Guidance on the Use of eFlow Nebulizers (Altera® and Trio®)
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The PARI eFlow® electronic nebulizer is a new-generation aerosol delivery platform that incorporates technologic advances that significantly improve inhaled medication delivery. The aerosol generator (or aerosol head) of the eFlow platform consists of a vibrating, porous, stainless steel membrane with thousands of tiny laser-drilled holes. It is small, quiet, portable, and operates with batteries or AC current. It produces aerosol faster and is more efficient than jet nebulizers, making it very attractive for use with CF drugs. The aerosol head operates by vibrating rapidly next to the liquid drug, thus pumping the liquid through the tiny holes to create the aerosol for inhalation.

The eFlow is also more efficient at delivering drug to the lungs because it doesn't waste as much as jet nebulizers. There is almost no drug left in the chamber at the end of nebulization, and the aerosol chamber conserves nebulized drug during patient exhalation, making more drug available for the next inhalation (see Figure 1). For a brief demonstration of how the eFlow works, see the video on the PARI website at http://www.paripharma.com/technologies1.htm

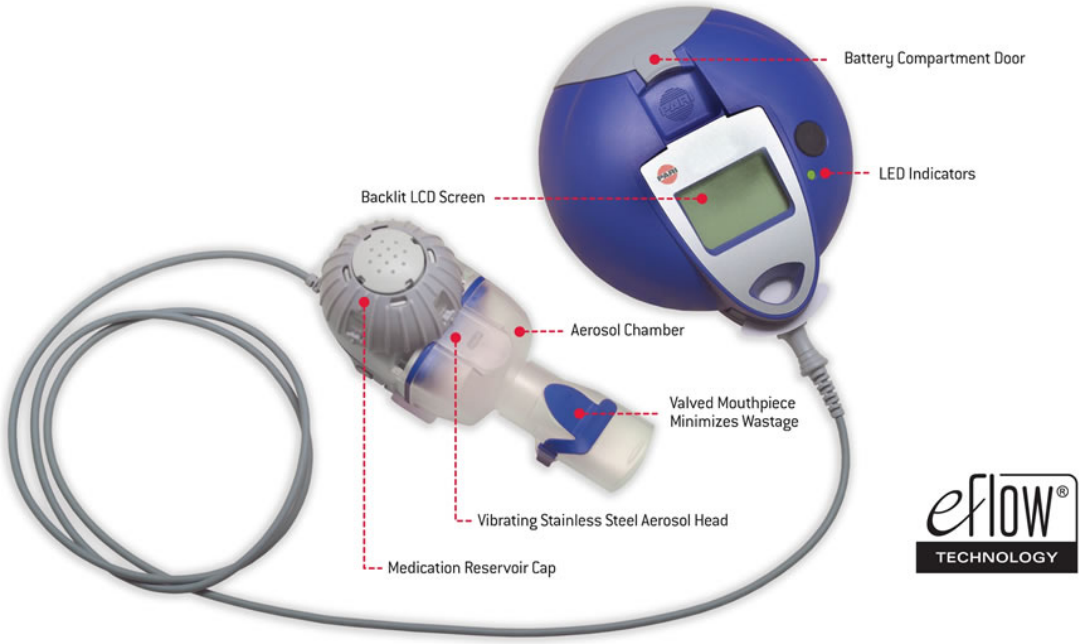

Figure 1. The eFlow consists of an electronic "controller unit" (right) and a "handset" (left). The aerosol head is mounted inside the handset and operates without noise.

There are two commercial types of the eFlow in the U.S. The Trio® (formerly the eFlow SCF) is available from a limited number of specialty pharmacies that provide CF drugs to patients, and compound drugs for use with the Trio. The Altera® is the name for the eFlow customized for use with Cayston® (aztreonam lysine for inhalation), a recently approved inhaled antibiotic. The Trio and Altera have very similar configurations and function. With the approval of Cayston, these eFlow devices will be more widely available to CF patients. Though the labeling for the Altera nebulizer states that it is only to be used for Cayston, we expect there will be a desire to use it for other CF medications to reduce the delivery time. Since these other drugs have not been adequately clinically tested with eFlow, it is *crucial* to understand the benefits and the risks of off-label use of these drugs, and how to properly use, clean and maintain the device.

The first prescription of Cayston comes with the Altera nebulizer, one controller unit and two handsets. Thereafter, each refill will come with a new handset. Cayston approved for use 3 times a day, and each dose takes about 2 minutes to nebulize. If handled properly, the aerosol head can last for 3-6 months or longer, depending on how many times it is used. That means that after a cycle of Cayston, the aerosol handset should still operate effectively for several more weeks. The main reason that the handset stops working is that the tiny holes in the membrane get clogged over time, so it takes longer to nebulize a dose (Figure 2). To prevent this, it is very important to clean the handset immediately after each use. It is also recommended that the handsets be disinfected after each use.

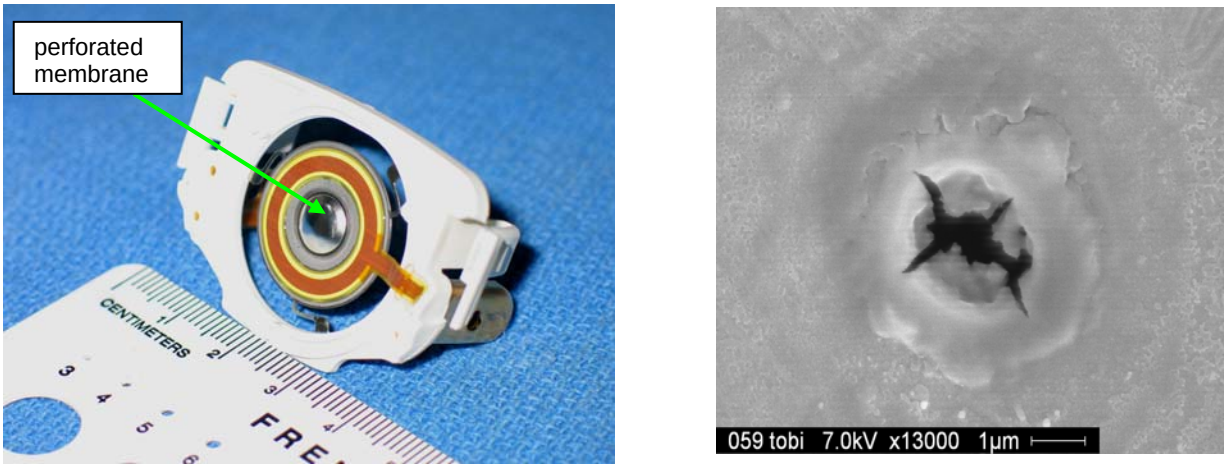

Figure 2. The metal membrane in the center of the nebulizing head has thousands of microscopic holes that cannot be seen with the naked eye (left). The holes can become clogged over time (right; magnified x 13,000).

Using the Altera or Trio with CF Drugs

The eFlow devices were designed to be used with specific drugs. It is important to recognize that there are no clinical trials to validate the effectiveness or safety of other CF drugs with eFlow nebulizers. The information about the use of eFlow with other drugs comes mostly from bench aerosol studies, small scintigraphy and pharmacokinetic studies, and anecdotal experience. These studies show that the predicted lung dose using the eFlow is about twice that of the PARI LC PLUS™, and about 4 times that of less efficient t-piece nebulizers.[1-3]

Because of the large treatment burden in CF, there is a natural temptation to use the eFlow with other drugs (off-label) to reduce that burden. Please note that the following information is not a recommendation to use off-label drugs with eFlow devices; rather it is a guide for those who choose to do so. The goal of this document is to provide guidance on the safe use of the eFlow based on available information, and to minimize potential toxicity due to high drug exposures.

- **TOBI®** comes in ampules containing 300 mg in 5 mL of fluid. The PARI LC PLUS jet nebulizer combined with the DeVilbiss® Pulmo-Aide® compressor is the approved delivery system for this drug. Aerosol device studies and small pharmacokinetic studies show that about half the dose of tobramycin in the eFlow would approximate the lung dose of TOBI delivered by the LC PLUS.[1, 4-5]

- **Hypertonic saline** is commercially available as Hypersal™ 7% in 4 mL ampules, or is prepared by pharmacies in varying concentrations. Since the eFlow leaves almost no residual (unlike jet nebulizers), 2.5 to 3 mL should approximate a routine nebulizer dose.

- **Dornase alfa** (ampules of 2.5 mL = 2.5 mg) can be delivered with a number of approved nebulizers. The eFlow does not damage the protein drug during nebulization.[9] While the eFlow can deliver 2-4 times as much as the approved nebulizers,[3] this drug is very safe, so there is minimal concern about increased side effects with a higher dose. It is possible that the higher lung dose will allow some people who take dornase alfa twice a day to reduce the frequency to once daily and still retain the benefit, though this would have to be tested clinically in each individual.

- **Bronchodilators** - Inhaled $beta_2$-agonists and anticholinergic agents are not without side effects, so a doubling or quadrupling of drug delivery to the patient may actually increase toxicity risk without an increase in benefit (dose-response curve plateaus at low doses). If the eFlow were used for bronchodilators, a significant reduction in nominal dose may be necessary to avoid toxicity. These drugs have side effects including fast heartbeat, muscle tremors, and nervousness. With the efficient eFlow, it is very important to reduce the dose of these drugs by at least half to avoid toxicity. If side effects still occur, lower the dose again, or consider alternate delivery systems.[2]

- **Colymycin (colistin)** comes in 150 mg vials, and is mixed with sterile water or saline to nebulize. The CF pulmonary clinical practice guideline "Chronic Medications for Maintenance of Lung Health" states that there was insufficient evidence to recommend the use of colistin.[6] Since colistin is not approved by the FDA for inhalation, there is no gold standard for delivery. The eFlow is 2 to 3 times more efficient than most jet nebulizers used for colistin. Commonly between 75 mg (1/2 vial) to 150 mg (full vial) of colistin is used in jet nebulizers. With the eFlow, it is estimated that between 50 to 75 mg (1/3 to 1/2 vial) would achieve similar levels of colistin in the lungs.[7,8]

- **Budesonide in Respules** is an inhaled steroid suspension, with tiny particles of drug suspended in fluid. The pulmonary clinical practice guideline "Chronic Medications for Maintenance of Lung Health" recommends against the routine use of inhaled corticosteroids in CF unless there is co-existing asthma.[6] Since the particles of drug can plug up the holes in the eFlow membrane, one should not use this drug with this device.

Drug	Usual Jet Nebulizer Dose	Suggested eFlow Dose
TOBI	**300 mg**	**150 mg**
Hypertonic Saline	**4 mL**	**2.5 - 3 mL**
Dornase alfa	**1 ampule**	**1 ampule**
Bronchodilators	**1 ampule**	**½ ampule**
Colistin	**75 - 150 mg**	**50 - 75mg**
Budesonide Respules	**1 ampule**	**Do not use**

Cleaning and Disinfecting eFlow Devices

Instructions for cleaning and disinfection come with the devices, so the emphasis here will be on how to maintain the function of the aerosol heads for as long as possible.

- Immediately after each use, disassemble the handset and wash the pieces as directed. If there is not enough time to wash in soapy water and rinse, then at a minimum rinse the parts with tap water and let it run through the aerosol head for at least 10-15 seconds. If this is not done each time, there is a risk that dried drug residue will block the membrane and cause it to malfunction. After washing, either place the parts in the sterilizer or let the parts air dry completely on a clean towel between uses.

- If using more than one drug with a single handset, rinse well between drugs to avoid drug interactions in the reservoir.

- **Never** touch, scrub, or brush the metal aerosol head. It is easily dented or scratched, which will cause it to malfunction.

- Many techniques for disinfection should not be used with the eFlow devices, including bleach, hydrogen peroxide, alcohol, and boiling. The Altera instructions recommend disinfectants like Control 3, but an electronic steam sterilizer like those used for baby bottles (e.g., Nuk® Quick 'n Ready, Figure 3) may also be used. (Do not use the type of sterilizers that are placed in the microwave) The steam sterilizers not only disinfect the devices quickly, but they also help to maintain the life of the aerosol head (Figure 3). A video demonstrating how to clean and disinfect the Altera using an electronic steam sterilizer is available on the CF Foundation's YouTube channel - http://www.youtube.com/cysticfibrosisusa#p/a/u/0/R0Drtlo7XFA.

Figure 3. Baby bottle steam sterilizers can be used for eFlow handsets and jet nebulizers.

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