water
Triacetin, up to 5% in water
Tween 80, up to 2%
Water, distilled

Note that the solvents listed on the other side of this instruction sheet are known to be compatible with the reservoir material of the pump. Caution must be taken to ensure the chosen solvent is also 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 Compatibility Test Kit is available to allow you to assess agent and solvent compatibility with ALZET pumps. The test kit provides you with the necessary pump component materials for testing your agents and vehicles before use with the micro-osmotic pumps. DURECT 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 free base form.
3. When the agent is known to bind tenaciously to various polymeric materials.

To order an ALZAID 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 pumping rate highly unpredictable. Also, solutions with precipitated solute particles must be filtered before use. Solutions should be at room temperature when filling the pump.

ALZET pumps are capable of delivering homogeneous viscous solutions with a viscosity of less than 100,000 centipoise. Suspensions may be delivered from the pump if they do not precipitate. To ensure uniform delivery, suspensions must remain homogeneous throughout the duration of delivery.

V. Implantation of the ALZET Micro-Osmotic Pump *In Vivo*

The ALZET Micro-Osmotic Pump can be implanted subcutaneously in an animal that weighs at least 10 grams. 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 subcutaneous connective tissues apart. The pump is inserted into the pocket with the flow moderator pointing away from the incision. The skin incision can be closed with a wound clip or sutures.

For intraperitoneal placement, make a small midline incision in the skin below the rib cage of an animal weighing at least 20 grams. Another small incision in the abdominal muscle is made directly under the cutaneous incision. The 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 a wound clip or sutures. **Be sure to remove the pump upon completion of the delivery duration, or by day 42* after implantation.** (*This explantation date is calculated based on nominal duration. Refer to the equation in Section VI, part C, and the actual release rate and fill volume specifications to calculate the exact delivery duration and maximum explantation date for this lot of micro-osmotic pumps.)

For additional information about surgical procedures, contact ALZET Technical Support at **800-692-2990** (U.S. and Canada.) A video demonstrating several surgical implantation procedures is available at no charge.

VI. Operation of the ALZET Micro-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 1004 pumps that you received, and the method by which these figures were determined. After a 48 hour start-up transient, the Model 1004 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 the osmotic pumps is to measure their pumping rate *in vitro* in 0.9% saline at 37°C (± 0.5°C). This *in vitro* method gives a good measure of reproducibility – over time within pumps and between pumps – and allows an estimate of the pumping rate to be expected in homeothermic animals for which 0.9% saline is isotonic. For example, in rats and mice the pumping rate of subcutaneously or intraperitoneally implanted osmotic pumps is within 5% of the *in vitro* rate.

A. *In Vitro* Qualification Test

A random sample of 20 ALZET pumps is selected from the same lot as the product which you have received. These pumps are filled with a dye solution according to the method described in Section III. The values for the Mean Fill Volume, including standard deviation, appear in the lot specifications section on the other side of this instruction sheet.

After filling, each ALZET pump is submersed in 0.9% saline at 37°C (± 0.5°C). These pumps are transferred to test tubes containing fresh saline at regular intervals through day 28. The output from each pump is analyzed against a standard. Over the 48 to 672-hour (28 day) time period, each pump operates at a constant rate. From DURECT's experience, the coefficient of variation of each pump's time-dependent pumping rate is less than 10%, with a standard error of the mean of 5% (SEM). The variation in *in vitro* pumping rates among pumps on a given day and within a given pump across 28 days appears in the lot specifications on the other side of this instruction sheet.

B. Start-Up Time

If an ALZET pump is loaded at room temperature (23°C) with a solution also at room temperature, and then placed in isotonic saline at 37°C, the pumping rate will not reach steady state for several hours. If your experiment requires immediate pumping, DURECT suggests you place the prefilled pumps in 0.9% saline for at least 48 hours at 37°C before implantation. **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.

$$D = (V/Q)\ (0.95)$$

In this equation, D is the duration (hr), V is the pump's reservoir volume (µl) as given in the specifications, and Q is the pumping rate (µl/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:

$$Q = Q_o\ [0.135\ e^{(0.054T)} - 0.004\pi + 0.03]$$

Here Q_o is the specified pumping rate of the pumps at 37°C in 0.9% saline (µl/hr), T is the ambient temperature (°C), and π is the osmotic activity of the pump environment (atm).

The above formula is useful in the range of $\pi = 0$ to 25 atm and T = 4°C to 42°C. At normal mammalian osmolality of 310 mOsm/l, the osmotic pressure (π) is 7.5 atm. The equation is predictive within ± 10%. Environmental temperatures above 42°C have been found to cause fluctuating delivery rates and are not recommended. This equation is applicable only to the Model 1004. Note that as Q decreases in proportion to the environmental temperature, the pumping duration increases.

VII. Use of The ALZET Micro-Osmotic Pump With a Catheter or Brain Infusion Kit

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 does not alter the pumping rate of the pump. To operate the pump with a catheter, perform the following steps:

1. Using a pair of scissors or pliers, break the white flange from the flow moderator. When removing the flange, be careful not to bend or crush the stainless steel tube.

2. Attach the stainless steel tube to a piece of polyethylene or vinyl catheter tubing with an inside diameter (I.D.) 0.58 mm - 0.76 mm (0.02 inches - 0.03 inches). Polyethylene tubing, commonly called PE-60 (I.D. = 0.03 inches), is a good choice for most applications. After attachment, the catheter should cover about 3 - 4 mm of the length of the tube.

3. Fill the catheter and attached stainless steel tube using a syringe. Leave the syringe attached to the distal part of the catheter.

4. Following the instructions above (Section lll) fill the ALZET pump.

5. Insert the flow moderator all the way into the pump until the catheter is flush with the surface of the pump. The syringe attached to the distal end of the catheter can now be removed.

6. Place the pump in sterile 0.9% saline at 37°C for 48 hours. This 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 applications.** The pump and catheter can now be implanted.

VIII. Verifying the Accuracy of ALZET Micro-Osmotic Pumps

To verify that experimental results are derived from continuous administration of the drug solution, DURECT recommends that ALZET pump users verify the blood levels of drug at several points during the course of infusion and measure the residual volume in the pump reservoir after explantation. In the event that determination of circulating blood levels is not possible or is technically undesirable, users should still measure residual volume in the pump reservoir after explantation.

Note that the weight of a partially empty or discharged pump cannot be used to determine the quantity of drug delivered because the pump imbibes water during operation. Likewise, cutting open a spent pump is not a reliable means of verifying pump performance.

A. Determination of Average Pumping Rate

The reservoir volume of ALZET Micro-Osmotic Pumps is slightly larger than that required to assure pumping for the complete 28 days. As a result, at the end of 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 1.0 ml syringe. Recovery of the drug solution can be enhanced by flushing the reservoir with additional solvent. The active agent in the solution which was recovered from the reservoir can then be assayed by 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 isotonic saline at 37°C (± 0.5°C). In the event that the user finds it necessary 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 compatible with the pump and be easy to analyze in isotonic saline. (One such indicator is FD&C Blue #1 dye, available from Sensient Colors, 2515 N. Jefferson, St. Louis, MO 63106; 1-800-325-8110 x7475; catalog #05601.)

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

Step 3. Place the ALZET pump into a 20 ml test tube prefilled with 15 ml of isotonic saline and pre-incubated at 37°C (± 0.5°C). Cap the tube to prevent evaporation.

Step 4. Record the starting time of the incubation.

Step 5. Transfer the ALZET pump to a new test tube filled with 15 ml of isotonic saline approximately every 24 hours. Record the precise time of the transfer and/or the time interval between transfers.

Step 6. Repeat Step 5 for 28 days.

Step 7. Analyze 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 in the solution initially loaded into the ALZET pump, calculate the volume pumped during each interval. Divide by the time interval in hours to obtain the hourly volume pumping rate. Note that when FD&C blue #1 dye is used, the recommended wavelength for spectrophotometric analysis is 630 nm.

IX. Additional Technical Information About ALZET Micro-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 request:

- A technical information manual
- A video of commonly used surgical implantation procedures
- Custom searches of the ALZET Osmotic Pump Bibliography of publications
- Presentation materials for authors presenting their work
- Information about ALZET Brain Infusion Kits, ALZET Catheters and other ALZET products

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

ALZET Technical Support
DURECT Corporation
10260 Bubb Road
Cupertino, CA 95014

800-692-2990 (U.S. and Canada)
408-367-4036 (Outside the U.S.)
408-865-1406 (Facsimile)
alzet@durect.com (e-mail)
www.alzet.com

X. Warranty

For a period of 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 period indicated when used in accordance with the written instructions delivered with such Product.

The sole and exclusive remedy for any breach of warranty shall be the replacement, at no cost to the customer, of those units of Product which have been shown to DURECT's reasonable satisfaction to have been defective.

THIS WARRANTY IS IN LIEU OF ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE, WHICH ARE HEREBY EXCLUDED. IN NO EVENT SHALL DURECT BE LIABLE FOR 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 OF THE PRODUCT GIVING RISE TO SUCH LIABILITY.

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