CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR) POTENTIATOR(S)

Orkambi™ (lumacaftor/ivacaftor)
Kalydeco® (ivacaftor)

Drug Regimen Review Center
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Introduction

Cystic fibrosis (CF) is a complex genetic disease characterized by thick viscous secretions leading to recurrent lung infections, bronchiectasis, and progressive deterioration in lung function. CF is primarily seen in Caucasians (1:2,500 vs. 1:13,500 Hispanics; 1:10,900 Native Americans; 1:15,100 African Americans; and 1:100,000 Asians), and it is the most common lethal, genetic disease in this population. CF affects 30,000 children and adults in the US (70,000 worldwide), and there are approximately 1000 new cases of CF diagnosed each year.

In healthy patients the epithelial cells transport chloride through cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels, and sodium and water accompany the ion flux via osmosis, which results in thin, moist mucus lining epithelium. In patients with CF, there are mutations in the CFTR gene. There are more than 1,800 known mutations in the CFTR gene. The mutations cause abnormal chloride transport across epithelial cells and mucosal surfaces which results in decreased secretion of chloride and increased reabsorption of sodium and water with a resultant dehydrated epithelium, and impaired mucociliary clearance due to the thick and sticky secretions. This affects the lungs/lung epithelium, the intestinal tract, pancreatic ducts, hepatobiliary tree, reproductive tract (vas deferens/ovaries), and sweat ducts.

Complications such as lung infections and poor growth result due to the increased viscosity of secretions that are difficult to clear and problems with digestion and absorption of food.

Manifestations/Signs and Symptoms of CF:
A. Gastrointestinal & Hepatic: Small bowel obstruction because stool becomes dry and hard and cannot be evacuated; biliary cirrhosis because bile ducts become obstructed by mucus and bile builds up in the liver and destroy tissue (liver disease); lack of enzymes released (prevented by mucus) to allow breakdown of food and absorption of nutrients.
B. Endocrine: Obstructed pancreatic ducts and alterations in pancreatic enzymes, deficiency in lipase causing foul smelling and greasy stools and increased frequency, and insulin deficiency and glucose intolerance.
C. Exocrine: High concentrations of sodium and chloride in sweat glands (very salty tasting skin), salt depletion in hot weather, and could affect body cooling.
D. Pulmonary: Persistent obstruction of airways causing inflammatory response (persistent coughing, phlegm, wheezing or shortness of breath) and facilitates bacterial growth so patients may experience frequent lung infections including pneumonia and bronchitis (most commonly Pseudomonas aeruginosa)/infections, extensive lung damage and respiratory failure.
E. Reproductive: Male infertility - sterility in 95% of males due to obstruction of epididymis, vas deferens & seminal vesicles.
F. Hematologic: anemia (iron deficiency due to malabsorption).
G. Skeletal systems: osteopenia and osteoporosis (due to vitamin D malabsorption, delayed puberty and endocrine development, poor nutrition, limited physical activity and chronic acidosis); arthritis (due to immune complexes formed as a result of chronic pulmonary infections).

The symptoms and severity of CF vary widely. CF typically begins early in life with more than 75% diagnosed by the age of 2. Serious problems may be experienced from birth, but some patients may experience a milder version of the disease that does not show up until later in life (teens or young adults). About 50% of the CF population is 18 years or older, and nowadays many CF patients have a life expectancy into their 30’s, 40’s, and beyond (median life expectancy is 41 years). Although there is no cure for CF, treatments have improved greatly in recent years.
CF is diagnosed if one of the following is present (1) one or more clinical feature of CF (2) history of CF in a sibling, or (3) positive newborn screening test; plus one of the following (1) two CF mutations† (genetic testing), or (2) two positive sweat chloride tests (high levels of chloride indicate CF).²

† CF is an autosomal recessive disease (one of several ways that a trait, disorder, or disease can be passed down through families) meaning two copies of an abnormal gene must be present in order for the disease or trait to develop.⁸ “People with CF have inherited two copies of the defective CF gene -- one copy from each parent. Both parents must have at least one copy of the defective gene. People with only one copy of the defective CF gene are called carriers, but they do not have the disease. Each time two CF carriers have a child, the chances are:

• 25 percent (1 in 4) the child will have CF
• 50 percent (1 in 2) the child will be a carrier but will not have CF
• 25 percent (1 in 4) the child will not be a carrier and will not have CF.”³

Patients with CF receive various treatments to manage the disease on a daily basis. The goals of treatment include (1) airway clearance to prevent lung infections i.e. albuterol, pulmozyme (dornase alfa), or hypertonic saline (HyperSal) via nebulization, (2) controlling of lung infections i.e. aerolized antibiotics for chronic infection in patients colonized with P.aeruginosa (TOBI/tobramycin & Cayston/aztreonam recommended by guidelines) , (3) nutritional treatment i.e. pancreatic enzymes, vitamin ADEK, iron, and other nutritional supplementation (tube feedings and high calorie shakes and formulas), (4) preventing and treating intestinal blockage, (5) Gastrointestinal treatment i.e. Actigall (ursodiol) for biliary cirrhosis.²,⁹ Mortality is mostly (85%) attributable to lung disease.²

More recent developments to target the root cause of the disease lead to the FDA approval of cystic fibrosis transmembrane conductance regulator (CFTR) potentiators (ivacaftor and lumacaftor/ivacaftor combination).³,⁵ It is expected that these CFTR modulators could extend life expectancy by decades for some people with CF.³

In January 2012, the FDA approved Kalydeco®(ivacaftor), a CFTR potentiator.⁴ This medication was initially only approved for use in patients with the G551D mutation of CF ages 6 and older, but this was extended in 2014 to include younger patients and any of 10 mutations (representing about 8 percent of the U.S. CF population).³ This medication is currently only indicated for use in patients 2 years of age or older who have one of the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H.¹⁰ “Patients with ≥1 copy of the G551D mutation to the CFTR gene represent 4% of the CF population [about 1,200 patients in the US]”.⁴

In July 2015, the FDA approved Orkambi™ (lumacaftor/ivacaftor), another CFTR potentiator for the treatment of cystic fibrosis (CF). This medication is indicated for use in patients 12 years of age or older who are homozygous for the F508del mutation in the CFTR gene.¹¹ This is the most common mutation (globally, 46% of patients with CF have two copies and 33% have one copy of this mutation) and in these people little to no CFTR protein reaches the cell surface.⁵ Orkambi™ is currently the only CFTR potentiator available to treat patients with the homozygous F508del genotype.

“Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface”¹² so in other words it “moves the flawed CFTR protein to its correct location”.² “Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface”¹² which improves salt and water regulation (absorption and secretion).²
Both ivacaftor and lumacaftor were granted orphan drug status in the US, and lumacaftor was also granted fast track status in the US. The approximate cost per patient per year has been reported as $259,000 with Orkambi™ (2015) and $294,000 (2012) with Kalydeco®.

Methodology

A Cochrane Library literature search for systematic reviews was conducted. The Agency for Healthcare Research and Quality (AHRQ; www.guideline.gov), the FDA website (including product labeled information), UpToDate, Micromedex and Lexicomp were searched for safety information, systematic reviews, clinical trials, and guidelines. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were searched for first. After review of the sources, the following were examined: (a) The 2013 Cystic Fibrosis Pulmonary Guidelines (b) One Cochrane review and one other review (Centre for Reviews and Dissemination; review that met the criteria for the Database of Abstracts of Reviews of Effects) – Appendix 2, (c) The RCT supporting efficacy of Orkambi™, and (d) product labels for Orkambi™ (lumacaftor/ivacaftor) and Kalydeco®(ivacaftor).

Clinical Guidelines

In the United States, the Pulmonary Clinical Practice Guidelines Committee, supported by the Cystic Fibrosis Foundation, recommend the use of mutation-specific targeted therapy as first-line treatment in CF patients with relevant mutations. Specifically, they mention Kalydeco®, one of the components of Orkambi™ that is manufactured and sold separately. The committee strongly recommends using Kalydeco® in “individuals with CF, 6 years of age and older, with at least one G551D CFTR mutation...” in order “to improve lung function and quality of life and reduce exacerbations.” It is important to note that this recommendation does not take into account the 2015 FDA-approved indication expansion for Kalydeco® to pediatric patients 2 to less than 6 years of age, because these guidelines have not been updated since 2013. Orkambi™ is not mentioned in the CF guidelines for this same reason. Please refer to appendix 3 for additional information.

Clinical Efficacy

Please refer to appendix 2 for systematic review(s) and randomized controlled trial(s)(RCTs).

No systematic reviews were identified in the Cochrane Library for lumacaftor.

The authors of a recent Cochrane review (Patel et al. 2015) concluded that “both G551D phase 3 trials (n = 219) demonstrated a clinically relevant impact of the potentiator ivacaftor on outcomes at 24 and 48 weeks, providing evidence for the use of this treatment in adults and children (over six years of age) with cystic fibrosis and the G551D mutation (class III). There is no evidence to support the use of ivacaftor in people with the ΔF508 mutation (class II) (n = 140). Trials on ivacaftor in people with different mutations are ongoing.”

In another recent systematic review and cost-effectiveness analysis of ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation, the authors (Whiting P et al. 2014) concluded that “The available evidence suggests that ivacaftor is a clinically effective treatment for patients with CF and the G551D mutation; the high cost of ivacaftor may prove an obstacle in the uptake of this treatment. The main priority for further research is the long-term effectiveness of ivacaftor.”
The abstract of the publication reporting on the efficacy of Orkambi™ in patients with cystic fibrosis homozygous for Phe508del CFTR (2 copies of mutation) has been included in appendix 2, table 4.17 Approximately 45% of patients are homozygous for this allele.2 Two phase 3 RCTs (double-blind, placebo-controlled) were conducted where patients (CF patients homozygous for Phe508del CFTR; 12 years of age or older; n=1108) were assigned to lumacaftor and ivacaftor.17 “In both studies, there were significant improvements in the primary end point in both lumacaftor-ivacaftor dose groups; the difference between active treatment and placebo with respect to the mean absolute improvement in the percentage of predicted FEV1 ranged from 2.6 to 4.0 percentage points (P<0.001), which corresponded to a mean relative treatment difference of 4.3 to 6.7% (P<0.001).”17 The effectiveness of Orkambi™ in younger patients (6-11 years old) is being evaluated in a phase 3 study.2

Safety

Common adverse drug reactions (ADRs) reported for the two different CFTR potentiators include nausea, diarrhea, nasopharyngitis, upper respiratory tract infection, and rash.10,11 Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor and the product labels for Orkambi™ and Kalydeco® therefore recommend baseline and follow-up examinations in pediatric patients initiating these medications.10,11 Additionally, elevation of liver transaminases (AST/ALT) has been reported in patients taking either of these medications. Therefore, liver function tests (LFTs) are recommended in all patients before therapy initiation and throughout therapy.10,11 Despite these shared ADRs, it is important to note that there are several ADRs associated with Orkambi™ that have not been reported with Kalydeco®. These include: dyspnea, fatigue, influenza, abnormal respiration, and elevated blood creatine phosphokinase.11

Regarding specific contraindications and precautions, dose adjustments for both Orkambi™ and Kalydeco® are recommended in patients taking strong CYP3A4 inhibitors and in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C). Also, these medications should not be taken concomitantly with strong CYP3A4 inducers. There are precautions that are unique to each agent. Kalydeco® should not be used in patients who are homozygous for the F508del mutation in the CFTR gene (not effective).10 Patients starting Orkambi™ should be monitored for respiratory events, as they occur more frequently during therapy initiation.11

Please refer to appendix 1 for additional information (e.g. precautions).

Place in therapy and potential criteria to be reviewed

Factors and limitations to consider:

- **Not a substitute** for other cystic fibrosis treatments
- **Special Populations**: If the CFTR genotype of the patient is unknown, FDA requires a CF mutation test to be carried out first to detect the presence or absence of a CF mutation and bi-directional sequencing second to determine the patient’s mutation status.
- **Comorbidities/Hepatic impairment**: LFT testing is recommended prior to starting both Orkambi™ and Kalydeco®. This is important to track the progression of the patient’s hepatic function while on either of these medications. It is also important because if the patient has hepatic dysfunction (Child-Pugh Class B
or C) dose adjustments will be necessary. Additionally, after therapy initiation of both Orkambi™ and Kalydeco®, LFT testing is recommended every 3 months during the first year and annually thereafter.

- **Pregnancy:** Both Orkambi™ and Kalydeco® are pregnancy category B.
- **Breastfeeding:** Both lumacaftor and ivacaftor are excreted into the milk of lactating female rats.
- **Adverse effects & CYP3A drug interactions:** Refer to safety section & appendix 1.
- **Duplication of therapy:** Kalydeco® and Orkambi™ both contain ivacaftor so should not be used together.
- **Monitoring:** Refer to appendix 1.
- **Efficacy/Patients who may benefit:** Refer to labelled indications, clinical efficacy section and clinical guideline recommendations.
Utah Medicaid Utilization Data

The data provided below is for 2012-2015 (to date and 2015 therefore do not represent a full year).

<table>
<thead>
<tr>
<th>GENERIC</th>
<th>BRAND</th>
<th>ROUTE</th>
<th>1/1/2012 - 12/31/2012</th>
<th>1/1/2013 - 12/31/2013</th>
<th>1/1/2014 - 12/31/2014</th>
<th>1/1/2015 - 7/31/2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>RX PT RX PT RX PT RX PT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivacaftor</td>
<td>KALYDECO TABLET 150MG</td>
<td>Oral</td>
<td>10 3 48 6 72 7 33 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumacaftor-Ivacaftor</td>
<td>ORKAMBI TABLET 200-125</td>
<td>Oral</td>
<td>0 0 0 0 0 0 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL PATIENTS WITH CF DIAGNOSIS**: 8 100.00%

**TOTAL UNIQUE PATIENTS ON CF THERAPY**: 8

* Diagnosis date within 60 days before or 60 days after receiving CF product.
**Age and Sex**

* Age at first fill.

**Prescribers**

<table>
<thead>
<tr>
<th>Prescriber Type</th>
<th>Total Prescribers 2012-15</th>
<th>Total Claims 2012-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Nurse Practitioner</td>
<td>1       25.00%</td>
<td>46  28.22%</td>
</tr>
<tr>
<td>Pulmonologist</td>
<td>2       50.00%</td>
<td>50  30.67%</td>
</tr>
<tr>
<td>Pediatric Pulmonologist</td>
<td>1       25.00%</td>
<td>67  41.10%</td>
</tr>
</tbody>
</table>
Conclusions

Kalydeco® and Orkambi™ have been shown to be beneficial in patients with specific CF mutations. Data is lacking on long-term safety and efficacy of these drugs.

Cost is a significant limitation of these drugs. At an approximate cost per patient per year of $294,000 (Kalydeco® 2012\textsuperscript{1,4,13}), it costs approximately $2,058,000 to treat 7 patients with this medication (as per 2015 utilization to date). Orkambi™ (lumacaftor/ivacaftor) was FDA approved in July 2015, and there has been no utilization in the Utah Medicaid population to date. However, it is important to consider that Orkambi™ is FDA approved for use in patients 12 years of age or older who are homozygous for the $F_{508}del$ mutation in the CFTR gene (which Kalydeco® is not FDA-approved for), and this is the most common mutation (globally approximately 46\%) so increased utilization is expected.\textsuperscript{11} It is important to keep in mind that these medications do not cure CF, but treat the condition so treatment/management costs of CF will continue to accumulate.

Based on utilization data available to date, there are no serious concerns with regards to utilization of these drugs in the Utah Medicaid population. However, based on efficacy and safety data available, clinical guideline recommendations, and potential expected increased use, ensuring FDA-approved labelled use is important.
Potential clinical criteria

You may wish to consider the following criteria (limiting it to labelled indications):

For Kalydeco:
1. Must be used for treatment of cystic fibrosis, and
2. Must be age 2 or older, and

For Orkambi:
1. Must be for treatment of cystic fibrosis, and
2. Must be age 12 or older, and
3. Laboratory confirmation that patient is homozygous for the F508del mutation in the CFTR gene (FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene).

Clinical Notes

- Avoid combination of ivacaftor with strong CYP3A4 inducers (e.g. rifampin, St John’s wort). Use with strong CYP3A4 Inducers may substantially decrease the serum concentration of Ivacaftor.¹⁰⁻¹²

ICD-9

277.0 Cystic fibrosis
   277.00 Cystic fibrosis without mention of meconium ileus
   277.01 Cystic fibrosis with meconium ileus
   277.02 Cystic fibrosis with pulmonary manifestations
   277.03 Cystic fibrosis with gastrointestinal manifestations
   277.09 Cystic fibrosis with other manifestations
## Appendix 1 – Drug information

### Table 1: Cystic Fibrosis Drug Table of Mutation-Specific Targeted Therapies

*Source: Product Labels¹⁰,¹¹*

<table>
<thead>
<tr>
<th>Drug &amp; Dosage Form</th>
<th>Dosing</th>
<th>Labeled Indications</th>
<th>Off-Label Uses</th>
<th>Adverse Drug Reactions</th>
<th>Contraindications/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orkambi™</strong> (lumacaftor/ivacaftor)</td>
<td>2 tablets twice daily with fat-containing food</td>
<td>Treatment of cystic fibrosis in patients 12 years of age or older who are homozygous for the F508del mutation in the CFTR gene</td>
<td>No known off-label uses and no other studies currently being carried out for use in other disease states.¹⁹</td>
<td>Dyspnea, Nasopharyngitis, Nausea, Diarrhea, Upper respiratory tract infection, Fatigue, Rash, Flatulence, Rhinorrhea, Influenza, Elevated blood creatine phosphokinase, Abnormal respiration</td>
<td></td>
</tr>
<tr>
<td><strong>Kalydeco®</strong> (ivacaftor)</td>
<td>Patients 2 - &lt;6 years old:</td>
<td>Treatment of cystic fibrosis in patients ≥ 2 years old with one of the following mutations on the CFTR gene: G551D, G1244E, G1349D, G178R, G551S,</td>
<td>No known off-label uses.²⁰</td>
<td>Headache, Oropharyngeal pain, Upper respiratory tract infection, Nasal congestion, Abdominal pain, Nasopharyngitis, Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Oral tablet <em>(brand only)</em></td>
<td>• 200/125 mg</td>
<td></td>
<td></td>
<td>• <strong>This drug is NOT effective in the treatment of patients homoyzgous for the F508del mutation in the CFTR gene.</strong></td>
<td></td>
</tr>
<tr>
<td>Oral granules supplied in unit dose packets</td>
<td></td>
<td></td>
<td></td>
<td>• If starting the drug on a patient already on a strong CYP3A inhibitor, reduce the dose to 1 tablet daily for the first week. Then, continue with normal dosing.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Avoid concomitant use of this drug with strong CYP3A inducers.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Patients with moderate hepatic impairment (Child-Pugh Class B) should reduce the dose to 2 tablets in the morning and 1 tablet in the evening.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• LFT testing is recommended before starting the drug and while the patient is on the drug.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Respiratory events were more commonly seen during treatment initiation.</td>
<td></td>
</tr>
</tbody>
</table>

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¹⁰ Product Labels
¹¹ Product Labels
<table>
<thead>
<tr>
<th><strong>(brand only)</strong></th>
<th>50 mg</th>
<th>75 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hours with fat-containing food</td>
<td>S1251N, S1255P, S549N, S549R, or R117H.</td>
</tr>
<tr>
<td>Patient ≥ 6 years old:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg tablet every 12 hours with fat-containing food</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serious, rare – Cataracts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated AST/ALT</td>
<td></td>
</tr>
</tbody>
</table>

- Avoid taking this drug with foods containing grapefruit or Seville oranges.
- Avoid concomitant use of this drug with strong CYP3A inducers.
- Patients with moderate hepatic impairment (Child-Pugh Class B) should reduce the dose to 1 tablet or 1 packet once daily.
- Use caution when starting on patients with severe hepatic impairment (Child-Pugh Class C). Recommended dose: 1 tablet or 1 packet once daily (or less frequently).
- LFT testing is recommended before starting the drug and while the patient is on the drug.
## Appendix 2 – Systematic review(s) and Randomized Controlled Trial(s)

### Table 2: Cochrane Reviews

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Objectives</th>
<th>Main Results</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel S et al</td>
<td>Potentiators (specific therapies for class III and IV mutations) for</td>
<td>“To evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with cystic fibrosis.”</td>
<td>“We included four randomised controlled trials (n = 378), lasting from 28 days to 48 weeks, comparing the potentiator ivacaftor to placebo. Trials differed in terms of design and participant eligibility criteria, which limited the meta-analyses. The phase 2 trial (n = 19) and two phase 3 trials (adult trial (n = 167), paediatric trial (n = 52)), recruited participants with the G551D mutation (class III). The fourth trial (n = 140) enrolled participants homozygous for the ΔF508 mutation (class II). Risks of bias in the trials were moderate. Random sequence generation, allocation concealment and blinding of trial personnel were well-documented. Participant blinding was less clear throughout all trials; in three trials, some participant data were excluded from the analysis. Selective outcome reporting was apparent in three trials. All trials were sponsored by industry and supported by other non-pharmaceutical funding bodies. No trial reported any deaths. Significantly higher quality of life scores in the respiratory domain were reported by the adult phase 3 G551D trial at 24 weeks, mean difference 8.10 (95% confidence interval (CI) 4.77 to 11.43) and 48 weeks, mean difference 8.60 (95% CI 5.27 to 11.93); but not by the paediatric phase 3 G551D trial. The adult phase 3 G551D trial reported improvements in relative change from baseline in forced expiratory volume at one second at 24 weeks, mean difference 16.90% (95% CI 13.60 to 20.20) and 48 weeks, mean difference 16.80% (95% CI 13.50 to 20.10); as did the paediatric G551D trial at 24 weeks, mean difference 17.4% (P &lt; 0.0001). No improvements in quality of life were reported for the ΔF508 mutation (class II) G551D trial.”</td>
<td>“Both G551D phase 3 trials (n = 219) demonstrated a clinically relevant impact of the potentiator ivacaftor on outcomes at 24 and 48 weeks, providing evidence for the use of this treatment in adults and children (over six years of age) with cystic fibrosis and the G551D mutation (class III). There is no evidence to support the use of ivacaftor in people with the ΔF508 mutation (class II) (n = 140). Trials on ivacaftor in people with different mutations are ongoing.”</td>
</tr>
</tbody>
</table>
life or lung function were reported in the ΔF508 participants. Combined data from both phase 3 G551D trials demonstrated increased reporting of cough, odds ratio 0.57 (95% CI 0.33 to 1.00) and increased episodes of decreased pulmonary function, odds ratio 0.29 (95% CI 0.10 to 0.82) in the placebo group. The adult phase 3 G551D trial demonstrated increased reporting of dizziness amongst the ivacaftor group, OR 10.55 (95% CI 1.32 to 84.47). No trial showed a difference between treatment arms in the number of participants interrupting or discontinuing the trial drug. In the phase 3 G551D trials, fewer participants assigned to ivacaftor developed serious pulmonary exacerbations. When considering all data for exacerbations, participants taking ivacaftor in the adult phase 3 G551D study developed fewer exacerbations, odds ratio 0.54 (95% CI 0.29 to 1.01). In the other G551D studies and in the ΔF508 study, there was no difference between groups in the number of participants who developed pulmonary exacerbations. Combined data from both phase 3 G551D trials demonstrated significant improvements in absolute change from baseline in forced expiratory volume at one second (% predicted) at 24 weeks, mean difference 10.80% (95% CI 8.91 to 12.69) and 48 weeks, mean difference 10.44% (95% CI 8.56 to 12.32); also in weight at 24 weeks, mean difference 2.37 kg (95% CI 1.68 to 3.06) and 48 weeks, mean difference 2.75 kg (95% CI 1.74 to 3.75). No improvements in these outcomes were reported in the ΔF508 participants. Significant reductions in sweat chloride concentration were reported in both G551D and ΔF508 participants: in combined data from both phase 3 G551D trials at 24 weeks, mean difference -48.98 mmol/L (95% CI -52.07 to -45.89) and 48 weeks, mean difference -49.03 mmol/L (95% CI -52.11 to -45.94); and from the
ΔF508 trial at 16 weeks, mean difference -2.90 mmol/L (95% CI -5.60 to -0.20).

"Abstract
Background
Cystic fibrosis is the most common inherited life-shortening illness in Caucasians and caused by a mutation in the gene that codes for the cystic fibrosis transmembrane regulator protein (CFTR), which functions as a salt transporter. This mutation most notably affects the airways of people with cystic fibrosis. Excess salt absorption by defective CFTR dehydrates the airway lining and leads to defective mucociliary clearance. Consequent accumulation of thick, sticky mucus makes the airway prone to chronic infection and progressive inflammation; respiratory failure often ensues. Additionally, abnormalities with CFTR lead to systemic complications like malnutrition, diabetes and subfertility.

Since the discovery of the causative gene, our understanding of the structure and function of CFTR and the impact of different mutations has increased and allowed pharmaceutical companies to design new mutation-specific therapies targeting the underlying molecular defect. Therapies targeting mutation classes III and IV (CFTR potentiators) aim to normalise airway surface liquid and help re-establish mucociliary clearance, which then has a beneficial impact on the chronic infection and inflammation that characterises lung disease in people with cystic fibrosis. These therapies may also affect other mutations.

Objectives
To evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with cystic fibrosis.

Search methods
We searched the Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the reference lists of relevant articles and reviews. Last search: 05 March 2015.

We searched the EU Clinical Trials Register, clinicaltrials.gov (US Clinical Trials Register) and the International Clinical Trials Registry Platform (ICTRP). Last search of clinical trial registries: 06 February 2014.

Selection criteria
Randomised controlled trials of parallel design comparing CFTR potentiators to placebo in people with cystic fibrosis. In a post hoc change we excluded trials combining CFTR potentiators with other mutation-specific therapies. These will be considered in a separate review.

Data collection and analysis
The authors independently extracted data and assessed the risk of bias in included trials; they contacted trial authors for additional data. Meta-analyses were undertaken on outcomes at a number of time points.

Main results
We included four randomised controlled trials (n = 378), lasting from 28 days to 48 weeks, comparing the potentiator ivacaftor to placebo. Trials differed in terms of design and participant eligibility criteria, which limited the meta-analyses. The phase 2 trial (n = 19) and two phase 3 trials (adult trial (n = 167), paediatric trial (n = 52)), recruited participants with the G551D mutation (class III). The fourth trial (n = 140) enrolled participants homozygous for the ΔF508 mutation (class II).

Risks of bias in the trials were moderate. Random sequence generation, allocation concealment and blinding of trial personnel were well-documented. Participant blinding was less clear throughout all trials; in three trials, some participant data were excluded from the analysis. Selective outcome reporting was apparent in three trials. All trials were sponsored by industry and supported by other non-pharmaceutical funding bodies.

No trial reported any deaths. Significantly higher quality of life scores in the respiratory domain were reported by the adult phase 3 G551D trial at 24 weeks, mean difference 8.10 (95% confidence interval (CI) 4.77 to 11.43) and 48 weeks, mean difference 8.60 (95% CI 5.27 to 11.93); but not by the paediatric phase 3 G551D trial. The adult phase 3 G551D trial reported improvements in relative change from baseline in forced expiratory volume at one second at 24 weeks, mean difference 16.90% (95% CI 13.60 to 20.20) and 48 weeks, mean difference 16.80% (95% CI
No improvements in quality of life or lung function were reported in the ΔF508 participants. Combined data from both phase 3 G551D trials demonstrated increased reporting of cough, odds ratio 0.57 (95% CI 0.33 to 1.00) and increased episodes of decreased pulmonary function, odds ratio 0.29 (95% CI 0.10 to 0.82) in the placebo group. The adult phase 3 G551D trial demonstrated increased reporting of dizziness amongst the ivacaftor group, OR 10.55 (95% CI 1.32 to 84.47). No trial showed a difference between treatment arms in the number of participants interrupting or discontinuing the trial drug. In the phase 3 G551D trials, fewer participants assigned to ivacaftor developed serious pulmonary exacerbations. When considering all data for exacerbations, participants taking ivacaftor in the adult phase 3 G551D study developed fewer exacerbations, odds ratio 0.54 (95% CI 0.29 to 1.01). In the other G551D studies and in the ΔF508 study, there was no difference between groups in the number of participants who developed pulmonary exacerbations. Combined data from both phase 3 G551D trials demonstrated significant improvements in absolute change from baseline in forced expiratory volume at one second (% predicted) at 24 weeks, mean difference 10.80% (95% CI 8.91 to 12.69) and 48 weeks, mean difference 10.44% (95% CI 8.56 to 12.32); also in weight at 24 weeks, mean difference 2.37 kg (95% CI 1.68 to 3.06) and 48 weeks, mean difference 2.75 kg (95% CI 1.74 to 3.75). No improvements in these outcomes were reported in the ΔF508 participants. Significant reductions in sweat chloride concentration were reported in both G551D and ΔF508 participants: in combined data from both phase 3 G551D trials at 24 weeks, mean difference -48.98 mmol/L (95% CI -52.07 to -45.89) and 48 weeks, mean difference -49.03 mmol/L (95% CI -52.11 to -45.94); and from the ΔF508 trial at 16 weeks, mean difference -2.90 mmol/L (95% CI -5.60 to -0.20).

Authors' conclusions
Both G551D phase 3 trials (n = 219) demonstrated a clinically relevant impact of the potentiator ivacaftor on outcomes at 24 and 48 weeks, providing evidence for the use of this treatment in adults and children (over six years of age) with cystic fibrosis and the G551D mutation (class III). There is no evidence to support the use of ivacaftor in people with the ΔF508 mutation (class II) (n = 140). Trials on ivacaftor in people with different mutations are ongoing.

Plain language summary
Ivacaftor (marketed as Kalydeco®), a new specific therapy for cystic fibrosis

Review Question
What is the effect of ivacaftor on clinical outcomes (survival, quality of life and lung function) in people with cystic fibrosis?

Background
In people with cystic fibrosis, airway surfaces don't have enough water due to the action of an abnormal protein. This makes it difficult to clear thick and sticky mucus and leads to these people developing lung infections. Ivacaftor works on the abnormal protein in people with certain cystic fibrosis mutations (class III and IV) such as the G551D mutation (class III). It aims to help the airways retain more water allowing them to clear mucus more effectively, so these people develop fewer lung infections. The drug may also affect other classes of mutation and there are trials currently being run to look at this.

Ivacaftor was aimed at people with class III and IV mutations, but up to now it has only been studied in those with the G551D (class III) and ΔF508 (class II) mutations.

Trial Characteristics
We included four trials (378 volunteers) comparing ivacaftor to placebo (a dummy treatment with no active medication). Three trials enrolled 238 volunteers between them with at least one copy of the G551D mutation; one trial enrolled 140 volunteers with two copies of the ΔF508 mutation (class II). The trials lasted between 4 and 48 weeks. The evidence is up to date as of 05 March 2015.
None of the trials reported any deaths. Both children and adults with the G551D mutation taking ivacaftor showed improvements in lung function (forced expiratory volume at one second), but only the adults reported higher quality of life scores. Participants with the ΔF508 mutation did not show improvements in either of these outcomes.

Volunteers with the G551D mutation in the placebo groups reported more coughing and experienced more episodes of decreased pulmonary function. More adults taking ivacaftor reported episodes of dizziness. Similar small numbers of volunteers (both mutations) taking ivacaftor and placebo had to delay the course of medication, or withdraw from the trial altogether, due to unfavourable side effects (e.g. psychological issues, liver disease, severe breathing problems, fatigue, arthritis).

More children and adults with the G551D mutation experienced serious pulmonary exacerbations (flare ups of their lung disease) whilst taking placebo. More adults taking placebo developed these lung flare ups than those taking ivacaftor. Adults taking ivacaftor were admitted to hospital less often and had fewer courses of intravenous antibiotics for flare ups. People with the ΔF508 mutation, had a similar number of flare ups whether taking placebo or ivacaftor.

Adults and children with the G551D mutation taking ivacaftor increased their weight; but not those with ΔF508. Evidence suggests that ivacaftor is an effective treatment for people (over six years of age) with cystic fibrosis and the G551D mutation, but not for those with the ΔF508 mutation. Trials of ivacaftor in people with different genetic mutations are underway.

Quality of the evidence
In most of the trials, the volunteers were put into different treatment groups completely at random, so we were satisfied that those taking part had an equal chance of being in either group (placebo or ivacaftor). We are also satisfied that in most trials no one could work out which group the next volunteer would be put into, so that healthier people did not receive the treatment and make the results seem better. We could not be sure whether the people taking part in the trial or the clinicians running the trial knew who was receiving which treatments and what effect this knowledge might have on the results. Unfortunately, none of the trials reported all their results clearly; sometimes they did not report them in a way that we could use in the review and sometimes they did not report the data at all. This affected the certainty with which we judged the overall results.

Trial Funding Sources
All trials were sponsored by Vertex Pharmaceuticals Incorporated. The National Institute of Health (NIH), the Cystic Fibrosis Foundation (CFF) and other non-pharmaceutical funding bodies also supported the trials.”
<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Objectives</th>
<th>Main Results</th>
<th>Author’s Conclusions</th>
<th>CRD Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whiting P et al (2014)¹⁶</td>
<td>Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis.</td>
<td>“To review the clinical effectiveness and cost-effectiveness of ivacaftor for the treatment of CF in patients aged ≥ 6 years who have the G551D mutation.”</td>
<td>“Three studies were included: a randomised controlled trial (RCT) in adults (n = 167) (≥ 12 years), a RCT in children (n = 26) (6-11 years), and an open-label extension study of the two RCTs. Both RCTs reported significantly greater changes from baseline in all measures of lung function in patients receiving ivacaftor than in those receiving placebo. The mean difference in change in percentage predicted FEV1 was 10.5 [95% confidence interval (CI) 8.5 to 12.5] percentage points in the adults’ study and 10.0 (95% CI 4.5 to 15.5) percentage points in the children’s study at 48 weeks. Improvements in lung function were seen across all subgroups investigated (age, sex, study region and lung function). There were significantly greater improvements in the ivacaftor group than in the placebo group for all outcomes assessed (exacerbations, quality of life, sweat chloride and weight) with the exception of quality of life in children. Improvements were maintained in the open-label trial. Adverse events were mainly minor and comparable across treatment groups. Both RCTs reported more withdrawals in the placebo group than in the ivacaftor group.”</td>
<td>“The available evidence suggests that ivacaftor is a clinically effective treatment for patients with CF and the G551D mutation; the high cost of ivacaftor may prove an obstacle in the uptake of this treatment. The main priority for further research is the long-term effectiveness of ivacaftor.”</td>
<td>This systematic review has not been analyzed by CRD. However, it has met the criteria for inclusion on DARE.</td>
</tr>
</tbody>
</table>
Table 4: Select Randomized Controlled Trials (RCTs)

Wainwright CE, Elborn JS, Ramsey BW et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. (2015)\textsuperscript{17}

“Background Cystic fibrosis is a life-limiting disease that is caused by defective or deficient cystic fibrosis transmembrane conductance regulator (CFTR) protein activity. Phe508del is the most common CFTR mutation. Methods We conducted two phase 3, randomized, double-blind, placebo-controlled studies that were designed to assess the effects of lumacaftor (VX-809), a CFTR corrector, in combination with ivacaftor (VX-770), a CFTR potentiator, in patients 12 years of age or older who had cystic fibrosis and were homozygous for the Phe508del CFTR mutation. In both studies, patients were randomly assigned to receive either lumacaftor (600 mg once daily or 400 mg every 12 hours) in combination with ivacaftor (250 mg every 12 hours) or matched placebo for 24 weeks. The primary end point was the absolute change from baseline in the percentage of predicted forced expiratory volume in 1 second (FEV\textsubscript{1}) at week 24. Results A total of 1108 patients underwent randomization and received study drug. The mean baseline FEV\textsubscript{1} was 61% of the predicted value. In both studies, there were significant improvements in the primary end point in both lumacaftor-ivacaftor dose groups; the difference between active treatment and placebo with respect to the mean absolute improvement in the percentage of predicted FEV\textsubscript{1} ranged from 2.6 to 4.0 percentage points (P<0.001), which corresponded to a mean relative treatment difference of 4.3 to 6.7% (P<0.001). Pooled analyses showed that the rate of pulmonary exacerbations was 30 to 39% lower in the lumacaftor-ivacaftor groups than in the placebo group; the rate of events leading to hospitalization or the use of intravenous antibiotics was lower in the lumacaftor-ivacaftor groups as well. The incidence of adverse events was generally similar in the lumacaftor-ivacaftor and placebo groups. The rate of discontinuation due to an adverse event was 4.2% among patients who received lumacaftor-ivacaftor versus 1.6% among those who received placebo. Conclusions These data show that lumacaftor in combination with ivacaftor provided a benefit for patients with cystic fibrosis homozygous for the Phe508del CFTR mutation. (Funded by Vertex Pharmaceuticals and others; TRAFFIC and TRANSPORT ClinicalTrials.gov numbers, NCT01807923 and NCT01807949.)”
## Recommendations

### Major Recommendations

Definitions of recommendation grade (A, B, C, D, or I), estimate of net benefit (Substantial, Moderate, Small, or Zero/Negative), and certainty of net benefit (High, Moderate, or Low) are provided at the end of the "Major Recommendations" field.

### Summary of Recommendations Unchanged From Previous Guidelines

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation</th>
<th>Certainty of Net Benefit</th>
<th>Estimate of Net Benefit</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Inhaled tobramycin—moderate to severe disease*</td>
<td>For individuals with cystic fibrosis (CF), 6 years of age and older, with moderate to severe lung disease and <em>Pseudomonas aeruginosa</em> persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations.</td>
<td>High</td>
<td>Substantial</td>
<td>A</td>
</tr>
<tr>
<td>Inhaled tobramycin—mild disease*</td>
<td>For individuals with CF, 6 years of age and older, with mild lung disease and <em>P. aeruginosa</em> persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations.</td>
<td>Moderate</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Dornase alfa—moderate to severe disease*</td>
<td>For individuals with CF, 6 years of age and older, with moderate to severe lung disease, the CF Foundation strongly recommends the chronic use of dornase alfa to improve lung function, improve the quality of life, and reduce exacerbations.</td>
<td>High</td>
<td>Substantial</td>
<td>A</td>
</tr>
<tr>
<td>Treatment</td>
<td>Recommendation</td>
<td>Certainty of Net Benefit</td>
<td>Estimate of Net Benefit</td>
<td>Recommendation</td>
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<tr>
<td>Dornase alfa—mild disease*</td>
<td>For individuals with CF, 6 years of age and older, with asymptomatic or mild lung disease, the CF Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.</td>
<td>High</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Inhaled hypertonic saline</td>
<td>For individuals with CF, 6 years of age and older, the CF Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and quality of life and reduce exacerbations.</td>
<td>Moderate</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Azithromycin with <em>P. aeruginosa</em></td>
<td>For individuals with CF, 6 years of age and older, with <em>P. aeruginosa</em> persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin to improve lung function and reduce exacerbations.</td>
<td>High</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Oral antistaphylococcal antibiotics, prophylactic use</td>
<td>For individuals with CF, the CF Foundation recommends against the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.</td>
<td>Moderate</td>
<td>Negative</td>
<td>D</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the routine use of inhaled corticosteroids to improve lung function or quality of life and reduce pulmonary exacerbations.</td>
<td>High</td>
<td>Zero</td>
<td>D</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the chronic use of oral corticosteroids to</td>
<td>High</td>
<td>Negative</td>
<td>D</td>
</tr>
<tr>
<td>Treatment</td>
<td>Recommendation</td>
<td>Certainty of Net Benefit</td>
<td>Estimate of Net Benefit</td>
<td>Recommendation</td>
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<tr>
<td>Other inhaled antibiotics</td>
<td>For individuals with CF, 6 years of age and older, with <em>P. aeruginosa</em> persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations.</td>
<td>Low</td>
<td>–</td>
<td>I</td>
</tr>
<tr>
<td>Oral antipseudomonal antibiotics</td>
<td>For individuals with CF, 6 years of age and older, with <em>P. aeruginosa</em> persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life or reduce exacerbations.</td>
<td>Low</td>
<td>–</td>
<td>I</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function and quality of life or reduce exacerbations.</td>
<td>Low</td>
<td>–</td>
<td>I</td>
</tr>
<tr>
<td>Inhaled or oral N-acetylcysteine, or inhaled glutathione</td>
<td>For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function and quality of life or reduce exacerbations.</td>
<td>Low</td>
<td>–</td>
<td>I</td>
</tr>
</tbody>
</table>
Inhaled anticholinergics

For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations.

Certainty of Net Benefit: Low
Estimate of Net Benefit: –
Recommendation: I

*Severity of lung disease is defined by forced expiratory volume in 1 second (FEV₁) % predicted as follows: normal, >90% predicted; mildly impaired, 70%–89% predicted; moderately impaired, 40%–69% predicted; and severely impaired, <40% predicted (Flume et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2007;176:957–969).

New and Modified Recommendations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation</th>
<th>Certainty of Net Benefit</th>
<th>Estimate of Net Benefit</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivacaftor</strong>*</td>
<td>For individuals with CF, 6 years of age and older, with at least one G551D CF transmembrane conductance regulator (CFTR) mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations.</td>
<td>High</td>
<td>Substantial</td>
<td>A</td>
</tr>
<tr>
<td><strong>Inhaled aztreonam—moderate to severe disease†</strong></td>
<td>For individuals with CF, 6 years of age and older, with moderate to severe lung disease and Pseudomonas aeruginosa persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.</td>
<td>High</td>
<td>Substantial</td>
<td>A</td>
</tr>
<tr>
<td><strong>Inhaled aztreonam—mild disease†</strong></td>
<td>For individuals with CF, 6 years of age and older, with mild lung disease and P. aeruginosa persistently present in cultures</td>
<td>Moderate</td>
<td>Moderate</td>
<td>B</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation</th>
<th>Certainty of Net Benefit</th>
<th>Estimate of Net Benefit</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic use of aztreonam</td>
<td>of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chronic use of ibuprofen (age &lt;18 yr)</td>
<td>For individuals with CF, between 6 and 17 years of age, with an FEV1 ≥60% predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 μg/ml, to slow the loss of lung function.</td>
<td>Moderate</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Chronic use of ibuprofen (age ≥18 yr)</td>
<td>For individuals with CF, 18 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations.</td>
<td>Low</td>
<td>–</td>
<td>I</td>
</tr>
<tr>
<td>Azithromycin without <em>P. aeruginosa</em></td>
<td>For individuals with CF, 6 years of age and older, without <em>P. aeruginosa</em> persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations.</td>
<td>Moderate</td>
<td>Small</td>
<td>C</td>
</tr>
<tr>
<td>Chronic inhaled β2-adrenergic receptor agonists</td>
<td>For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against chronic use of inhaled β2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations.</td>
<td>Low</td>
<td>–</td>
<td>I</td>
</tr>
<tr>
<td>Oral antistaphylococcal antibiotics, chronic use</td>
<td>For individuals with CF, 6 years of age and older, with <em>Staphylococcus aureus</em> persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend</td>
<td>Low</td>
<td>–</td>
<td>I</td>
</tr>
</tbody>
</table>
**Recommendation for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.**

*CF Foundation personnel did not participate in any activity related to ivacaftor.

†Severity of lung disease is defined by forced expiratory volume in 1 second (FEV1) % predicted as follows: normal, >90% predicted; mildly impaired, 70%–89% predicted; moderately impaired, 40%–69% predicted; and severely impaired, <40% predicted (Flume et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007;176:957–969).

**Definitions:**

**U.S. Preventive Services Task Force Evidence Grading***

<table>
<thead>
<tr>
<th>Certainty of Net Benefit</th>
<th>Magnitude of Net Benefit</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Substantial</td>
</tr>
<tr>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Low</td>
<td>I (insufficient evidence)</td>
</tr>
</tbody>
</table>

The overall strength of the evidence is based on the certainty of the magnitude of benefit defined as benefit minus harm.

**Quality of the Evidence***

**High.** The available evidence includes consistent results from well designed, well conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

**Moderate.** The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

**Low.** The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: limited number or size of studies; important flaws in study design or methods; inconsistency of findings across
individual studies; gaps in the chain of evidence; findings not generalizable; lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

**Strength of Recommendation***

**A.** The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.

**B.** The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

**C.** The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

**D.** The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this service.

**I.** The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

*Adapted from: U.S. Preventive Services Task Force Grade Definitions.

**Clinical Algorithm(s)**

None provided"
References

7. 2015 ICD-10-CM Diagnosis Code E84.9 Cystic fibrosis, unspecified. [http://www.icd10data.com/ICD10CM/Codes/E00-E89/E70-E88/E84-/-E84.9](http://www.icd10data.com/ICD10CM/Codes/E00-E89/E70-E88/E84-/-E84.9).