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Drug Class Literature Scan: Inhaled Drugs for Cystic Fibrosis

Date of Review: December 2021

Date of Last Review: January 2016
Literature Search: 10/01/15 – 09/03/21

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- The following literature was identified from this scan: 6 systematic reviews and meta-analyses, 2 clinical practice guidelines, 1 new drug, 1 randomized controlled trial and 2 new safety alerts.
- A Cochrane review found inhaled mannitol 400 mg was more effective than control (subtherapeutic mannitol 50 mg) for improvement in lung function based on forced expiratory volume in one second (FEV_1) and percent FEV_1 -predicted (FEV_1%), in studies lasting up to 6 months in patients with cystic fibrosis (CF).[1]
- Dornase alfa was studied in a Cochrane review and was found to be more effective than placebo for improving lung function and reducing pulmonary exacerbations.[2] Studies that compared dornase alfa to hypertonic saline or inhaled mannitol (up to 475 mg) were not conclusive of a clear benefit of one intervention over another based on low quality evidence.[2]
- A Cochrane review evaluated antibiotic strategies for eradicating *Pseudomonas aeruginosa* (*P. aeruginosa*) in adults and children with CF. Inhaled tobramycin was more effective than placebo for microbiological eradication of *P. aeruginosa* from the respiratory tract.[3] All other findings for inhaled antibiotics demonstrated no difference between comparisons and most of the evidence was of low to very low quality.
- A Cochrane review studied therapies for preventing recurrence of infection with *P. aeruginosa* in individuals with CF.[4] Only one study met inclusion criteria. The trial compared inhaled tobramycin 300 mg twice daily every 3 months without regard to culture results (cycled therapy) versus inhaled tobramycin 300 mg twice daily only in the 3-month period after positive culture results for *P. aeruginosa* (culture-based therapy). Culture-based therapy was more likely to have recurrence of infection by the final study visit (up to 563 days) compared to those in the cycled therapy (hazard ratio [HR] 2.04; 95% confidence interval [CI], 1.28 to 3.26).[4]
- One Cochrane review evaluated inhaled antibiotics for the treatment of pulmonary exacerbations and a second Cochrane review studied nebulized hypertonic saline in patients with CF. Both reviews were not able to draw strong conclusions due to low or very low quality of evidence available for analysis.[5,6]
- National Institute for Health and Care Excellence (NICE) Guidelines recommend the use of dornase alfa first-line for patients with CF requiring mucoactive therapy.[7] The treatment of *P. aeruginosa* should include inhaled antibiotics (e.g., tobramycin or aztreonam) in combination with oral or intravenous (IV) antibiotics. Tobramycin dry-powder inhaler (DPI) can be considered for patients who are deemed to be appropriate candidates for nebulized tobramycin.[7] These recommendations are also supported by NICE quality standards for patients with CF.[8]

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- The Food and Drug Administration (FDA) approved mannitol DPI in adult patients with CF as add-on maintenance therapy.[9] Mannitol DPI 400 mg twice daily demonstrated improvements over the control (inhaled mannitol 50 mg twice daily) with a mean change in baseline FEV_1 ranging from 51-68 mL.[9] Mannitol DPI is associated with bronchospasm and all patients should undergo a tolerance test, under supervision, before using for mainten ance therapy. Due to the risk versus benefit, mannitol DPI is considered a second-line therapy for patients unable to tolerate other mucolytics.
- Two new FDA safety alerts have been issued since the last review. Updated labeling reflects a new warning for anaphylaxis and hypersensitivity reactions with inhaled amikacin. A warning was added for inhaled tobramycin for total, irreversible, bilateral congenital deafness in pediatric patients whose mothers received an aminoglycoside (streptomycin) during pregnancy,.[10,11]

Recommendations:

- Maintain inhaled mannitol as non-preferred on the preferred drug list (PDL). No changes to the PDL are warranted based on the current review.
- After evaluation of costs in executive session, recommend making tobramycin in sodium chloride nebulized solution preferred and tobramycin nebulizer solution non-preferred.

Summary of Prior Reviews and Current Policy

- The last review of the inhaled CF agents was in January of 2016. There was insufficient direct comparative evidence between i nhaled tobramycin and inhaled aztreonam for *P. aeruginosa.* After executive session the committee recommended that Kitabis Pak be preferred and TOBI, TOBI Podhaler and generic tobramycin be non-preferred.
- There were 33 claims for inhaled CF therapies quarter 2 of 2021.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence -based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

<u>Cochrane – Inhaled Mannitol for Cystic Fibrosis</u>

The focus of a 2020 Cochrane review was the use of inhaled mannitol in adults and children with CF.[1] The main outcomes were respiratory function, quality of life and harms associated with treatment. A literature search ending December 2019 yielded 6 trials (n=784). Overall risk of bias was deemed low except for the requirement that all participants pass a mannitol screening test before being enrolled in the trial. Additionally, all trials were funded by the drug manufacturer.

Trial durations were from 12 days to 6 months. Mannitol was compared to control (low-dose mannitol or non-respirable mannitol) in 5 trials and compared to dornase alfa in the remaining trial.[1] Two trials had additional 6-month, open-label extensions.

Results from 2 large trials were pooled (**Table 1**), but the other trials did not have outcomes that allowed for pooled assessment. Improvements in lung function parameters with mannitol 400 mg were demonstrated in patients regardless of concomitant use of dornase alfa. For the secondary outcome of pulmonary exacerbations, mannitol 400 mg was more effective than control based on the results of 2 pooled studies (relative risk [RR] 0.71; 95% CI, 0.51 to 0.98, P=0.04). One trial (n=28) evaluated the comparison between mannitol versus dornase alfa versus mannitol plus dornase alfa but did not find a difference between the groups based on very low quality evidence. A subgroup analysis found age did not have an effect on treatment efficacy. There was moderate quality of evidence of no difference in the incidence of mild, moderate or severe adverse reactions between inhaled mannitol 400 mg and control. Common adverse reactions in both groups included cough, hemoptysis, bronchospasm, pharyngeal pain and post-tussive vomiting.[1] The evidence for mannitol compared to non-respirable mannitol control (inpatient and outpatient) was very low or low quality, and therefore findings will not be presented in detail.

Table 1. Results for Inhaled Mannitol use in Patients with Cystic Fibrosis (Pooled results from 2 Trials [n=600] at 6 months)[1]

Outcome	Results	Quality of Evidence	Interpretation
Change from baseline in HRQoL	No difference between groups for age-appropriate versions of the CFQ-R questionnaire (multiple domains) Respiratory: mannitol 400 mg vs. control*: MD -0.99 (95% CI -4.50 to 2.52; p=0.58)	Low	*No difference in HRQoL found based on CFQ-R respiratory domain.*
Change from baseline in FEV_1 mL	mannitol 400 mg vs. control*: MD 86.5 mL (95% CI, 45.2 to 127.9 mL; p<0.00001)	Moderate	*Mannitol 400 mg improved lung function based on FEV_1 vs. control*
Change from baseline in lung function FEV_1% predicted	mannitol 400 mg vs. control*: MD 3.89% (95% CI, 1.69% to 6.08%; P=0.0005)	Moderate	*Mannitol 400 mg improved lung function based on FEV_1% predicted vs. control.*
Change from baseline in FVC mL	mannitol 400 mg vs. control*: MD 102.17 mL (95% CI, 48.40 to 155.94 mL; p=0.00002)	Moderate	*Mannitol 400 mg improved lung function based on FVC vs. control.*
Change from baseline in FEF_{25-75} mL/s	mannitol 400 mg vs. control*: MD 42.67 mL (95% CI, -28.07 to 113.42 mL; p=0.24)	Moderate	*No difference lung function found based on FEF_{25-75}.*
Key: *Control = mannitol 50 mg. Abbreviations: CFQ-R – Cystic Fibrosis Questionnaire-Revised version; FEF_{25-75}- mild expiratory flow; FEV_1 – forced expiratory volume at 1 second; FVC – forced vital capacity; HRQoL – health-related quality of life; MD – mean difference; NA – not applicable; HRQL – health related quality of life			

Only patients who tolerated mannitol were eligible for the trials which may be a limitation of the applicability of evidence. There was insufficient evidence for clinically meaningful outcomes such as pulmonary exacerbations, hospitalizations, and symptom relief.

Cochrane – Dornase Alfa for Cystic Fibrosis

The effect of dornase alfa on morbidity and mortality outcomes in participants with CF was the focus of a 2021 Cochrane review.[2] Nineteen trials were identified which included 2565 participants, comprised of adults (4 trials) and children (4 trials) and 11 trials comprised of adults and children.[2] Dornase alfa was compared to placebo and other mucolytic therapies (e.g., hypertonic saline, mannitol). Trial durations lasted from 6 days to 3 years. The author determined that there was high risk or unclear risk of bias in at least one risk of bias domain for the included trials. No trial reported mortality outcomes; primary outcomes included changes in lung function, pulmonary exacerbations and changes in quality of life.

Results were not pooled for most findings, as most outcomes only had results from one trial or there was too much heterogeneity between the trials to pool results. Results for outcomes which are based on moderate to high quality evidence are presented in **Table 2**.[2] Comparisons of dornase alfa to placebo did not demonstrate quality of life differences based on the Cystic Fibrosis Questionnaire-Revised version [CFQ-R]. There was evidence from one study in children that dornase alfa administered daily resulted in improved mean changes in FEV_1 (L), mean relative percentage of FVC (L), and mean relative percentage if quality of life scores compared to alternating days of dornase alfa (all low quality evidence).[2] No difference between dornase alfa and hypertonic saline was found on the number of pulmonary exacerbations at 3 months, but there was a benefit of dornase alfa over hypertonic saline for the mean relative percentage increase in FEV_1 (L) (MD 8.00; 95% CI, 2.00 to 14.00) based on low quality evidence.[2] In children, a comparison of dornase alfa to mannitol (up to 475 mg) could not demonstrate a statistical benefit of dornase alfa for changes in FEV1 (L) or FVC (L). More participants who received dornase alfa had pulmonary exacerbations compared to mannitol (RR 1.10; 95% CI, 0.25 to 4.84) (all low quality evidence).[2] In children, there were no differences in most outcomes between dornase alfa plus mannitol compared to dornase alfa alone based on low quality of evidence. Fewer participants experienced a pulmonary exacerbation who received dornase alfa alone compared to dornase alfa plus mannitol (RR 0.55; 95% CI, 0.16 to 1.92) (very low quality evidence).[2] Common adverse events with dornase alfa included voice alteration and rash.

Table 2. Effects of Dornase Alfa Compared to Placebo in Participants with Cystic Fibrosis[2]

Outcome	Results	Quality of Evidence	Comments
Relative mean percentage change in FEV_1 % predicted at 3 months	MD 7.30% (95% CI, 4.04 to 10.56); p<0.0001	Moderate	Dornase alfa was more effective in improving FEV_1 % predicted compared to placebo
Relative mean percentage change in FEV_1 % predicted at 6 months	MD 5.80% (95% CI, 3.99 to 7.61); p<0.00001	High	Dornase alfa was more effective in improving FEV_1 % predicted compared to placebo
Relative mean percentage change in FVC % predicted at 3 months	MD 5.10% (95% CI, 1.23 to 8.97); p=0.001	Moderate	Dornase alfa was more effective in improving FVC % predicted compared to placebo
Relative mean percentage change in FVC % predicted at 6 months (once daily)	MD 3.80% (95% CI, 2.62 to 4.98): p<0.00001	High	Dornase alfa was more effective in improving FVC % predicted compared to placebo
Number of people experiencing pulmonary exacerbations	RR 0.78 (95% CI, 0.62 to 0.96); p=0.02	Moderate	Dornase alfa was more effective reducing exacerbations compared to placebo

Abbreviations: CI – confidence interval; FEV_1 – forced expiratory volume at 1 second; FVC – forced vital capacity; MD – mean difference; RR – relative risk.

Cochrane – Antibiotic Strategies for Eradicating *Pseudomonas Aeruginosa* in People with Cystic Fibrosis

A 2017 Cochrane review evaluated at the evidence for early treatment of *P. aeruginosa* infection in children and adults with CF.[3] Specific outcomes of interest were: superiority of a particular antibiotic, organism eradication, delay in the onset of chronic infection, and clinical improvement. Combination treatments of inhaled, oral or IV antibiotics were compared to placebo, usual treatment or other combinations of antibiotics therapies (e.g., inhaled, oral or IV). Seven trials (n=744) met inclusion criteria with durations lasting from 28 days to 27 months.[3] Only 2 trials included adult patients. Many of the trials enrolled a small number of patients and 3 trials were over 10 years old. Much of the evidence was considered to be of low or very low quality and all trials had unclear risk of bias in some domains.

Two trials evaluated the use of inhaled tobramycin compared to placebo. For the outcome of microbiological eradication from the respiratory secretions at 2 months, tobramycin was more effective than placebo odds ratio (OR) 0.15 (95% CI, 0.03 to 0.65) (very low quality of evidence).[3] Low quality of evidence from 1 trial demonstrated no difference between inhaled tobramycin plus oral ciprofloxacin compared to inhaled colistin plus oral ciprofloxacin for eradication of *P. aeruginosa* (OR 1.28; 95% CI, 0.72 to 2.29; p-value not reported).[3] There was moderate quality evidence of more adverse events with inhaled tobramycin plus oral ciprofloxacin compared to inhaled colistin plus oral ciprofloxacin, 18% vs. 16%, respectively.[3] One randomized trial found moderate quality evidence that cycled based inhaled tobramycin was more effective than culture-based inhaled tobramycin for the outcome of *P. aeruginosa* eradication from the respiratory tract (OR 0.51; 95% CI, 0.31 to 0.82; p-value not reported). For the outcome of growth and nutritional status, based on weight and height, no differences were found between groups (moderate quality evidence). There was no difference in the amount of infective pulmonary exacerbation between cycled based inhaled tobramycin and culture-based inhaled tobramycin (OR 0.75; 95% CI, 0.48 to 1.17; p-value not reported).[3] There was no difference in the incidence of adverse events between groups. There was moderate quality evidence that there was no difference in eradication of *P. aeruginosa* from the respiratory tract between cycled and culture-based inhaled tobramycin therapy plus placebo compared to ciprofloxacin added to cycled and culture-based inhaled tobramycin (OR 0.89; 95% CI, 0.55 to 1.44) (moderate quality of evidence).[3] There was no difference between groups on growth and nutritional status, frequency of infective pulmonary exacerbations, number of other micro-organisms isolated from the respiratory tract or adverse events.

Limitations to the evidence are the inclusion of mostly children in the trials and imprecision of the results. Additionally, a majority of evidence was graded as low or very low quality also adding to the inability to draw strong conclusions.

Cochrane – Treatments for Preventing Recurrence of Infection with *Pseudomonas Aeruginosa* in People with Cystic Fibrosis

A 2019 Cochrane review evaluated secondary prevention strategies, including inhaled antibiotics, on the incidence of freedom from *P. aeruginosa* infection following eradication.[4] Only 1 trial (n=306) met inclusion criteria, with analysis of only 253 participants since the other participants did not have eradication of *P. aeruginosa* infection following an initial 28-day course of inhaled tobramycin therapy.[4] Participants had a CF diagnosis, were 51% female, and had a mean age of 6 years. Median follow-up was 494 days. The trial compared cycled therapy, which was inhaled tobramycin solution 300 mg twice daily every 3 months without regard to culture results, versus culture-based therapy, which was inhaled tobramycin solution 300 mg twice daily only in the 3-month period that culture results were positive for *P. aeruginosa.* Fifty-three percent of participants in each group also underwent a second comparison with the addition of oral ciprofloxacin 15-20 mg/kg/dose twice daily for 14 days to each of the previously described regimens.[4] Important outcomes were time to next isolation of *P. aeruginosa,* FEV_1 changes and pulmonary exacerbations.

The trial was at low risk of bias except that the study was funded by the manufacturer. One set of results were presented, irrespective of whether the participants also received ciprofloxacin. There was moderate quality of evidence that culture-based therapy was more likely to have a recurrence by their final study visit (up to 563 days) compared to those in the cycled therapy (HR 2.04; 95% CI, 1.28 to 3.26; p=0).[4] There was no difference found in the rate of

pulmonary exacerbations between groups based on moderate quality evidence and no difference found in FEV_1 changes based on very low quality of evidence. There was also no difference found between the groups in the incidences of severe adverse reactions or emergence of novel bacteria.

The high enrollment of children limits the applicability to adult CF populations. There was insufficient evidence on time to development of chronic *P. aeruginosa* or quality of life outcomes.

Cochrane – Inhaled Antibiotics for Pulmonary Exacerbations in Cystic Fibrosis

A 2018 Cochrane review evaluated the use of inhaled antibiotics in adults and children with CF.[5] One hundred sixty-seven participants from 4 trials were included. Two trials compared inhaled antibiotics to IV antibiotics and two trials compared inhaled antibiotics plus IV antibiotics to IV antibiotics alone. Inhaled antibiotics studied were tobramycin, carbenicillin, ceftazidime and amikacin and IV antibiotics were ticarcillin, tobramycin and ceftazidime.[5] The outcomes evaluated quality of life, survival and reduced time off of school or work. High risk of bias was present for all included trials.

Evidence for all outcomes were considered very low quality. One small trial (n=18) demonstrated perceived improvement in quality of life for both inhaled antibiotic and IV antibiotic groups.[5] There was no difference found in lung function in the trials that compared inhaled antibiotics versus IV antibiotics or in the trials that compared inhaled antibiotics plus IV antibiotics versus IV antibiotics alone.

There was insufficient evidence to conclude if inhaled antibiotics, alone or in combination with IV antibiotics, are more effective than IV antibiotics alone at improving lung function or quality of life.

Cochrane – Nebulised Hypertonic Saline for Cystic Fibrosis

A Cochrane review evaluated the evidence that compared hypertonic saline with other mucolytic therapies or placebo in participants with CF.[6] Seventeen trials enrolling 966 participants were included. Participants ranged from 4 months to 63 years of age. Hypertonic saline (3% to 7% given twice daily) was compared to placebo and the following active treatments: rhDNase, amiloride, and mannitol.[6] All trials were considered to be at high risk of bias due to allocation concealment issues. Outcomes evaluated were lung function (e.g., FEV_1 % predicted) lung clearance index, measures of sputum clearance, and pulmonary exacerbations. Due to heterogeneity, some of the results were not pooled.

The evidence for all outcomes was low to very low quality. In placebo-controlled trials, hypertonic saline was more effective at increasing the mean change from baseline of the FEV_1 by 3.44% (95% CI, 0.67 to 6.21), with no change in lung clearance index between the groups measured at 4 weeks.[6] There was insufficient evidence to compare adverse events. Four trials demonstrated a higher rate of sputum clearance with hypertonic saline compared to placebo. One trial in patients with acute exacerbation of lung disease found hypertonic saline improved short-term lung function by 5.10% versus placebo (95% CI, -14.67% to 24.87%).[6]

One trial found that rhDNase was more effective than hypertonic saline at increasing FEV1%-predicted in patients with moderate to severe lung disease (MD 8.00%; 95% CI, 2.00 to 14.00).[6] Other active treatment comparisons found no difference and were considered very low-quality evidence.

After review, 9 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[12–19]

New Guidelines:

NICE – Cystic Fibrosis: Diagnosis and Management

The 2017 NICE guideline covered the management of CF.[7] The guideline includes recommendations from 2 previously published guidelines on mannitol DPI, colistimethate sodium and tobramycin DPI for the treatment of *P aeruginosa*. Updated recommendations for mucoactive agents and antibiotics are discussed below.

Recommendations for Mucoactive Agents:

- Mucoactive therapies should be offered to people with CF who have clinical evidence of lung disease; specifically rhDNase (dornase alfa; recombinant human deoxcyribonuclease) is recommended as a first-line treatment option.[7]
- If there is evidence of an inadequate response to rhDNase based on lung function or clinical evaluation, then combination therapy with rhDNase and hypertonic sodium chloride or hypertonic sodium chloride alone should be considered.[7]
- Mannitol DPI for children and young people should be considered if they are unable to take rhDNase and hypertonic sodium chloride due to intolerance or due to suboptimal response.[7]
- Mannitol DPI for adults is recommended for individuals unable to tolerate rhDNase, have rapidly declining lung function (FEV_1 decline is 2% or greater annually), or who are not candidates for the use of other osmotic agents.[7]

Recommendations for the treatment of pulmonary infection, including oral and inhaled antibiotic therapies:

- Treatment of an active *Staphylococcus aureus* (*S. aureus)* infection should be with oral anti-*S. aureus* agent.[7]
- Treatment of *P. aeruginosa* should consist of oral or IV antibiotics in combination with an inhaled antibiotic.
    - If eradication is not obtained despite treatment, the use of sustained treatment with an inhaled antibiotic should be considered.[7]
    - A combination of an oral antibiotic or combination of 2 IV antibiotics should be considered depending on infection severity of *P. aeruginosa*.
- Patients with chronic *Burkholderia cepacian* complex infection and declining pulmonary status should be considered for sustained treatment with an inhaled antibiotic for infection suppression (antibiotic choice should be based on advice from microbiological specialist).[7]
- *Haemophilus influenzae* should be treated with oral or IV antibiotic depending on infection severity.[7]
- Patients with *Aspergillus fumigatus* with declining pulmonary status should be treated with an antifungal agent determined by a microbiological specialist.
- Patients with repeated pulmonary exacerbations or deteriorating lung function should be considered for long-term treatment with azithromycin at an immunomodulatory dose (dose that is less than the minimum inhibitory dose). If pulmonary exacerbations and deteriorating lung function persist with long-term azithromycin, then oral corticosteroids should be considered and azithromycin should be discontinued.[7]

Recommendations for tobramycin DPI:

- Use in patients with chronic *P. aeruginosa* pulmonary infection if nebulized tobramycin is considered appropriate.[7]

NICE – Cystic Fibrosis Quality Standards 2018

NICE updated its recommendations for quality standards CF in 2018. Quality standards for drug therapy for people with CF were provided for those who are candidates for a mucoactive agent or if they were infected with *P.aeruginosa*.[8] The following quality statements are provided:

- Patients with CF and chronic *P. aeruginosa* should have sustained inhaled antibiotic therapy.[8] *P. aeruginosa* can cause worsening signs and symptoms and reduced lung function in patients with chronic infection (3 or more isolates in the preceding 12 months). Inhaled antibiotic use on a chronic basis can help maintain lung function and quality of life.

- Patients with CF and have clinical evidence of lung disease should be prescribed rhDNase (e.g., dornase alfa) as a first-line mucoactive agent.[8] Mucoactive agents help to clear the sticky mucus that accumulates in the lungs of patients with CF, which predisposes them to infection. Evidence has shown that mucoactive therapies help to maintain lung function and prevent infection.

After review, 3 guidelines were excluded due to poor quality.[20,21,22]

New Indications:

Mannitol Inhalation Powder (Bronchitol®): In October 2020, the FDA approved mannitol DPI as add-on maintenance therapy to improve pulmonary function in adult patients with CF who are 18 years and older.[9] All adult patients should pass a tolerance test using inhaled mannitol. The dose is 10 capsules (400 mg) twice daily by oral inhalation, with the second dose taken 2-3 hours before bedtime.[9]

The Bronchitol® tolerance test (BTT) is required because of the risk of bronchospasm, which can be severe.[9] The BTT must be administered under the supervision of a healthcare provider who is able to treat severe bronchoconstriction. Patients who do not pass the BTT should not be prescribed inhaled mannitol. Patients should premedicate with a short-acting bronchodilator before each administration of inhaled mannitol. Bronchospasms may also occur with maintenance use of inhaled mannitol.[9] If bronchospasms occur, patients should discontinue treatment with inhaled mannitol and treat with a short-acting bronchodilator.

Inhaled mannitol was studied in 3, 26-week, double-blind, randomized controlled trials in children and adult patients with CF.[9] The trials differed by age and FEV_1: patients 18 years of age or older with baseline FEV_1 >40% to <90% of predicted; 6 years of age or older with baseline FEV_1 $\geq$30% to <90% predicted; or patients 6 years of age or older with baseline FEV_1 $\geq$40% to <90% of predicted.[9] Standard of care CF therapies (e.g., bronchodilators, inhaled antibiotics, and dornase alfa) were allowed except inhaled hypertonic saline was not permitted. Trials studied twice daily inhaled mannitol 400 mg versus control (50 mg inhaled mannitol), premedicating with a short-acting bronchodilator (e.g., albuterol or equivalent).[9]

The primary outcome was mean change in pre-dose FEV_1 (mL) from baseline. In the first trial (n=423), the mean change in pre-dose FEV_1 between inhaled mannitol and control was 51 mL (95% CI, 6 to 97 mL; p=0.028).[9] Similar findings were demonstrated in the second and third trial, with a mean change favoring inhaled mannitol versus control (68 mL; 95% CI, 24 to 113 mL, and 52 mL; 95% CI, -3 to 107 mL, respectively).[9] The second and third trials included patients under the age of 18 years; however, inhaled mannitol is not indicated in this population.

Common adverse events noted in clinical trials included cough, hemoptysis, oropharyngeal pain, vomiting, bacteria in sputum, pyrexia and arthralgia. Patients who experience hemoptysis with the use of inhaled mannitol should discontinue use.[9]

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Amikacin[10]	Arikayce Kit	March 2020	Warnings	Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported.
Tobramycin[11]	NA	April 2020	Warnings	Aminoglycosides, including tobramycin, have been associated with several reports of total, irreversible, bilateral congenital deafness in pediatric patients whose mothers received the aminoglycoside, streptomycin. Patients should be informed of hazard to fetus.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
dornase alfa	PULMOZYME	SOLUTION	Y
sodium chloride for inhalation	SODIUM CHLORIDE	VIAL-NEB	Y
tobramycin/nebulizer	KITABIS PAK	AMPUL-NEB	Y
tobramycin/nebulizer	TOBRAMYCIN	AMPUL-NEB	Y
amikacin liposomal/neb.accessr	ARIKAYCE	VIAL-NEB	N
aztreonam lysine	CAYSTON	VIAL-NEB	N
mannitol	BRONCHITOL	CAP W/DEV	N
tobramycin	BETHKIS	AMPUL-NEB	N
tobramycin	TOBRAMYCIN	AMPUL-NEB	N
tobramycin	TOBI PODHALER	CAP W/DEV	N
tobramycin	TOBI PODHALER	CAPSULE	N
tobramycin in 0.225% sod chlor	TOBI	AMPUL-NEB	N
tobramycin in 0.225% sod chlor	TOBRAMYCIN	AMPUL-NEB	N

Appendix 2: New Comparative Clinical Trials

A total of 334 citations were manually reviewed from the initial literature search. After further review, 333 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 4. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Flume, et al[23] MC, DB, PG, RCT 26 weeks	Inhaled mannitol 400 mg twice daily Vs. Inhaled mannitol 50 mg twice daily (control) Maintenance antibiotic therapy and rhDNase therapy was permitted	Adult with CF, FEV_1 40% to 90% predicted (n=423)	FEV_1 averaged over the 26-week treatment period	Mannitol 400 mg: 63 mL Mannitol 50 mg: 8 mL MD 54 mL (95% CI, 8 to 100 mL) P=0.020	Randomization was appropriate and double-dummy design adequately masked treatment. Limitations to the study include the averaging of FEV_1 over 26 weeks which increases the magnitude of benefit. Change from baseline FEV_1 at 26 weeks was not statistically different between groups. The mean change from baseline in FVC average over 26 weeks was not statistically different between groups. Ninety-seven percent of patients were White which significantly reduces applicability to real world populations.

Abbreviations: CF = cystic fibrosis; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MC = multi-center; MD = mean difference; PG = parallel group; RCT = randomized clinical trial; rhDNase = recombinant human deoxyribonuclease

Appendix 3: Abstracts of Comparative Clinical Trials

Efficacy and safety of inhaled dry-powder mannitol in adults with cystic fibrosis: An international, randomized controlled study

Flume P, Amelina E, Daines C, Charlton B, et al

Abstract

Background: Mannitol is a mucoactive hyperosmotic agent used as add-on therapy in patients with cystic fibrosis (CF), administered twice-daily (BID) via a small, portable, breath-actuated dry-powder inhaler. This study was conducted to provide confirmatory evidence of mannitol's efficacy and safety in adults.

Methods: This multicenter, double-blind, randomized, parallel-group, controlled clinical trial recruited adults (aged ≥18 years) with CF, and forced expiratory volume in 1 second (FEV1) 40-90% predicted. Subjects received either mannitol 400 mg or mannitol 50 mg (control), BID via dry-powder inhaler for 26 weeks. Primary endpoint: FEV1 averaged over the 26-week treatment period.

Results: Of 423 subjects randomized (209 or 214 receiving mannitol 400 mg BID or control, respectively), 373 (88.2%) completed the study, with a similar proportion completing in the two groups. For FEV1 averaged over 26 weeks, mannitol 400 mg BID was statistically superior to control (adjusted mean difference 54 mL [95% CI 8, 100 mL]; p = 0.020). This was supported by sensitivity analyses of the primary endpoint, and by observed improvements in secondary pulmonary function endpoints (eg, absolute adjusted mean difference in percent predicted FEV1 averaged over 26 weeks 1.21% [0.07%, 2.36%]; p = 0.037). Adverse events were mainly mild or moderate in severity, with treatment-related adverse events in 15.5 and 12.2% of subjects receiving mannitol 400 mg BID and control, respectively.

Conclusions: In adults with CF, mannitol 400 mg BID inhaled as a dry-powder statistically significantly improved lung function (FEV1) compared with control, with this improvement supported by sensitivity analyses and secondary pulmonary function endpoints. Mannitol had a good overall safety and tolerability profile. ClinicalTrials.gov: NCT02134353.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to September 03, 2021

Search Strategy:

#	Searches	Results
1	dornase alfa.mp.	259
2	tobramycin.mp.	8144
3	amikacin.mp.	11037
4	sodium chloride.mp. or Sodium Chloride/	81324
5	aztreonam.mp. or Aztreonam/	3566
6	Mannitol/ or mannitol.mp.	24070
7	1 or 2 or 3 or 4 or 5 or 6	124119
8	limit 7 to (english language and humans and yr="2015 -Current")	8096
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	334

Appendix 5: Key Inclusion Criteria

Population	Adults and children with cystic fibrosis
Intervention	Inhaled drugs for cystic fibrosis
Comparator	Placebo or active treatments
Outcomes	Mortality, improvement in lung function, improvement in symptoms, organism eradication, quality of life
Timing	As needed and scheduled maintenance therapy
Setting	Outpatient