Clinical Policy Bulletin: Nebulizers

Number: 0065

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Small Volume Nebulizer

Aetna considers the use of a small volume nebulizer and related compressor medically necessary durable medical equipment (DME) for any of the following indications:

A. To administer antibiotics (gentamicin, amikacin, or tobramycin, Footnotes*** to members with cystic fibrosis (CF) or bronchiectasis
B. To administer beta-adrenergics (albuterol, isoproterenol, isoetharine, levalbuterol, metaproterenol), anticholinergics (ipratropium), corticosteroids (budesonide), and cromolyn for the management of chronic obstructive pulmonary diseases (COPD) (e.g., chronic bronchitis, emphysema, asthma, etc.): Footnotes*
or
C. To administer dornase alfa (Pulmozyme)Footnotes** to members with CF or primary ciliary dyskinesia (Note: the use of Pulmozyme for other non-CF indications (e.g., asthma, chronic bronchitis, Niemann-Pick type C, and post-lung transplantation [not an all-inclusive list]) is considered experimental and investigational); or
D. To administer epinephrine for the treatment of croup; or
E. To administer formoterol (Perforomist) or arformoterol (Brovana) for the management of COPD when medical necessity criteria in Pharmacy Clinical Policy Bulletin on "Long-Acting Beta Agonists" are met; or
F. To administer treprostinil inhalation solution (Tyvaso) via an ultrasonic pulsed delivery device (the Tyvaso Inhalation System) or iloprost (Ventavis) via a controlled dose inhalation drug delivery system (i.e., the I-neb or the Prodose nebulizer) to members with pulmonary hypertension; or
G. To administer mucolytics (other than dornase alpha) (acetylcysteine) for persistent thick or tenacious pulmonary secretions; or
H. To administer pentamidine to members with HIV, pneumocystosis, or complications of organ transplants; or
I. To administer colistin for multi-drug resistant P. aeruginosa pneumonia failing to improve on IV therapy
J. To administer aztreonam inhalation solution (Cayston) to persons with CF with Pseudomonas aeruginosa.†

Aetna considers small volume nebulizers and related compressors experimental and investigational for all other indications because their effectiveness for indications other than the ones listed above has not been established.

Footnotes* For criterion (B) to be met, the physician must have considered use of a metered dose inhaler (MDI) with and without a reservoir or spacer device and decided that, for medical reasons, it was not sufficient for the administration of needed inhalation drugs.

Footnotes** More than 1 nebulizer may be considered medically necessary for members who are prescribed nebulized dornase alpha (Pulmozyme) plus other nebulized medications. The Food and Drug Administration (FDA)-approved product labeling of dornase alpha instructs that it should not be diluted or mixed with other drugs in the nebulizer. The labeling explains that mixing of dornase alpha with other drugs could lead to
adverse physicochemical and/or functional changes in dornase alpha or the admixed compound.

Footnotes*** Note on the Pari-C Plus Vented Jet Nebulizer: Aetna considers the Pari-C Plus breath-enhanced or vented jet nebulizer medically necessary for pulmonary administration of aerosolized tobramycin because there is some evidence from direct comparative studies with standard unvented jet nebulizers to suggest that the Pari-C Plus vented jet nebulizer is necessary to deliver adequate concentrations of tobramycin to the lung (e.g., Coates et al, 1998; Campbell and Saiman, 1999; Weber et al, 1994; Eisenberg et al, 1997; Ramsey et al, 1999). Consensus guidelines from the Cystic Fibrosis Foundation recommend use of the Pari-C Plus Jet Nebulizer for delivery of tobramycin to individuals with CF (Campbell and Saiman, 1999). The Kitabis Pak is a co-packaging of tobramycin Inhalation solution and Pari-LC Plus Reusable Nebulizer in a patient convenience kit. Aetna does not consider the Pari-LC Jet Plus brand of nebulizer medically necessary for nebulization of budesonide inhalation suspension (Pulmicort Respules). The Pari-LC Jet Plus Nebulizer was used in controlled clinical trials of nebulized budesonide for FDA approval. However, subsequent studies have demonstrated that brands of jet nebulizers other than Pari-LC Jet Plus are also capable of delivering a clinically effective dose of inhaled budesonide (Szefler, 1999). By contrast, ultrasonic nebulizers have been found in clinical studies to be inefficient at delivering inhaled budesonide and are not recommended for this indication (Nikander, 1994; Nikander, 1999).

† Note on the Altera Nebulizer System: Aetna considers the Altera Nebulizer System medically necessary only to administer aztreonam inhalation solution (Cayston) to persons with CF with Pseudomonas aeruginosa. The FDA-approved labeling for Cayston states that it should only be administered with the Altera Nebulizer System.

II. Large Volume Nebulizer:

Aetna considers a large volume nebulizer, related compressor, and water or saline medically necessary DME to deliver humidity to a person with thick, tenacious secretions, with any of the following indications:

A. Administration of pentamidine for members with HIV, pneumocystosis, and complications of organ transplants;
B. Bronchiectasis;
C. Cystic fibrosis;
D. Tracheobronchial stent;
E. Tracheostomy.

Aetna considers a large volume nebulizer and related compressor experimental and investigational for all other indications because their effectiveness for indications other than the ones listed above has not been established.

III. Ultrasonic Nebulizers:

Aetna considers the use of ultrasonic nebulizers medically necessary DME for delivery of tobramycin (Tobi) for members with CF who meet the criteria for a standard nebulizer.

Because there is no proven medical benefit to nebulizing particles of other drugs to diameters smaller than achievable with a pneumatic model, ultrasonic nebulizers are considered medically necessary only when all of the following criteria are met:

A. The member meets the criteria for a standard nebulizer; and
B. The primary care physician and specialist indicate that the member has been compliant with other nebulizer and medication therapy; and
C. The use of a standard nebulizer has failed to control the member’s disease and prevent the member from utilizing the hospital or emergency room.

Aetna considers ultrasonic nebulizers experimental and investigational for all other indications because their effectiveness for indications other than the ones listed above has not been established.

IV. Battery Powered Compressors:

A battery-powered compressor is rarely medically necessary. Accompanying documentation must be submitted justifying its medical necessity.
V. Accessories:

A. Aetna considers disposable large volume nebulizers convenience items. A non-disposable unfilled nebulizer filled with water or saline by the member/caregiver is an acceptable alternative.

B. Note: Kits and concentrates for use in cleaning respiratory equipment are not covered. This is consistent with Medicare's policy.

VI. Replacement:

For members with DME benefits, Aetna considers replacement of nebulizers medically necessary on an individual basis if both of the following criteria are met:

A. The primary care physician and/or specialist confirm that the member has been compliant with the nebulizer and anticipate the need for continued use to prevent a hospital admission or emergency room visits; and

B. The warranty has expired.

The following table lists the usual maximum frequency of replacement for accessories that is considered medically necessary.

- Administration set, small volume filtered pneumatic nebulizer: 1/month
- Administration set, small volume non-filtered pneumatic nebulizer, disposable: 2/month
- Administration set, small volume non-filtered pneumatic nebulizer, non-disposable: 1 per 6 months
- Aerosol mask, used with DME nebulizer: 1/month
- Corrugated tubing, disposable, used with large volume nebulizer: 100 feet/2 months
- Corrugated tubing, non-disposable, used with large volume nebulizer: 10 feet/year
- Dome and mouthpiece, used with small volume ultrasonic nebulizer: 2/year
- Face tent: 1/month
- Filter, disposable, used with aerosol compressor: 2/month
- Filter, non-disposable, used with aerosol compressor or ultrasonic generator: 1 per 3 months
- Immersion external heater for nebulizer: 1 per 3 years
- Nebulizer, durable glass or autoclavable plastic, bottle type, not used with oxygen: 1 per 3 years
- Small volume non-filtered pneumatic nebulizer, disposable: 2/month
- Tracheostomy mask or collar: 1/month
- Water collection device, used with large volume nebulizer: 2/month.

VII. Nebulized Corticosteroids for the Treatment of Nasal Polyps and Viral Wheezing

Aetna considers the use of nebulized corticosteroids for the treatment of nasal polyps, including in the pre- and post-polypectomy periods, experimental and investigational because of insufficient evidence of the clinical value of nebulized corticosteroids over established forms of nasal corticosteroid administration (e.g., nasal spray, metered-dose nasal inhaler).

Aetna considers the use of nebulized corticosteroids for the prevention and treatment of viral wheezing experimental and investigational because the effectiveness of this approach has not been established.

VIII. Nebulized Lidocaine as Pain Relief for Nasogastric Tube Insertion in Children

Aetna considers the use of nebulized lidocaine as pain relief for nasogastric tube insertion in children experimental and investigational because the effectiveness of this approach has not been established.

IX. Nebulized Lidocaine for the Treatment of Chronic Cough

Aetna considers the use of nebulized lidocaine for the treatment of chronic cough experimental and investigational because the effectiveness of this approach has not been established.

X. Nebulized Magnesium

Aetna considers nebulized magnesium for the treatment of pediatric asthma experimental and investigational because the effectiveness of this approach has not been established.

See also CPB 0593 - Aerosolized or Irrigated Anti-infectives for Sinusitis
Background

In this policy, the actual equipment (i.e., electrical devices) are referred to as either a compressor (when nebulization of liquid is achieved by means of air flow) or as a generator (when nebulization of liquid is achieved by means of ultrasonic vibrations). The term nebulizer is generally used for the actual chamber in which the nebulization of liquid occurs and is an accessory to the equipment. The nebulizer is attached to an aerosol compressor or an ultrasonic generator in order to achieve a functioning delivery system for aerosol therapy.

The plan of care must contain the specific condition of the patient justifying the medical necessity of each item. The order for any drug must clearly specify the type of solution to be dispensed to the patient and the administration instructions for that solution. The type of solution is described by a combination of

i. the name of the drug and the concentration of the drug in the dispensed solution and the volume of solution in each container, or

ii. the name of the drug and the number of milligrams/grams of drug in the dispensed solution and the volume of solution in that container.

A narrative diagnosis and/or an ICD-9 diagnosis code describing the condition must be present on each order. An ICD-9 code describing the condition that necessitates nebulizer therapy must be included on each claim for equipment, accessories, and/or drugs. The patient's medical record must contain information that supports the medical necessity for all equipment, accessories, drugs and other supplies that are ordered.

Chronic infection with *Pseudomonas aeruginosa* is associated with progressive deterioration in lung function in cystic fibrosis (CF) patients. Nebulized antibiotics/anti-infectives (e.g., colistin and tobramycin) have been used in the management of these patients.

In a prospective double-blind placebo-controlled study, Jensen et al (1987) assessed the effects of colistin inhalation in 40 patients with CF and chronic broncho-pulmonary *P. aeruginosa* infection. Active treatment consisted of inhalation of colistin 1 million units twice-daily for 3 months and was compared to placebo inhalations of isotonic saline. Significantly more patients in the colistin inhalation group completed the study as compared to the placebo group (18 versus 11). Colistin treatment was superior to placebo treatment in terms of a significantly better clinical symptom score, maintenance of pulmonary function and inflammatory parameters. The authors recommended colistin inhalation therapy for CF patients with chronic *P. aeruginosa* lung infection as a supplementary treatment to frequent courses of intravenous anti-pseudomonas chemotherapy.

Pai and Nahata (2001) noted that aerosolized tobramycin doses ranging from 80 mg 2 or 3 times daily to 600 mg 3 times daily have been used in various clinical trials. At an 80-mg dose, preservation of pulmonary function with little or no improvement over the baseline was reported. Tobramycin, nebulized at 600 mg 3 times daily, significantly improved clinical and pulmonary functions and reduced the density of *P. aeruginosa* in the sputum. No ototoxicity or nephrotoxicity was reported at either dose. An increased risk of emergence of resistant strains of *P. aeruginosa* was noted at all doses, after prolonged use.

Tobramycin solution for inhalation (TOBI) received U.S. Food and Drug Administration approval for the maintenance therapy of patients 6 years or older with CF who have between 25 % and 75 % of predicted forced expiratory volume in 1 second (FEV(1)), are colonized with *P. aeruginosa*, and are able to comply with the prescribed medical regimen. TOBI was not approved for the therapy of acute pulmonary exacerbations in patients with CF, nor was it approved for use in patients without CF (Prober et al, 2000).

In a randomized clinical trial, Hodson et al (2002) evaluated the safety and effectiveness of tobramycin nebulizer solution (TNS) and nebulized colistin in CF patients chronically infected with *P. aeruginosa*. A total of 115 patients, aged 6 yrs or older, were randomized to receive either TNS or colistin, twice-daily for 4 weeks. The primary end point was an evaluation of the relative change in lung function from baseline, as measured by FEV(1) % predicted. Secondary end points included changes in sputum *P. aeruginosa* density, tobramycin/colistin minimum inhibitory concentrations and safety assessments. TNS produced a mean 6.7 % improvement in lung function (p = 0.006), while there was no significant improvement in the colistin-treated patients (mean change 0.37 %). Both nebulized antibiotic regimens produced a significant decrease in the sputum *P. aeruginosa* density, and there was no development of highly resistant strains over the course of the study. The safety profile for both nebulized antibiotics was good. Tobramycin nebulizer solution significantly improved lung function of patients with CF chronically infected with *P. aeruginosa*, but colistin did not, in this study of 1-month's duration. Both treatments reduced the bacterial load.
In a review on the role of nebulized antibiotics for the treatment of respiratory infections, Klepser (2004) stated that data regarding this topic are scarce. At this time, data support the use of aerosolized tobramycin solution for inhalation in CF patients infected or colonized by *P. aeruginosa*. Apart from this situation, widespread aerosolized administration of other agents in CF and non-CF patient populations should not be advocated.

There is a lack of adequate evidence supporting the use of nebulized opioids for dyspnea. Foral et al (2004) performed a structured review of the evidence for the use of nebulized morphine for the relief of dyspnea in persons with chronic obstructive pulmonary disease. The investigators concluded that there is inadequate evidence from placebo-controlled studies to support the use of nebulized morphine for the relief of dyspnea in patients with chronic obstructive pulmonary disease (COPD). These investigators reported that published studies vary considerably in the dose, opioid used, administration schedule, and methodology. One study found improved exercise capacity in 11 patients not reproducible in a larger sample, and another study found benefit in 54 terminal patients. All other studies found no benefit. These investigators noted, furthermore, that recently published Global Initiative for Lung Disease guidelines have specifically stated that opioids are contraindicated in COPD management due to the potential respiratory depression and worsening hypercapnia. The authors concluded that nebulized opioids should be discouraged in COPD, as current data do not support their use.

In a systematic review, Viola et al (2008) assessed the effectiveness of 4 drug classes (opioids, phenothiazines, benzodiazepines, and systemic corticosteroids) for relieving dyspnea experienced by advanced cancer patients. Search sources included Medline, Embase, HealthSTAR, CINAHL, and the Cochrane Library. Four reviewers selected evidence using pre-defined criteria: controlled trials not limited to cancer and involving the specified drug classes for dyspnea treatment. Three systematic reviews, 1 with meta-analysis, 2 practice guidelines, and 28 controlled trials were identified. Most examined the effect of opioids, generally morphine, on dyspnea. Although the results of individual trials were mixed, the systematic review with meta-analysis detected a significant benefit for dyspnea with systemic opioids; 2 small placebo-controlled trials in cancer patients found systemic morphine reduced dyspnea, and dihydrocodeine also significantly reduced dyspnea in 4 placebo-controlled trials. Nebulized morphine was not effective in controlling dyspnea in any study or the meta-analysis. No controlled trials examined systemic corticosteroids in the treatment of cancer patients, and of the other non-opioid drugs examined, only oral promethazine, a phenothiazine, showed some benefit in the relief of dyspnea. Studies varied in methodological quality. The authors concluded that systemic opioids, administered orally or parenterally, can be used to manage dyspnea in cancer patients. Oral promethazine may also be used, as a 2nd-line agent if systemic opioids can not be used or in addition to systemic opioids. Nebulized morphine, prochlorperazine, and benzodiazepines are not recommended for the treatment of dyspnea, and promethazine must not be used parenterally.

There is insufficient evidence of the clinical value of nebulized corticosteroids for the treatment of nasal polyps, including in the pre- and post- polypectomy periods, over established forms of nasal corticosteroid administration (e.g., nasal spray, metered-dose nasal inhaler). Bikhazi (2004) stated that "no clinical studies have yet documented nebulized nasal steroid benefit".

There is inadequate evidence to support the use of nebulizers over spacers for delivery of beta-agonists in acute asthma. In a Cochrane review that compared holding chambers (spacers) versus nebulizers for beta-agonist treatment of acute asthma (Cates et al, 2006a), it was found that MDIs with spacer produced outcomes that were at least equivalent to nebulizer delivery. Spacers may have some advantages compared to nebulizers for children with acute asthma.

Evidence is limited to support the use of nebulizers over spacers for delivering inhaled corticosteroids in chronic asthma. In a Cochrane review that compared holding chambers versus nebulizers for inhaled steroids in chronic asthma (Cates et al, 2006b), it was concluded that budesonide in high dose delivered by the particular nebulizer used in the only double-blinded study that could be included in this review was more effective than budesonide 1,600 ug via a large volume spacer. However, it is unclear if this was an effect of nominal dose delivered or delivery system. Cost, compliance and patient preference are important determinants of clinical effectiveness that still require further assessment. Future studies are needed to ascertain the relative effectiveness of inhaled corticosteroids delivered by different combinations of nebulizer/compressor compared to holding chamber. Moreover, further studies evaluating these delivery methods are needed in infants and pre-school children, as these are groups that are likely to be considered for treatment with nebulized corticosteroids.

Nasogastric tube (NGT) insertion is a common procedure in children that is very painful and distressing. There is insufficient evidence to support the use of nebulized lidocaine for NGT insertion. In a randomized, double-blind, placebo-controlled trial, Babl et al (2009) examined if nebulized lidocaine reduce the pain and distress of NGT insertion in young children. Patients were eligible if they were aged from 1 to 5 yrs with no co-morbid disease and a clinical indication for a NGT. Nebulization occurred for 5 mins, 5 mins before NGT insertion. Video recordings before, during, and after the procedure were rated using the Face, Legs, Activity, Cry, and Consolability (FLACC) pain and distress
assessment tool (primary outcome measure) and pain and distress visual analog scale scores (secondary outcome measures). Difficulty of insertion and adverse events were also assessed. A total of 18 subjects were nebulized with 2 % lidocaine and 18 subjects with normal saline. Nebulization was found to be highly distressing; FLACC scores during NGT insertion were very high in both groups. There was a trend in the post-NGT insertion period toward lower FLACC scores in the lidocaine group. Visual analog scale scores for this post-insertion period were significantly lower in the lidocaine arm for pain and distress. There were no significant differences between groups in terms of difficulty of insertion and the number of minor adverse events. The study was terminated early because of the distress and treatment delay associated with nebulization. The authors concluded that NGT insertion results in very high FLACC scores irrespective of lidocaine use. They stated that nebulized lidocaine cannot be recommended as pain relief for NGT insertion in children. The delay and distress of nebulization likely outweigh a possible benefit in the post-insertion period.

Kuo et al (2010) performed a systematic review of current knowledge concerning the use of nebulized lidocaine to reduce the pain of NGT insertion in order to develop evidence-based guidelines. In addition, a meta-analysis of appropriate randomized controlled trials (RCTs) was performed. The databases included PubMed (1996 to 2009), ProQuest (1982 to 2009), CINAHL (1982 to 2009), and the Cochrane Central Register of Controlled Trials (2009), and reference lists of articles. Experts in this field also were contacted. Two investigators selected the research based on inclusion criteria and reviewed each study's quality according to the Jadad scale. Five RCTs with 212 subjects were identified. A total of 113 (58 %) subjects were women. The mean age of treatment and control groups was 59.6 and 55 years, respectively. The countries of studies were the United States, United Kingdom, Australia, Canada, and Thailand. In the treatment groups, the use of lidocaine concentration was 4 % and 10 %. The pooled effect size was 0.423 (95 % confidence interval: 0.204 to 0.880; Z = -2.301; p = 0.021), indicating that the use of nebulized lidocaine before NGT insertion can decrease pain by 57.7 %. The authors concluded that there is insufficient evidence to recommend the dosage, concentration, or delivery method. They stated that further research is needed to articulate a comprehensive clinical guideline.

Cayston (aztreonam for inhalation solution) has been approved by the FDA to improve respiratory symptoms in cystic fibrosis patients with Pseudomonas aeruginosa. The FDA approval of Cayston was based on a randomized, double-blind, placebo-controlled, multi-center trial in 164 subjects. Subjects received either Cayston (75 mg) or volume-matched placebo administered by inhalation 3 times a day for 28 days. Patients were required to have been off antibiotics for at least 28 days before treatment with study drug. The primary efficacy endpoint was improvement in respiratory symptoms on the last day of treatment with Cayston or placebo. Statistically significant improvements were seen in both adult and pediatric patients, but were substantially smaller in adult patients. The treatment difference at 28 days between Cayston-treated and placebo-treated patients for percent change in forced expiratory volume in 1 second (FEV1) was statistically significant at 10 %. Improvements in FEV1 were comparable between adult and pediatric patients. Two weeks after completion of drug treatment, the difference in FEV1 between Cayston and placebo groups had decreased to 6 %.

Cayston is supplied as a single-use vial of sterile, lyophilized aztreonam to be reconstituted with 1-ml ampule of sterile diluent designed for administration via inhalation using an Altera Nebulizer System. The recommended dose of Cayston for both adults and pediatrics 7 yrs of age and older is 1 single-use vial (75 mg of aztreonam) reconstituted with 1 ml of sterile diluent administered 3 times a day for a 28-day course (followed by 28 days off Cayston therapy). Dosage is not based on weight or adjusted for age. Doses should be taken at least 4 hours apart.

An UpToDate review on “Primary ciliary dyskinesia (immotile-cilia syndrome (Bergstrom, 2012) states that “Daily chest physiotherapy is important in compensating for diminished or absent mucociliary clearance. The effectiveness of DNase and other mucolytic agents, such as hypertonic saline and acetylcysteine, has not been fully assessed in PCD, but may be tried, particularly in patients with recurrent infections or ongoing respiratory symptoms”.

Lim and colleagues (2013) stated that the long-term safety of patient-administered nebulized lidocaine for control of chronic cough has not been established. These researchers performed a retrospective, case-series study of adults who received a prescription and nurse education for nebulized lidocaine for chronic cough between 2002 and 2007. A survey questionnaire inquiring about adverse events (AEs) and the effectiveness of nebulized lidocaine was developed and administered to these individuals after the nebulized lidocaine trial. They conducted 2 mailings and a post-mailing phone follow-up to non-responders. When AEs were reported in the questionnaire response, a structured phone interview was conducted to obtain additional details. Of 165 eligible patients, 99 (60 %) responded to the survey. Responders were a median age of 62 years (range of 29 to 87 years); 77 (79 %) were women, and 80 (82 %) were white. The median duration of cough was 5 years before treatment with nebulized lidocaine. Of the patients who used nebulized lidocaine (93 % of survey responders), 43 % reported an AE. However, none of these events required an emergency visit, hospitalization, or antibiotic therapy for aspiration pneumonia. The mean (SD) of the pre-treatment cough severity score was 8.4 (1.6) and post-treatment was 5.9 (3.4) (p < 0.001). Of the patients reporting improvement
in cough symptoms (49 %), 80 % reported improvement within the first 2 weeks. The authors concluded that adults tolerated self-administration of nebulized lidocaine for difficult-to-control chronic cough. No serious AEs occurred while providing symptomatic control in 49 % of patients. The findings of this retrospective case-series study need to be validated by well-designed studies.

Truesdale and Jurdi (2013) noted that persistent cough can disrupt daily activities such as conversation, eating, breathing, and sleeping, and it can become extremely debilitating both physically and mentally. Pharmacological treatments include dextramethorphan, opioid cough suppressants, benzonatate, inhaled ipratropium, and guaifenesin. Successful cough suppression has also been demonstrated in several studies with the use of nebulized lidocaine. Nebulized lidocaine also appears to be well-tolerated by patients with minimal side effects including dysphonia, oropharyngeal numbness, and bitter taste. Moreover, the authors concluded that studies conducted thus far have been small, so larger RCTs comparing nebulized lidocaine to placebo need to be conducted in the future.

Furthermore, an UpToDate review on “Treatment of subacute and chronic cough in adults” (Weinberger and Silvestri, 2013) does not mention the use of nebulized lidocaine as a therapeutic option.

In a double-blind RCT, Doull et al (1997) determined the effect of regular prophylactic inhaled corticosteroids on wheezing episodes associated with viral infection in school age children. A total of 104 children aged 7 to 9 years who had had wheezing in association with symptoms of upper and lower respiratory tract infection in the preceding 12 months were included in this study. After a run-in period of 2 to 6 weeks, children were randomly allocated twice-daily inhaled beclomethasone dipropionate 200 ug or placebo through a Diskhaler for 6 months with a wash-out period of 2 months. Children were assessed monthly. Main outcome measures were FEV1; bronchial responsiveness to methacholine (PD20); percentage of days with symptoms of upper and lower respiratory tract infection with frequency, severity, and duration of episodes of upper and lower respiratory symptoms and of reduced peak expiratory flow rate. During the treatment period there was a significant increase in mean FEV1 (1.63 versus 1.53 L; adjusted difference 0.09 1 (95 % confidence interval [CI]: 0.04 to 0.14); p = 0.001) and methacholine PD20 12.8 versus 7.2 mumol/L; adjusted ratio of means 1.7 (1.2 to 2.4); p = 0.007) in children receiving beclomethasone dipropionate compared with placebo. There were, however, no significant differences in the percentage of days with symptoms or in the frequency, severity, or duration of episodes of upper or lower respiratory symptoms or of reduced peak expiratory flow rate during the treatment period between the 2 groups. The authors concluded that although lung function is improved with regular beclomethasone dipropionate 400 ug/day, this treatment offered no clinically significant benefit in school age children with wheezing episodes associated with viral infection.

Guilbert and Bacharier (2011) noted that virus-induced wheezing in infants who have not experienced previous wheezing, termed bronchiolitis, leads to significant morbidity, and can be particularly difficult to treat. Despite a multitude of trials, no consistent benefits in clinical outcomes have been observed when inhaled bronchodilators, corticosteroids (systemic or inhaled), or montelukast have been studied during bronchiolitis episodes. However, a post-hoc analysis reported that while infants who wheezed with rhinovirus did not derive benefit from oral corticosteroid therapy during the acute severe rhinovirus-induced episode, they appeared less likely to develop recurrent wheezing over the following year. This finding, if confirmed, suggests a distinct pathogenesis and therapeutic approach for infants diagnosed with rhinovirus-induced wheezing illnesses. The authors concluded that the management of these wheezing episodes remains a distinct clinical challenge. While research over the last 2 decades had shed substantial light on this problem, clinicians remained uncertain as to the optimal management strategies in this heterogeneous population.

A review on “Bronchiolitis” by the Egton Medical Information Systems Limited (Knott, 2013) stated that “Corticosteroids -- trials have consistently failed to provide evidence of benefit. A large multicenter randomized controlled trial (RCT), comparing the use of a single dose of oral dexamethasone with placebo in children diagnosed with bronchiolitis in Emergency Departments, failed to show any significant differences in the rates of hospital admission, respiratory status after four hours or longer-term outcomes”.

Verma et al (2013) stated that bronchiolitis is one of the major causes for hospital admissions in infants. Managing bronchiolitis, both in the out-patient and in-patient settings remain a challenge to the treating pediatrician. The effectiveness of various interventions used for infants with bronchiolitis remains unclear. These researchers evaluated the evidence supporting the use of currently available treatment and preventive strategies for infants with bronchiolitis and provided practical guidelines to the practitioners managing children with bronchiolitis. They performed a search of articles published on bronchiolitis using PubMed. The areas of focus were diagnosis, treatment and prevention of bronchiolitis in children. Relevant information was extracted from English language studies published over the last 20 years. In addition, the Cochrane Database of Systematic Reviews was searched. Supportive care, comprising of taking care of oxygenation and hydration, remains the corner-stone of therapy in bronchiolitis. Pulse oximetry helps in guiding the need for oxygen administration. Several recent evidence-based reviews have suggested that bronchodilators or corticosteroids lack efficacy in bronchiolitis and should not be routinely used. A number of other
novel therapies (e.g., nebulized hypertonic saline, heliox, CPAP, montelukast, surfactant, and inhaled furosemide) have been evaluated in clinical trials, and although most of them did not show any beneficial results, some like hypertonic saline, surfactant, CPAP have shown promising results.

In a double-blind RCT, Clavenna et al (2014) evaluated the effectiveness of nebulized beclomethasone in preventing the recurrence of viral wheezing. Outpatient children aged 1 to 5 years with at least 1 episode of viral wheezing in the last 12 months, presenting to any of 40 Italian pediatricians for an upper respiratory tract infection, were randomly allocated to receive beclomethasone 400 μg or placebo twice-daily for 10 days. Medications were administered through a nebulizer. A clinical evaluation was performed by the pediatrician at the start and end of the treatment period. A subjective evaluation of symptoms and effectiveness of treatment was performed by the parents. The primary end-point was the incidence of viral wheezing diagnosed by the pediatricians during the 10-day treatment period. A total of 525 children were enrolled in the study, 521 of whom were visited at the end of the treatment period. Wheezing was diagnosed by the pediatricians in 47 children (9.0 % [95 % CI: 6.7 to 11.3]), with no statistically significant differences between treatment groups (beclomethasone versus placebo relative risk: 0.61 [95 % CI: 0.35 to 1.08]). The treatment was considered helpful by 63 % of parents (64 % in the beclomethasone group versus 61 % in the placebo group). In all, 46 % of children still had infection symptoms at the end of the treatment period, with no differences between groups. The authors concluded that the findings from this study confirmed that inhaled steroids are not effective in preventing recurrence of viral wheezing. Moreover, no benefits were found in reducing symptoms of respiratory tract infections.

Furthermore, in an eMedicine review on “Bronchiolitis Treatment & Management”, DeNicola (2014) stated that “Steroid treatment has not been shown to decrease the long-term incidence of wheezing or asthma after RSV infection. Nebulized steroid treatment has not been proven efficacious”.

In a Cochrane review, Bjornson et al (2013) evaluated the safety (frequency and severity of side effects) and effectiveness (measured by croup scores, rate of intubation and health care utilization such as rate of hospitalization) of nebulized epinephrine versus placebo in children with croup, evaluated in an emergency department (ED) or hospital setting. These investigators searched CENTRAL 2013, Issue 6, MEDLINE (1966 to week 3 of June 2013), EMBASE (1980 to July 2013), Web of Science (1974 to July 2013), CINAHL (1982 to July 2013) and Scopus (1996 to July 2013). Randomized controlled trials or quasi-RCTs of children with croup evaluated in an ED or admitted to hospital were selected for analysis. Comparisons were: nebulized epinephrine versus placebo, racemic nebulized epinephrine versus L-epinephrine (an isomer) and nebulized epinephrine delivered by intermittent positive pressure breathing (IPPB) versus nebulized epinephrine without IPPB. Primary outcome was change in croup score post-treatment. Secondary outcomes were rate and duration of intubation and hospitalization, croup return visit, parental anxiety and side effects. Two authors independently identified potentially relevant studies by title and abstract (when available) and examined relevant studies using a priori inclusion criteria, followed by methodological quality assessment. One author extracted data while the second checked accuracy. They used the standard methodological procedures expected by the Cochrane Collaboration. A total of 8 studies (225 participants) were included. In general, children included in the studies were young (average age less than two years in the majority of included studies). Severity of croup was described as moderate-to-severe in all included studies; 6 studies took place in the inpatient setting, 1 in the ED and one setting was not specified. Six of the 8 studies were deemed to have a low-risk of bias and the risk of bias was unclear in the remaining 2 studies. Nebulized epinephrine was associated with croup score improvement 30 minutes post-treatment (3 RCTs, standardized mean difference (SMD) -0.94; 95 % confidence interval [CI]: -1.37 to -0.51; I(2) statistic = 0 %). This effect was not significant 2 and 6 hours post-treatment. Nebulized epinephrine was associated with significantly shorter hospital stay than placebo (1 RCT, MD -32.0 hours; 95 % CI: -59.1 to -4.9). Comparing racemic and L-epinephrine, no difference in croup score was found after 30 minutes (SMD 0.33; 95 % CI: -0.42 to 1.08). After 2 hours, L-epinephrine showed significant reduction compared with racemic epinephrine (1 RCT, SMD 0.87; 95 % CI: 0.09 to 1.65). There was no significant difference in croup score between administration of nebulized epinephrine via IPPB versus nebulization alone at 30 minutes (1 RCT, SMD -0.14; 95 % CI: -1.24 to 0.95) or 2 hours (SMD -0.72; 95 % CI: -1.86 to 0.42). None of the studies sought or reported data on adverse effects. The authors concluded that nebulized epinephrine is associated with clinically and statistically significant transient reduction of symptoms of croup 30 minutes post-treatment. Evidence does not favor racemic epinephrine or L-epinephrine, or IPPB over simple nebulization. The authors noted that data and analyses were limited by the small number of relevant studies and total number of participants and thus most outcomes contained data from very few or even single studies.

An UpToDate review on “Croup: Approach to management” (Woods, 2104a) states that “Corticosteroids and nebulized epinephrine have become the cornerstones of therapy”. Furthermore, an UpToDate review on “Croup: Pharmacologic and supportive interventions” (Woods, 2014b) states that “The administration of nebulized epinephrine to patients with moderate to severe croup often results in rapid improvement of upper airway obstruction …. Racemic epinephrine, which is a 1:1 mixture of the D- and L-isomers, was initially thought to produce fewer systemic side effects, such as tachycardia and hypertension. However, a randomized double-blind study comparing racemic epinephrine and L-
epinephrine in children with croup found no difference between the two preparations in 30-minute croup score, heart rate, blood pressure, respiratory rate, fraction of inspired oxygen, or oxygen saturation. This finding is particularly important outside of the United States, where racemic epinephrine is not readily available. Either form of epinephrine is acceptable to use in the United States. Racemic epinephrine is administered as 0.05 ml/kg per dose (maximum of 0.5 ml) of a 2.25 percent solution diluted to 3 ml total volume with normal saline. It is given via nebulizer over 15 minutes. L-epinephrine is administered as 0.5 ml/kg per dose (maximum of 5 ml) of a 1:1000 dilution. It is given via nebulizer over 15 minutes. Nebulized epinephrine treatments may be repeated every 15 to 20 minutes if warranted by the clinical course. Children who require repeated frequent dosing (e.g., three or more doses within two to three hours) to achieve stabilization of their respiratory function generally should be admitted to an intensive care unit or intermediate care setting (depending on the severity of persisting signs).

Florin and colleagues (2015) described utilization of 3 % hypertonic saline (HTS) in hospitalized infants and evaluated the association between HTS use and length of stay (LOS) in a real-world setting. This multi-center retrospective cohort study included infants less than or equal to 12 months of age hospitalized with bronchiolitis between October 2008 and September 2011 using the Pediatric Health Information System. Hypertonic saline use was categorized as trial, rescue, daily, or sporadic. Differences in LOS were compared after matching daily HTS recipients and non-recipients on propensity score. There were 63,337 hospitalizations for bronchiolitis; HTS was used in 24 of 42 hospitals and 2.9 % of all hospitalizations; HTS use increased from 0.4 % of visits in 2008 to 9.2 % of visits in 2011. There was substantial variation in HTS use across hospitals (range of 0.1 % to 32.6 %). When used, HTS was given daily during 60.6 % of hospitalizations, sporadically in 10.4 %, as a trial in 11.3 %, and as a rescue in 17.7 %. The propensity score-matched analysis of daily HTS recipients (n = 953) versus non-recipients (n = 953) showed no difference in mean LOS (HTS 2.3 days versus non-recipients 2.5 days; β-coefficient -0.04; 95 % CI: -0.15 to 0.07; p = 0.5) or odds of staying longer than 1, 2, or 3 days. Daily HTS recipients had a 33 % decreased odds of staying in the hospital greater than 4 days compared with non-recipients (OR 0.67; 95 % CI: 0.47 to 0.97; p = 0.03). The authors concluded that variation in HTS use and the lack of association between HTS and mean LOS demonstrated the need for further research to standardize HTS use and better define the infants for whom HTS will be most beneficial.

Boyden et al (2015) stated that dyspnea significantly impacts quality of life and is one of the most common symptoms in advanced illness. Systemically-administered opioids and benzodiazepines have been the most studied and utilized pharmacologic treatments for refractory dyspnea. Less attention has been given to the use of these medications and others when nebulized. These investigators reviewed the literature on the use of nebulized medications for the treatment of dyspnea related to cancer, COPD, CF, interstitial lung disease, or experimentally-induced dyspnea. A systematic review of peer-reviewed literature was conducted using Medline/PubMed, CINAHL, Cochrane, and Google Scholar. A total of 39 publications were included in this review, including 17 high-quality clinical research studies, as defined by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The evidence for nebulized morphine remains mixed, whereas a potential benefit was suggested for nebulized furosemide, hydromorphone, and fentanyl. No conclusions could be drawn as to which disease population derived greatest benefit from nebulized medications, or whether jet or ultrasonic nebulizers were more effective for the delivery of these medications. The authors concluded that more research is needed to assess the characteristics of specific diseases and the combination of different nebulizers and medications that may yield the greatest benefit, and to assess the safety and effectiveness of the chronic use of nebulized opioids and furosemide. They stated that until larger, longer-term studies are completed, the use of nebulized medications to treat dyspnea should be assessed on a case-by-case basis and may be considered if the hoped-for benefits outweigh potential harm.

Brovana (Arformoterol Inhalation Solution):

Brovana (arformoterol) is a Long Acting Beta2 Agonist (LABA) and the (R,R) enantiomer of formoterol, which contains both the (R,R) and (S,S) enantiomers. The (S,S) enantiomer is about 1,000 fold less potent as a beta agonist than the (R,R) enantiomer. Brovana (arformoterol) has a two fold greater potency than the racemic mixture of formoterol. It is an inhalation solution delivered via nebulizer.

Brovana (arformoterol) stimulates intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3′, 5′ adenosine monophosphate (cyclic AMP). Increased intracellular cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Brovana (arformoterol) is indicated for twice daily (morning and evening) maintenance treatment of bronchoconstriction in chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Brovana (arformoterol) is inappropriate in those with deteriorating COPD and increasing the dose beyond what is in the package label is not recommended.

In pivotal clinical studies involving more than 1,400 members, Brovana (arformoterol) demonstrated statistically
significant improvement in FEV1 compared to placebo. In other clinical studies, Brovana (arformoterol) demonstrated superior efficacy and faster onset of action compared to both salmeterol and placebo. Efficacy was defined as at least a 10% improvement in lung function as measured by FEV1 over a 12 week treatment period. Brovana (arformoterol) does not have outcomes studies to show impact on member mortality or progression of disease.

Brovana (arformoterol) inhalation solution is available as 15 mcg of arformoterol (equivalent to 22 mcg of arformoterol tartrate) in 2 ml unit dose vials. Brovana (arformoterol) is available in 30 or 60 vial package sizes.

The recommended dose of Brovana (arformoterol) for COPD is 15 mcg twice daily (morning and evening) by nebulization. A total daily dose greater than 30 mcg is not recommended.

Brovana (arformoterol) therapy is not indicated in the following:

- Acutely deteriorating COPD
- Concurrent use with other medications containing Long acting beta2 adrenergic agonists
- Asthma, in the absence of concurrent medication containing inhaled corticosteroid and comorbid COPD diagnosis.

Brovana (arformoterol) is not intended for rescue therapy or as monotherapy since the onset of bronchodilation occurs 20 minutes after administration and peak effect may not be observed until 1-3 hours after dosing.

Long Acting Beta2 Adrenergic Agonists carry a boxed warning. Long Acting Beta2 Adrenergic Agonists (LABAs) may increase the risk of Asthma related exacerbations, hospitalizations, and death. While LABAs may be considered without concurrent corticosteroid in COPD members, they should be avoided as monotherapy in asthma members.

This class labeling is based on analyses from the Salmeterol Multi center Asthma Research Trial (SMART), the Salmeterol Nationwide Surveillance study (SNS), and a meta analysis conducted by FDA in 2008 and discussed at the joint Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, held on December 10-11, 2008.

Effective February 2010, the FDA now requires a risk management program called a Risk Evaluation and Mitigation Strategy (REMS) for these products. The REMS for LABAs will include a revised Medication Guide written specifically for members, and a plan to educate healthcare professionals about the appropriate use of LABAs. In addition, FDA is requiring the manufacturers to conduct additional clinical trials to further evaluate the safety of LABAs when used in combination with inhaled corticosteroids.

The drug compatibility (physical and chemical), efficacy, and safety of Brovana (arformoterol) when mixed with other drugs in a nebulizer have not been established.

Brovana (arformoterol) is not indicated to treat Asthma. The safety and efficacy of Arformoterol have not been established in pediatric members.

Perforomist (Formoterol Fumarate):

Perforomist (formoterol fumarate) is a Long acting beta2 adrenergic agonist. Perforomist (formoterol fumarate) acts locally in the lung as a bronchodilator. The pharmacologic effects of beta2 adrenergic agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3’5’ adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Perforomist (formoterol fumarate) is indicated for long term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Formoterol fumarate is available as Perforomist in cartons of 60 individually wrapped unit dose vials. Each 2.5 mL low density polyethylene unit dose vial contains 2ml of 20mcg/2mL sterile solution for nebulization. Formoterol fumarate is also available as Foradil, a 12 mcg oral capsule inhaled via Aerolizer.

Perforomist (formoterol fumarate) is administered with a standard jet nebulizer (with a facemask or mouthpiece) connected to an air compressor and dosed at one 20mcg/2mL vial every 12 hours.

Perforomist (formoterol fumarate) therapy is not indicated for concurrent use with other medications containing Long acting beta2 adrenergic agonists.
Perforomist is not indicated for acute deteriorations of COPD, or for asthma, in the absence of concurrent medication containing inhaled corticosteroid and comorbid COPD diagnosis.

All Long Acting Beta2 Adrenergic Agonists carry a boxed warning. Long Acting Beta2 Adrenergic Agonists (LABAs) may increase the risk of asthma related exacerbations, hospitalizations, and death. While LABAs may be considered without concurrent corticosteroid in COPD members, they should be avoided as monotherapy in asthma members. This class labeling is based on analyses from the Salmeterol Multicenter Asthma Research Trial (SMART), the Salmeterol Nationwide Surveillance study (SNS), and a meta analysis conducted by FDA in 2008 and discussed at the joint Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, held on December 10–11, 2008.

**Tyvaso (Treprostinil):**

Tyvaso (treprostinil) is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

Tyvaso (treprostinil) Inhalation Solution is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness include predominantly patients with New York Heart Association (NYHA) Class III symptoms and etiologies of idiopathic or heritable PAH (56 percent) or PAH associated with connective tissue diseases (33 percent).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase Type 5 inhibitor).

Tyvaso (treprostinil) is a sterile formulation of treprostinil intended for administration by oral inhalation using the Optineb-ir Model ON-100/7 device. Tyvaso is supplied in 2.9 mL low density polyethylene (LDPE) ampules containing 1.74 mg treprostinil (0.6 mg/mL). One ampule contains a sufficient volume of medication for all four treatment sessions in a single day.

Tyvaso is dosed in four separate, equally spaced treatment sessions per day, during waking hours. The treatment should be approximately four hours apart. One ampule contains enough medicine for one day of treatment no matter how many breaths the doctor has prescribed.

Initial dosage: Therapy should begin with three breaths of Tyvaso per treatment session, four times per day.

Maintenance dosage: Dosage should be increased by an additional three breaths at approximately one-to-two week intervals, if tolerated, until the target dose of nine breaths (54 mcg of treprostinil) is reached per treatment session, four times per day.

Maximum recommended dosage is nine breaths per treatment session, four times daily.

Tyvaso is not indicated for concurrent use with another prostanoid, Flolan (epoprostenol), Remodulin (treprostinil), or Ventavis (iloprost).

Caution should be used in patients with hepatic or renal impairment.

The most common adverse events in clinical trials were infusion site pain and reactions, diarrhea, jaw pain, edema, vasodilation and nausea. Angioedema is possible.

Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of the Optineb-ir Model ON100/7 (an ultrasonic, pulsed-delivery device) and its accessories.

**Ventavis (Iloprost):**

Ventavis (iloprost) is a synthetic analogue of prostacyclin PGI2. Ventavis (iloprost) dilates systemic and pulmonary arterial vascular beds. It also affects platelet aggregation but the relevance of this effect to the treatment of pulmonary hypertension is unknown.

Ventavis (iloprost) is indicated for the treatment of pulmonary arterial hypertension, World Health Organization (WHO) Group I to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominantly patients with NYHA functional class III IV.
symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

Ventavis (iloprost) is supplied in 1 mL single-use ampules in two concentrations: 10 mcg/mL and 20 mcg/mL. The recommended first inhaled dose should be 2.5 mcg (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5 mcg and maintained at that dose. Ventavis (iloprost) should be taken six to nine times per day (no more than every two hours) during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 mcg (5 mcg 9 times per day).

The 20 mcg/ml concentration is intended for members stabilized on 5 mcg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing. Transitioning to the 20 mcg/mL concentrations using the I neb AAD System will decrease treatment times to help maintain member compliance.

Precaution: Ventavis (iloprost) inhalation can induce bronchospasm, especially in susceptible patient with hyperreactive airways. Ventavis iloprost) has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections. Such patient should be carefully monitored during therapy with Ventavis (iloprost).

Avoid oral ingestion of solution and contact with the skin or eyes.

Use only with designated delivery devices – Prodose AAD System or I neb AAD System.

Ventavis should not be initiated in persons with a systolic blood pressure less than 85 mmHg, because of a risk of syncope.

Ventavis (iloprost) is not indicated in persons with a known hypersensitivity to Iloprost.

Cayston (Aztreonam):

Cayston (aztreonam) inhalation solution is a monobactam antibiotic. Like other beta lactam antibiotics, aztreonam binds to penicillin binding proteins specifically PBP3 in P. aeruginosa, which are responsible for bacterial cell wall biosynthesis. Aztreonam inhibits bacterial cell wall biosynthesis resulting in cell lysis and death through binding PBP3.

Cayston (aztreonam) inhalation solution is indicated to improve respiratory symptoms in cystic fibrosis (CF) patients (adults and pediatric patients 7 years of age and older) with Pseudomonas aeruginosa. Safety and effectiveness have not been established in pediatric patients below the age of 7 years, patients with FEV1 <25% or >75% predicted, or patients colonized with Burkholderia cepacia.

To reduce development of drug resistant bacteria and maintain the effectiveness of Cayston and other antibacterial drugs, Cayston should be used only to treat patients with CF known to have pseudomonas aeruginosa of the lungs.

Aztreonam inhalation solution is available as Cayston in 75mg per vial with 0.17% sodium chloride diluent in 1mL/ampule. Each kit has a 28 day course of Cayston which contains 84 sterile vials of Cayston and 88 ampules of sterile diluent packed in 2 cartons (each carton contains a 14 day supply).

The recommended dose of Cayston for both adults and pediatric patients seven years of age and older is one single-use vial (75 mg of aztreonam) reconstituted with 1 mL of sterile diluent administered 3 times a day for a 28 day course (followed by 28 days off Cayston therapy).

Dosage is not based on weight or adjusted for age. Doses should be taken at least 4 hours apart.

Safety and effectiveness has not been established in pediatric patients below the age of 7 years, patients with FEV1 < 25% or > 75% predicted, or patients colonized with Burkholderia cepacia.

Cayston is administered by inhalation using an Altera Nebulizer System. Patients should use a bronchodilator before administration of Cayston. Short acting bronchodilators should be taken between 15 minutes and four hours prior to each dose of Cayston. Alternatively, long acting bronchodilators should be taken between 30 minutes and 12 hours prior to administration of Cayston.

For patients taking multiple inhaled therapies, the recommended order of administration is: bronchodilator, mucolytics and lastly, Cayston.

In Cayston’ clinical trial, all patients were required to take a dose of an inhaled bronchodilator (beta agonist) prior to taking a dose of Cayston or placebo.
According to the CF guidelines, for patients with CF (6 years of age and older), the Cystic Fibrosis Foundation recommends the chronic use of inhaled b2 adrenergic receptor agonists to improve lung function. Grade of recommendation: B.

**Tobramycin Inhalation:**

Tobramycin for inhalation is an aminoglycoside antibiotic. Tobramycin acts primarily by disrupting protein synthesis by binding to 30S ribosomal subunit thereby altering cell membrane permeability leading to cell death. Tobramycin has in vitro activity against gram negative organisms including Pseudomonas aeruginosa.

Tobramycin for inhalation (Bethkis, Kitabis, Tobi, Tobi Podhaler, tobramycin) is indicated for the management of cystic fibrosis (CF) members with Pseudomonas aeruginosa.

A randomized placebo controlled trial of inhaled tobramycin delivered by jet nebulizer in patients with CF showed that it was well tolerated, and was associated with improved pulmonary function, decreased density of P aeruginosa in sputum, and decreased risk of hospitalization.

American College of Chest Physicians, in patients with idiopathic bronchiectasis, the prolonged administration of antibiotics may produce small benefits in reducing sputum volume and purulence, but may also be associated with intolerable side effects. Level of evidence, low; benefit, conflicting, grade of recommendation, I.

Long term (12 months) inhaled ceftazidime and tobramycin decreased the number of admissions and the length of stay compared to no inhaled antibiotics in patients with non cystic fibrosis bronchiectasis and chronic bronchial infection with pseudomonas aeruginosa. This prospective trial randomized patients (n=17) to either nebulized ceftazidime 1 gram every 12 hours plus tobramycin 100 milligrams every 12 hours or no antibiotics. The mean number of admissions and mean length of stay (days) was 0.6 and 13.1, respectively, for the antibiotic group and 2.5 and 57.9, respectively, for the no antibiotic group (p less than 0.05). Lung function declined in both groups. All patients in both groups had Pseudomonas aeruginosa in the 12 month sputum culture. Two patients discontinued; 1 in the antibiotic group due to bronchospasm and 1 in the no antibiotic group died of respiratory failure. Further controlled studies are needed to identify the optimum dose, frequency, and duration of antibiotic.

Tobramycin administration to non CF bronchiectatic Spanish patients (n=30) for endobronchial infection with PA appears to be safe and decreases risk of hospitalization and PA density in sputum. Nevertheless, pulmonary function and quality of life are not improved, and the risk of bronchospasm is appreciable. No significant differences were observed in number of exacerbations, antibiotic use, pulmonary function and quality of life.

Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV1 <25% or >75% predicted, or patients colonized with Burkholderia cepacia.

Tobramycin inhalation solution is available as Kitabis, Tobi, and tobramycin 300 mg in 5 ml single dose ampule in a carton of 56 ampules (one 28 day treatment) and as Bethkis 300 mg in 4 ml single dose ampule in a carton of 56 ampules (one 28 day treatment).

**Treatment:**

- **Tobramycin inhalation solution**
  - 300 mg by inhalation over approximately a 15 minute period every 12 hours. The drug should be administered using a jet (breath enhanced) nebulizer that delivers droplet particles between 1 and 5 microns. Administer in repeated cycles of 28 days on followed by 28 days off drug.
  - The 300 mg dose of tobramycin inhalation solution (Bethkis, Kitabis, Tobi, tobramycin) is the same for members regardless of age or weight.

- **Tobramycin inhalation powder**
  - Four 28 mg capsules (112 mg total dose) inhaled using the Podhaler every 12 hours. Administer in repeated cycles of 28 days on followed by 28 days off.
  - The 112 mg dose of tobramycin inhalation powder (Tobi Podhaler) is the same for members regardless of age or weight.

Prescribing tobramycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

The most common airway pathogen in patients with CF is Pseudomonas aeruginosa. Because chronic colonization of the airways with this bacterium is associated with a more rapid decline in lung function, aerosolized antibiotics have
been advocated both for eradication of initial infection and for suppression of the chronic infection.

Toramycin should not be mixed with other medications in the nebulizer.

Only small amounts of aerosolized tobramycin reach the systemic circulation and drug accumulation has not been demonstrated; therefore, routine monitoring of serum tobramycin concentrations is unnecessary if the patient is receiving the recommended dose of tobramycin and has normal renal function.

Patients with CF who are receiving tobramycin should be monitored for renal tubular toxicity (urinalysis, blood urea nitrogen, and creatinine) and eighth nerve toxicity (audiogram at 500–8000 Hz range) if they are receiving concomitant therapy with other nephrotoxic or ototoxic agents or have preexisting renal or auditory dysfunction, or recognized predisposition to toxicity (family history). In addition, any patient receiving tobramycin who develops signs or symptoms of auditory toxicity, such as tinnitus, should have an audiogram performed.

The initial dose of tobramycin should be given in the presence of a trained health care professional who will monitor the patient for wheezing and respiratory distress, and instruct the patient in the proper technique of delivery.

Patients or their caregivers should be trained to monitor for bronchospasm, urticaria, and perioral or periorbital edema, and be advised to stop the medication and consult their physician if any of these or other adverse reactions occur.

When aerosolized tobramycin administration is maintained, evaluation of long-term efficacy is recommended within six to 12 months of initiating therapy. Monitoring factors such as reduction in the frequency of hospitalization and intravenous antibiotic administration, sense of well-being, work or school performance, and absenteeism, and cough frequency is recommended.

TOBI Podhaler capsules should always be stored in the blister and each capsule should only be removed immediately before use.

Always use the new Podhaler device provided with each weekly pack.

Nebulized Morphine for the Relief of Dyspnea:

Kotrach and co-workers (2015) noted that few therapies exist for the relief of dyspnea in restrictive lung disorders. Accumulating evidence suggested that nebulized opioids selective for the mu-receptor subtype may relieve dyspnea by modulating intra-pulmonary opioid receptor activity. These researchers tested the hypothesis that nebulized fentanyl (a mu-opioid receptor agonist) relieves dyspnea during exercise in the presence of abnormal restrictive ventilatory constraints. In a randomized, double-blind, placebo-controlled, cross-over study, these investigators examined the effect of 250 μg nebulized fentanyl, chest wall strapping (CWS), and their interaction on detailed physiological and perceptual responses to constant work rate cycle exercise (85% of maximum incremental work rate) in 14 healthy, fit young men. By design, CWS decreased vital capacity (VC) by approximately 20% and mimicked the negative consequences of a mild restrictive lung disorder on exercise endurance time and on dyspnea, breathing pattern, dynamic operating lung volumes, and diaphragmatic electromyographic (EMG) and respiratory muscle function during exercise. Compared with placebo under both un-restricted control and CWS conditions, nebulized fentanyl had no effect on exercise endurance time, integrated physiological response to exercise, sensory intensity, unpleasantness ratings of exertional dyspnea. The authors concluded that these findings did not support a role for intra-pulmonary opioids in the neuro-modulation of exertional dyspnea in health; nor did they provide a physiological rationale for the use of nebulized fentanyl in the management of dyspnea due to mild restrictive lung disorders, specifically those arising from abnormalities of the chest wall and not affiliated with airway inflammation.

Nebulized Morphine for the Relief of Breathlessness:

Ekstrom and colleagues (2015) stated that patients with COPD often suffer from breathlessness, de-conditioning, and reduced health-related quality of life (HRQL) despite medical management. Opioids may relieve breathlessness at rest and on exertion in patients with COPD. In a systematic review and meta-analysis using Cochrane methodology, these researchers estimated the safety and effectiveness of opioids on refractory breathlessness, exercise capacity, and HRQL in patients with COPD. They searched Cochrane Central Register of Controlled Trials, Medline, and Embase up to September 8, 2014 for randomized, double-blind, placebo-controlled trials of any opioid for breathlessness, exercise capacity, or HRQL that included at least 1 participant with COPD. Effects were analyzed as SMDs with 95% CIs using random effect models. A total of 16 trials (15 cross-over trials and 1 parallel-group study, 271 participants, 95% with severe COPD) were included. There were no serious AEs. Breathlessness was reduced by opioids overall: SMD, -0.35 (95% CI: -0.53 to -0.17; I(2), 48.9%), by systemic opioids (8 studies, 118 participants): SMD, -0.34 (95% CI: -0.58 to -0.10; I(2), 0%), and less consistently by nebulized opioids (4 studies, 82 participants): SMD, -0.39 (95% CI: -0.71 to -0.07; I(2), 78.9%). The quality of evidence was moderate for systemic opioids and low for nebulized opioids.
on breathlessness. Opioids did not affect exercise capacity (13 studies, 149 participants): SMD, 0.06 (95% CI: -0.15 to 0.28; I², 70.7%); HRQL could not be analyzed. Findings were robust in sensitivity analyses; risk of study bias was low or unclear. The authors concluded that opioids improved breathlessness but not exercise capacity in severe COPD.

In a Cochrane review, Barnes and associates (2016) determined the effectiveness of opioid drugs in relieving the symptom of breathlessness in people with advanced disease due to malignancy, respiratory or cardiovascular disease, or receiving palliative care for any other disease. These investigators performed searches on CENTRAL, Medline, Embase, CINAHL, and Web of Science up to October 19, 2015. They also hand-searched review articles, clinical trial registries, and reference lists of retrieved articles. They included randomized, double-blind, controlled trials that compared the use of any opioid drug against placebo or any other intervention for the relief of breathlessness. The intervention was any opioid, given by any route, in any dose. These researchers imported studies identified by the search into a reference manager database. They retrieved the full-text version of relevant studies, and 2 review authors independently extracted data. The primary outcome measure was breathlessness and secondary outcome measures included exercise tolerance, oxygen saturations, AEs, and mortality. They analyzed all studies together and also performed subgroup analyses, by route of administration, type of opioid administered, and cause of breathlessness. Where appropriate, they performed meta-analysis; and assessed the evidence using the GRADE approach and created 3 “Summary of findings” tables. The authors included 26 studies with 526 participants. They evaluated the studies as being at high or unclear risk of bias overall. They only included RCTs, although the description of randomization was incomplete in some included studies. They aimed to include double-blind RCTs, but 2 studies were only single-blinded. There was inconsistency in the reporting of outcome measures. These researchers analyzed the data using a fixed-effect model, and for some outcomes heterogeneity was high. There was a risk of imprecise results due to the low numbers of participants in the included studies. For these reasons, the authors down-graded the quality of the evidence from high to either low or very low. For the primary outcome of breathlessness, the mean change from baseline dyspnea score was 0.09 points better in the opioids group compared to the placebo group (ranging from a 0.36 point reduction to a 0.19 point increase) (7 RCTs, 117 participants, very low quality evidence). A lower score indicated an improvement in breathlessness. A meta-analysis of the post-treatment dyspnea score was 0.28 points better in the opioid group compared to the placebo group (ranging from a 0.5 point reduction to a 0.05 point increase) (11 RCTs, 159 participants, low quality evidence). The evidence for the 6-minute walk test (6MWT) was conflicting. The total distance in 6MWT was 28 meters (m) better in the opioids group compared to placebo (ranging from 113 m to 58 m) (1 RCT, 11 participants, very low quality evidence). However, the change in baseline was 48 m worse in the opioids group (ranging from 36 m to 60 m) (2 RCTs, 26 participants, very low quality evidence). The AEs reported included drowsiness, nausea and vomiting, and constipation. In those studies, subjects were 4.73 times more likely to experience nausea and vomiting compared to placebo, 3 times more likely to experience constipation, and 2.86 times more likely to experience drowsiness (9 studies, 162 participants, very low quality evidence). Only 4 studies assessed QOL, and none demonstrated any significant change. The authors concluded that there is some low quality evidence that showed benefit for the use of oral or parenteral opioids to palliate breathlessness, although the number of included participants was small. These investigators found no evidence to support the use of nebulized opioids, and stated that further research with larger numbers of participants, using standardized protocols and with QOL measures included, is needed.

Nebulized Morphine for the Relief of Cancer-Related Cough:

And colleagues (2015) stated that cough is a distressing symptom in advanced cancer, and opioids have been used to relieve respiratory symptoms including dyspnea and cough. In addition to a central mechanism, opioids are thought to work peripherally via opioid receptors of the lung. Thus, direct inhalation of morphine has been investigated in chronic lung disease or cancer. These investigators reported their experience of a nebulized form of morphine to control intractable cough in patients with advanced cancer. Case 1 was a 63-year old female with terminal lung cancer complaining of a severe dry cough with dyspnea and sleeplessness. Case 2 was a 53-year old female with thymic cancer with multiple lung metastases suffering from severe cough accompanying chest pain and dyspnea. With usual treatment, cough did not improve in these patients. These researchers then administered a nebulized form of morphine (hydrochloro-morphine). When the morphine dose was increased to 10 mg and 15 mg, the patients' cough was relieved to a symptom level of moderate and mild, respectively. Without experiencing any severe systemic AEs of opioids, the patients continued nebulized morphine until death or discharge. The authors concluded that nebulized morphine was effective in controlling intractable cough due to cancer. These preliminary findings need to be validated by well-designed studies.

Nebulized Magnesium for the Treatment of Pediatric Asthma:

Alansari and colleagues (2015) noted that intravenous magnesium (Mg) sulfate, a rescue therapy added to bronchodilator and systemic steroid therapy for moderate and severe asthma, is uncommonly administered. In a
randomized clinical trial, these researchers hypothesized that nebulized Mg would confer benefit without undue risk. Patients aged 2 to 14 years with moderate and severe asthma (Pediatric Respiratory Assessment Measure [PRAM] severity score greater than or equal to 4) admitted to infirmary/observation unit care were randomized in a double-blind fashion to receive 800 mg nebulized Mg or normal saline placebo after all received intensive therapy with combined nebulized albuterol-ipratropium and intravenous methylprednisolone. Time to medical readiness for discharge was the primary outcome; sample size was chosen to detect a 15% absolute improvement. Improvement over time in PRAM severity score and other secondary outcomes were compared for the overall group and severe asthma subset. A total of 191 Mg sulfates and 174 placebo patients met criteria for analysis. The groups were similar with mean baseline PRAM scores greater than 7. Blinded active therapy significantly increased blood Mg level 2 hours post-treatment completion compared to placebo, 0.85 versus 0.82 mmol/L, p = 0.001. There were no important AEs. Accelerated failure time analysis showed a non-significantly shortened time to medical readiness for discharge of 14% favoring the Mg sulfate group, OR = 1.14, 95% CI: 0.93 to 1.40, p = 0.20. Mean times until readiness for discharge were 14.7 hours [SD 9.7] versus 15.6 hours [SD 11.3] for the investigational and placebo groups, respectively, p = 1.41. The authors concluded that the addition of nebulized Mg to combined nebulized bronchodilator and systemic steroid therapy failed to significantly shorten time to discharge of pediatric patients with moderate or severe asthma.

Schuh and associates (2016) stated that up to 30% of children with acute asthma are refractory to initial therapy, and 84% of this subpopulation needs hospitalization. Finding safe, non-invasive, and effective strategies to treat this high-risk group would substantially decrease hospitalizations, healthcare costs, and the psycho-social burden of the disease. Whereas intravenous Mg is effective in severe refractory asthma, its use is sporadic due to safety concerns, with the main treatment goal being to prevent intensive care unit admission. In contrast, nebulized Mg is non-invasive, allows higher pulmonary drug concentrations, and has a much higher safety potential due to the lower rate of systemic delivery. Previous studies of inhaled Mg showed disparate results due to the use of unknown/inefficient delivery methods and other methodological flaws. The study is a randomized, double-blind, controlled trial in 7 Canadian pediatric Emergency Departments (2-center pilot 2011 to 2014, Canada-wide November 2014 to December 2017). The trial will include 816 otherwise healthy children who are 2 to 17 years old, having had at least 1 previous wheezing episode, have received systemic corticosteroids, and have a PRAM greater than or equal to 5 points after 3 salbutamol and ipratropium treatments for a current acute asthma exacerbation. Eligible consenting children will receive 3 experimental treatments of nebulized salbutamol with either 600 mg of Mg sulfate or placebo 20 minutes apart, using an Aeroneb Go nebulizer, which has been shown to maximize pulmonary delivery while maintaining safety. The primary outcome is hospitalization within 24 hours of the start of the experimental therapy for persistent respiratory distress or supplemental oxygen. Secondary outcomes include all-cause hospitalization within 24 hours, PRAM, vital signs, number of bronchodilator treatments by 240 minutes, and the association between the difference in the primary outcome between the groups, age, gender, baseline PRAM, atopy, and “viral induced wheeze” phenotype. The authors stated that if effective, inhaled Mg may represent an effective strategy to minimize morbidity in pediatric refractory acute asthma. They noted that unlike previous works, this trial targets non-responders to optimized initial therapy who are the most likely to benefit from inhaled Mg.

Appendix

Severity of lung disease defined by FEV1 percentage of predicted as follows:

- Normal >90%
- Mildly impaired 70–89%
- Moderately impaired 40–69%, and
- Severely impaired <40% predicted.

The following table lists the usual maximum medically necessary frequency of replacement for accessories.

<table>
<thead>
<tr>
<th>Accessory</th>
<th>Usual Maximum Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face tent</td>
<td>One/month</td>
</tr>
<tr>
<td>Administration set, with small volume nonfiltered pneumatic nebulizer, disposable</td>
<td>Two/month</td>
</tr>
<tr>
<td>Small volume nonfiltered pneumatic nebulizer, disposable</td>
<td>Two/month</td>
</tr>
<tr>
<td>Administration set, with small volume nonfiltered pneumatic nebulizer, non-disposable</td>
<td>One/6 months; or One/3 months if used with a controlled</td>
</tr>
<tr>
<td>Item</td>
<td>Frequency</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Administration set, with small volume filtered pneumatic nebulizer</td>
<td>One/month</td>
</tr>
<tr>
<td>Large volume nebulizer, disposable, unvilled, used with aerosol compressor</td>
<td>Two/month</td>
</tr>
<tr>
<td>Corrugated tubing, disposable, used with large volume nebulizer, 100 feet</td>
<td>One unit (100 ft.)/2 months</td>
</tr>
<tr>
<td>Water collection device, used with large volume nebulizer</td>
<td>Two/month</td>
</tr>
<tr>
<td>Filter, disposable, used with aerosol compressor or ultrasonic generator</td>
<td>Two/month</td>
</tr>
<tr>
<td>Filter, nondisposable, used with aerosol compressor or ultrasonic generator</td>
<td>One/3 months</td>
</tr>
<tr>
<td>Aerosol mask, used with DME nebulizer</td>
<td>One/month</td>
</tr>
<tr>
<td>Dome and mouthpiece, used with small volume ultrasonic nebulizer</td>
<td>Two/year</td>
</tr>
<tr>
<td>Nebulizer, durable, glass or autoclavable plastic, bottle type, not used with oxygen</td>
<td>One/3 years</td>
</tr>
<tr>
<td>Tracheostomy mask, each</td>
<td>One/month</td>
</tr>
<tr>
<td>Immersion external heater for nebulizer</td>
<td>One/3 years</td>
</tr>
</tbody>
</table>

Source: NHIC, 2016.

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### CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”.*

#### Small Volume Nebulizer:

**CPT codes covered if selection criteria are met:**

- **94640** Pressurized or nonpressurized inhalation treatment for acute airway obstruction for therapeutic purposes and/or for diagnostic purposes such as sputum induction with an aerosol generator, nebulizer, metered dose inhaler or intermittent positive pressure breathing (IPPB) device [not covered for IPPB]

- **94642** Aerosol inhalation of pentamidine for pneumocystis carinii pneumonia treatment or prophylaxis

- **94664** Demonstration and/or evaluation of patient utilization of an aerosol generator, nebulizer, metered dose inhaler or IPPB device

- **99601** Home infusion/specialty drug administration, per visit (up to 2 hours)

- **+ 99602** each additional hour (List separately in addition to code for primary procedure)

**HCPCS codes covered if selection criteria are met:**

- **A7003** Administration set, with small volume nonfiltered pneumatic nebulizer, disposable

- **A7004** Small volume nonfiltered pneumatic nebulizer, disposable

- **A7005** Administration set, with small volume nonfiltered pneumatic nebulizer, non-disposable
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A7006</td>
<td>Administration set, with small volume filtered pneumatic nebulizer</td>
</tr>
<tr>
<td>E0565</td>
<td>Compressor, air power source for equipment which is not self-contained or cylinder driven</td>
</tr>
<tr>
<td>E0570</td>
<td>Nebulizer, with compressor</td>
</tr>
<tr>
<td>E0572</td>
<td>Aerosol compressor, adjustable pressure, light duty for intermittent use</td>
</tr>
<tr>
<td>J2545</td>
<td>Pentamidine isethionate, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per 300 mg</td>
</tr>
<tr>
<td>J7604</td>
<td>Acetylcysteine, inhalation solution, compounded product, administered through DME, unit dose form, per g</td>
</tr>
<tr>
<td>J7605</td>
<td>Arformoterol, inhalation solution, FDA approved final product, noncompounded, administered through DME, unit dose form, 15 mcg</td>
</tr>
<tr>
<td>J7606</td>
<td>Formoterol fumarate, inhalation solution, FDA approved final product, noncompounded, administered through DME, unit dose form, 20 mcg</td>
</tr>
<tr>
<td>J7607</td>
<td>Levalbuterol, inhalation solution, compounded product, administered through DME, concentrated form, 0.5 mg</td>
</tr>
<tr>
<td>J7608</td>
<td>Acetylcysteine, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per g</td>
</tr>
<tr>
<td>J7609</td>
<td>Albuterol, inhalation solution, compounded product, administered through DME, unit dose, 1 mg</td>
</tr>
<tr>
<td>J7610</td>
<td>Albuterol, inhalation solution, compounded product, administered through DME, concentrated form, 1 mg</td>
</tr>
<tr>
<td>J7615</td>
<td>Levalbuterol, inhalation solution, compounded product, administered through DME, unit dose, 0.5 mg</td>
</tr>
<tr>
<td>J7620</td>
<td>Albuterol, up to 2.5 mg and ipratropium bromide, up to 0.5 mg, FDA-approved final product, noncompounded, administered through DME</td>
</tr>
<tr>
<td>J7622</td>
<td>Beclomethasone, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7626</td>
<td>Budesonide, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, up to 0.5 mg</td>
</tr>
<tr>
<td>J7628</td>
<td>Bitolterol mesylate, inhalation solution, compounded product, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7629</td>
<td>Bitolterol mesylate, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7631</td>
<td>Cromolyn sodium, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per 10 mg</td>
</tr>
<tr>
<td>J7632</td>
<td>Cromolyn sodium, inhalation solution, compounded product, administered through DME, unit dose form, per 10 mg</td>
</tr>
<tr>
<td>J7633</td>
<td>Budesonide, inhalation solution, FDA-approved final product, noncompounded, administered through DME, concentrated form, per 0.25 mg</td>
</tr>
<tr>
<td>J7634</td>
<td>Budesonide, inhalation solution, compounded product, administered through DME, concentrated form, per 0.25 mg</td>
</tr>
<tr>
<td>J7635</td>
<td>Atropine, inhalation solution, compounded product, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7636</td>
<td>Atropine, inhalation solution, compounded product, administered through DME, unit dose</td>
</tr>
<tr>
<td>Code</td>
<td>Nebulizers</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>J7639</td>
<td>Dornase alfa, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per mg [Pulmozyme] [not covered for asthma and chronic bronchitis]</td>
</tr>
<tr>
<td>J7640</td>
<td>Formoterol, inhalation solution, compounded product, administered through DME, unit dose form, 12 mcg</td>
</tr>
<tr>
<td>J7641</td>
<td>Flunisolide, inhalation solution, compounded product, administered through DME, unit dose, per mg</td>
</tr>
<tr>
<td>J7642</td>
<td>Glycopyrrolate, inhalation solution, compounded product, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7643</td>
<td>Glycopyrrolate, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7644</td>
<td>Ipatroipium bromide, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7645</td>
<td>Ipatroipium bromide, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7647</td>
<td>Isoetharine HCL, inhalation solution, compounded product, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7648</td>
<td>Isoetharine HCL, inhalation solution, FDA-approved final product, noncompounded, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7649</td>
<td>Isoetharine HCL, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7650</td>
<td>Isoetharine HCL, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7657</td>
<td>Isoproterenol HCl, inhalation solution, compounded product, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7658</td>
<td>Isoproterenol HCl, inhalation solution, FDA-approved final product, noncompounded, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7659</td>
<td>Isoproterenol HCl, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7660</td>
<td>Isoproterenol HCl, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7667</td>
<td>Metaproterenol sulfate, inhalation solution, compounded product, concentrated form, per 10 mg</td>
</tr>
<tr>
<td>J7668</td>
<td>Metaproterenol sulfate, inhalation solution, FDA-approved final product, noncompounded, administered through DME, concentrated form, per 10 mg</td>
</tr>
<tr>
<td>J7669</td>
<td>Metaproterenol sulfate, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per 10 mg</td>
</tr>
<tr>
<td>J7670</td>
<td>Metaproterenol sulfate, inhalation solution, compounded product, administered through DME, unit dose form, per 10 mg</td>
</tr>
<tr>
<td>J7676</td>
<td>Pentamidine isethionate, inhalation solution, compounded product, administered through DME, unit dose form, per 300 mg</td>
</tr>
<tr>
<td>J7682</td>
<td>Tobramycin, inhalation solution, FDA-approved final product, noncompounded, unit dose form, administered through DME, per 300 milligrams</td>
</tr>
</tbody>
</table>
**Nebulizers**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7683</td>
<td>Triamcinolone, inhalation solution, compounded product, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7684</td>
<td>Triamcinolone, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7685</td>
<td>Tobramycin, inhalation solution, compounded product, administered through DME, unit dose form, per 300 mg</td>
</tr>
<tr>
<td>J7686</td>
<td>Treprostinil, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, 1.74 mg</td>
</tr>
<tr>
<td>Q4074</td>
<td>Iloprost, inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, up to 20 micrograms</td>
</tr>
<tr>
<td>S9061</td>
<td>Home administration of aerosolized drug therapy (e.g., Pentamidine); administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

- **B20** Human immunodeficiency virus [HIV] disease
- **B59** Pneumocystosis
- **B96.5** Pseudomonas (aeruginosa) (mallei) (pseudomallei) as the cause of diseases classified elsewhere
- **E84.0 - E84.9** Cystic fibrosis
- **I27.0** Primary pulmonary hypertension
- **I27.20 - I27.29** Other secondary pulmonary hypertension
- **J05.0** Acute obstructive laryngitis [croup]
- **J15.1** Pneumonia due to pseudomonas
- **J40 - J47.9** Chronic lower respiratory diseases [Pulmozye] [not covered for asthma and chronic bronchitis] [nebulized magnesium not covered for pediatric asthma]
- **J95.00 - J95.09** Tracheostomy complications
- **Q33.4** Congenital bronchiectasis
- **R09.3** Abnormal sputum
- **T86.00 - T86.99** Complications of transplanted organs and tissue
- **Z43.0** Encounter for attention to tracheostomy
- **Z93.0** Tracheostomy status

**ICD-10 codes not covered for indications listed in the CPB:**

- **E75.242** Niemann-Pick disease type C [not covered for Pulmozyme]
- **J98.11 - J98.19** Pulmonary collapse
- **R05** Cough [not covered for nebulized lidocaine]
- **Z94.2** Lung transplant status

**Large Volume Nebulizer:**

**CPT codes covered if selection criteria are met:**

- **94640** Pressurized or nonpressurized inhalation treatment for acute airway obstruction or for...
Nebulizers

sputum induction for diagnostic purposes (e.g., with an aerosol generator, nebulizer, metered dose inhaler or intermittent positive pressure breathing (IPPB) device)

94642  Aerosol inhalation of pentamidine for pneumocystis carinii pneumonia treatment or prophylaxis

94664  Demonstration and / or evaluation of patient utilization of an aerosol generator, nebulizer, metered dose inhaler or IPPB device

99601  Home infusion/specialty drug administration, per visit (up to 2 hours)

+ 99602  each additional hour (List separately in addition to code for primary procedure)

HCPCS codes covered if selection criteria are met:

A4619  Face tent
A7009  Reservoir bottle, non-disposable, used with large volume ultrasonic nebulizer
A7010  Corrugated tubing, disposable, used with large volume nebulizer, 100 ft
A7012  Water collection device, used with large volume nebulizer
A7013  Filter, disposable, used with aerosol compressor
A7015  Aerosol mask, used with DME nebulizer
A7017  Nebulizer, durable, glass or autoclavable plastic, bottle type, not used with oxygen
A7018  Water, distilled, used with large volume nebulizer, 1000 ml
A7525  Tracheostomy mask, each
A7526  Tracheostomy tube collar/holder, each
E0565  Compressor, air power source for equipment which is not self-contained or cylinder driven
E0572  Aerosol compressor, adjustable pressure, light duty for intermittent use
E0580  Nebulizer, durable, glass or autoclavable plastic, bottle type, for use with regulator or flowmeter
E0585  Nebulizer, with compressor and heater
E1372  Immersion external heater for nebulizer
J2545  Pentamidine isethionate, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, per 300 mg
S9061  Home administration of aerosolized drug therapy (e.g., Pentamidine); administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10 codes covered if selection criteria are met:

B20  Human immunodeficiency virus [HIV] disease
B59  Pneumocystosis
E84.0 - E84.9  Cystic fibrosis
J47.0 - J47.9  Bronchiectasis
J95.00 - J95.09  Tracheostomy complications
Q33.4  Congenital bronchiectasis
R09.3  Abnormal sputum
Nebulizers

T86.00 - T86.99 Complications of transplanted organs and tissue
Z43.0 Encounter for attention to tracheostomy
Z93.0 Tracheostomy status

**Ultrasonic Nebulizers:**

**HCPCS codes covered if selection criteria is met:**

- **A7014** Filter, non-disposable, used with aerosol compressor or ultrasonic generator
- **A7016** Dome and mouthpiece, used with small volume ultrasonic nebulizer
- **E0574** Ultrasonic/electronic aerosol generator with small volume nebulizer
- **J7682** Tobramycin, inhalation solution, FDA-approved final product, noncompounded, unit dose form, administered through DME, per 300 mg
- **J7685** Tobramycin, inhalation solution, compounded product, administered through DME, unit dose form, per 300 mg

**HCPCS codes not covered for indications listed in the CPB:**

- **J2001** Injection, lidocaine HCL for intravenous infusion, 10 mg

**ICD-10 codes covered if selection criteria are met:**

- **E84.0 - E84.9** Cystic fibrosis

**Accessories:**

**HCPCS codes not covered for indications listed in the CPB:**

- **A7007** Large volume nebulizer, disposable, unfilled, used with aerosol compressor
- **A7008** Large volume nebulizer, disposable, prefilled, used with aerosol compressor

**List of usual maximum frequency of replacement for accessories:**

**HCPCS codes covered if selection criteria are met:**

- **A4619** Face tent
- **A7003** Administration set, with small volume nonfiltered pneumatic nebulizer, disposable
- **A7004** Small volume nonfiltered pneumatic nebulizer, disposable
- **A7005** Administration set, with small volume nonfiltered pneumatic nebulizer, non-disposable
- **A7006** Administration set, with small volume filtered pneumatic nebulizer
- **A7010** Corrugated tubing, disposable, used with large volume nebulizer, 100 ft.
- **A7012** Water collection device, used with large volume nebulizer
- **A7013** Filter, disposable, used with aerosol compressor
- **A7015** Aerosol mask, used with DME nebulizer
- **A7016** Dome and mouthpiece, used with small volume ultrasonic nebulizer
- **A7017** Nebulizer, durable, glass or autoclavable plastic, bottle type, not used with oxygen
- **A7525** Tracheostomy mask, each
- **A7526** Tracheostomy tube collar/holder, each
- **E1372** Immersion external heater for nebulizer
## Nebulized Corticosteroids:

**HCPCS codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7622</td>
<td>Beclomethasone, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
<tr>
<td>J7626</td>
<td>Budesonide, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, up to 0.5 mg</td>
</tr>
<tr>
<td>J7627</td>
<td>Budesonide, inhalation solution, compounded product, administered through DME, unit dose form, up to 0.5 mg</td>
</tr>
<tr>
<td>J7633</td>
<td>Budesonide, inhalation solution, FDA-approved final product, noncompounded, administered through DME, concentrated form, per 0.25 mg</td>
</tr>
<tr>
<td>J7634</td>
<td>Budesonide, inhalation solution, compounded product, administered through DME, concentrated form, per 0.25 mg</td>
</tr>
<tr>
<td>J7641</td>
<td>Flunisolide, inhalation solution, compounded product, administered through DME, unit dose, per mg</td>
</tr>
<tr>
<td>J7683</td>
<td>Triamcinolone, inhalation solution, compounded product, administered through DME, concentrated form, per mg</td>
</tr>
<tr>
<td>J7684</td>
<td>Triamcinolone, inhalation solution, compounded product, administered through DME, unit dose form, per mg</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J00 - J06.9</td>
<td>Acute respiratory infections [viral wheezing]</td>
</tr>
<tr>
<td>J33.0 - J33.9</td>
<td>Nasal polyp</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

15. National Institute for Clinical Excellence (NICE). Inhaler devices for routine treatment of chronic asthma in older


70. Bergstrom S-E. Primary ciliary dyskinesia (immotile-cilia syndrome). Last reviewed August 2012. UpToDate Inc. Waltham, MA.


75. Weinberger SE, Silvestri RC. Treatment of subacute and chronic cough in adults. Last reviewed October 2013. UpToDate Inc., Waltham, MA.


Amendment to
Aetna Clinical Policy Bulletin Number: 0065 Nebulizers

There are no amendments for Medicaid.