Drug Use Research & Management Program
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Abbreviated Class Update: Medications for Cystic Fibrosis (CF)

Month/Year of Review: May 2014 **End date of literature search:** April 2014

Current PDL Class:

- Preferred: SODIUM CHLORIDE FOR INHALATION, TOBRAMYCIN 300MG/5ML (TOBI®), DORNASE ALFA (PULMOZYME)
- Non-Preferred: TOBRAMYCIN CAP (TOBI PODHALER®), TOBRAMYCIN 300MG/4ML (BETHKIS®), AZTREOMAN (CAYSTON®), IVACAFTOR (KALYDECO®)

Current PA Criteria: Appendix 1: PA in place to ensure appropriate drug use and limit to patient populations in which ivacaftor has been shown to be effective and safe.

Research Questions:

- Does any the new information change previous conclusions regarding effectiveness and safety of ivacaftor?
- Are there unique patients or situations where ivacaftor may be more effective or safer than currently available agents?

Previous Recommendations:

- There is moderate level of evidence to suggest that ivacaftor is superior to placebo in patients (≥12 years old) with the G551D mutation, as illustrated by an increase in FEV_1. There is also moderate evidence that ivacaftor is well tolerated with adverse effects resulting in discontinuations rates less than placebo. There are no head-to-head trials comparing ivacaftor to other CF treatments. Changes in FEV_1 with ivacaftor were similar to therapies used in the chronic management of CF. There is insufficient evidence to grade ivacaftor treatment in children under 12. Limited unpublished data suggests similar efficacy and safety as in patients over 12 years of age. Due to the robust nature of the results and benefits that outweigh the risks, use in this population is also recommended
- The efficacy and safety evaluation of ivacaftor is limited by small study populations; study durations of only one year and unpublished data. Ivacaftor has been shown to be effective only in the CF population with the G551D mutation, making ivacaftor a treatment option in only a small percentage of patients with CF. The effects of ivacaftor on long term disease progression are unknown.
- It is recommended to use clinical prior authorization criteria (Appendix) to limit the use of ivacaftor to patients that are six years and older, diagnosed with CF, have the G551D mutation in the CFTR gene, is prescribed by or in consultation with a pulmonologist or a practitioner at

an accredited Cystic Fibrosis Center, and has had an adequate trial of standard medication therapy. Renewal criteria will be implemented to monitor for a clinical response and adherence.

Conclusions:

- There is insufficient to low quality evidence based on one unpublished, phase III trial, that in addition to CF patients with the G551D mutation, ivacaftor is more effective than placebo in improving lung function as measured by FEV_1 in patients with 8 additional mutations. These include: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. Evidence does not support use of the drug in patients with the G970R mutation.
- There is low quality evidence that tobramycin 300mg/4ml is superior to placebo in lung function as measured by FEV_1 and noninferior to tobramycin 300mg/4ml.

Recommendations:

- Update PA criteria (appendix 1) to include additional CFTR mutations ivacaftor recently became approved for.
- Evaluate comparative cost of tobramycin 300mg/4ml (Bethkis®) in executive session.

Reason for Review:

In February, 2014, the FDA approved ivacaftor who have one of eight additional CF mutations. This review will evaluate the new indication and supporting evidence. This update will also evaluate the newer formulation of inhaled tobramycin 300mg/4ml (Bethkis®).

Background:

Cystic Fibrosis (CF) is a genetic disease which can affect multiple organs, in which lung disease is responsible for approximately 85% of the mortality.[1] Most available treatments for CF focus on symptom management, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[2] Many different mutations have been identified in the gene that causes GF. Ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator approved in 2012 for the treatment of CF in patients 6 years and older who have the G551D mutation in the CFTR gene (approximately 4% of CF patients).[3] Ivacaftor is meant to treat the underlying cause of cystic fibrosis, by influencing the basic CF defect.[4] Two additional medications that target the defects in CFTR production are currently being studied.

Ivacaftor has demonstrated superiority to placebo in patients 6 years of age and older with the G551D mutation, as illustrated by an increase in FEV_1.[5–7] There are no head to head trials comparing ivacaftor to other CF treatments and changes in FEV_1 with ivacaftor were similar to therapies used in the chronic management of CF. Another study was done in homozygous patients for the F508del-CFTR mutation which showed no benefit

in lung function or patient-reported outcomes; ivacaftor should not be used in this population.[8] Currently, ongoing studies are evaluating ivacaftor monotherapy in new disease populations, including children less than 6 years of age and additional mutations.

Methods:
A Medline literature search ending April 2014 Week 4 for meta-analyses or randomized active-controlled trials (RCT's) evaluating ivacaftor in patients with CF was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
A systematic review and cost-effectiveness analysis was done by NICE to evaluate ivacaftor for the treatment of patients with CF and the G551D mutation.[1] There were insufficient data to conduct a formal meta-analysis. Three studies were identified: a RCT in adults, a RCT in children, and an open-label extension study of the two RCTs. Both RCTs demonstrated significantly greater changes from baseline in lung function in patients on ivacaftor than placebo (10.5 mean difference, 95% CI 8.5 to 12.5 in adults and 10.0, 95% CI 4.5 to 15.5 in children). The number and severity of pulmonary exacerbations were also significantly reduced in the adult study (RR 0.60; 95% CI 0.41 to 0.85) at 48 weeks. Adverse events were minor and comparable across treatment groups. The most common adverse events were pulmonary exacerbation, cough, headache, upper respiratory tract infection and oropharyngeal pain. In addition, the high cost of ivacaftor may make it difficult for uptake of treatment. Long-term effectiveness research is still needed.

New Guidelines:
The CF Foundation's Pulmonary Clinical Practice Guidelines Committee updated their guideline for Chronic Medications for Maintenance of Lung Health in 2012.[2] However, these were completed before the additional mutations were included in the indication. Overall, the committee rated the certainty of net benefit for ivacaftor in patients with at least one G551D CFTR mutation as high and the net benefit as substantial. At the time of these guidelines, the committee concluded there was insufficient information ot make a recommendation for additional mutations.

New FDA Approved Indications:
In February 2014, the FDA approved ivacaftor for people with CF ages 6 and older who have one of eight additional mutations in the CFTR gene in addition to the previous approved G551D mutation. The additional mutations include G178R, S549N, S549R, G551S, S1251N, S1255P, and G1349D. In the United States, approximately 150 people have one of the additional eight mutations.

The expanded use is based on results of one unpublished two-part phase III clinical trial in people with $FEV_1 > 40\%$ with these mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, or G970R (KONNECTION trial).[3,9] Part 1 was a randomized, double-blind, placebo-

controlled cross-over study (8 weeks), and Part 2 was an open-label period where all patients received ivacaftor. The use of hypertonic saline was not permitted. Data did not support approval of the drug in patients with the G970R mutation. The primary endpoint was improvement in lung function, measured by the change from baseline in percent predicted FEV_1 at 8 weeks of treatment. For the overall population of the 9 mutations, ivacaftor resulted in a significant improvement in percent predicted FEV_1 (10.7;95% CI 7.3 to 14.1 p<0.0001) with a high degree of variability of response between the different mutations, with mean change from baseline ranging from 3 to 20. Efficacy in patients with the G970R mutation could not be established. This study has not been published and therefore cannot be assessed for quality. Results are not available from clinicaltrials.gov.

Randomized Controlled Trials: After exclusion of studies due to study design, only 2 RCTs were identified.

Study	Comparisons	Patient Population	Primary Objective	Results
Davies, et al.[7] RCT, DB, PC	Ivacaftor 150 mg every 12 hours vs. placebo	Patients with CF aged 6-11 years with a G551D CFTR mutation on at least one allele (n=52)	Absolute change from baseline through week 24 in percent predicted FEV_1	Mean change from baseline in FEV_1: Ivacaf: 12.5% Placebo: 0.1% P<0.001
Flume, et al.[8] RCT, DB, PC	Ivacaftor 150 mg every 12 hours vs. placebo	Patients with CF aged 12 or older, homozygous for the F508del-CFTR mutation (n=140)	Absolute change from baseline through week 16 in percent predicted FEV_1	Mean change from baseline in FEV_1 compared to placebo: 1.7% (95% CI -0.6 to 4.1) P=0.15

New Formulations:

Tobramycin inhalation solution has been available in a 300mg/5ml preparation since 1997. In late 2012, a higher concentrated formulation of 300mg/4ml solution of tobramycin (Bethkis®) was approved by the FDA for management of cystic fibrosis patients.[10,11] Approval was based on two RCTs comparing tobramycin to placebo and one open-label comparative trial of tobramycin 300mg/4ml and tobramycin 300mg/4ml (TOBI®).[11] In the two RCTs, tobramycin 300mg/4ml demonstrated superiority over placebo in change from baseline in FEV_1 percent predicted at week 4 (LS mean difference 11%; 954% CI 3 to 19; p=0.003 in study 1 and LS mean difference 6%; 95% CI 3 to 10; p<0.001).

The poor-quality open-label comparative study evaluated the two formulations in patients aged 6 years and older who were chronically colonized with *Pseudomonas aeruginosa*.[12] Results demonstrated that tobramycin 300mg/4ml was noninferior to tobramycin 300mg/5ml in FEV_1 with a difference of -0.5 (95% CI -2.6 to 1.6) and the lower limit for he 95% CI falling well above the predefined non-inferiority margin. However, there was

no justification provided for the non-inferiority margin in the trial. Pulmonary exacerbations were infrequent and similar between groups (3.8% in the 4ml group and 3.0% in the 5 ml group.

References:

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3. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. 2014.

4. Pettit RS. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. *Ann Pharmacother*. 2012;46(7-8):1065-1075. doi:10.1345/aph.1R076.

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9. De Boeck K, Paskavitz J, Chen X, Higgins M. M. Ivacaftor, a CFTR potentiator, in cystic fibrosis patients who have a non-G551D-CFTR gating mutation: Phase 3, Part 1 results. Pediatr. Pulmonol. 2013;48(S36):292. Abstract 241.

10. FDA Center for Drug Evaluation and Research. Bethkis (Tobramycin 300mg/4ml inhalaion solution) Summary Review. Application Number: 201820Orig1s000. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/201820_bethkis_toc.cfm.

11. Cornerstone Therapeutics. Bethkis (tobramycin inhalation solution 300mg/4ml) prescribing information. Available at: http://bethkis.com/wp-content/uploads/2013/11/BETHKIS-Tobramycin-Inalation-Solution-Full-Prescribing-Information-Web.pdf.

12. Mazurek H, Chiron R, Kucerova T, et al. Long-term efficacy and safety of aerosolized tobramycin 300 mg/4 ml in cystic fibrosis. *Pediatr Pulmonol*. 2014. doi:10.1002/ppul.22989.

Appendix 1 – Current PA Criteria:

Ivacaftor (Kalydeco®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which ivacaftor has been shown to be effective and safe.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the client have a diagnosis of cystic fibrosis and is 6 years of age or older?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Does the patient have a documented G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene? • If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a mutation.	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	**Yes:** Go to #5	**No:** Pass to RPH; Deny (medical appropriateness)
5. Is the patient on ALL or has had an adequate trial, if indicated and/or tolerated of the following medications below: - Dornase alfa (Pulmozyme®) AND - Hypertonic saline (Hyper-Sal®) AND - Inhaled or oral antibiotics (if appropriate)	**Yes:** Go to #6	**No:** Pass to RPH; Deny (medical appropriateness)
6. Is the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	**Yes:** Approve for 6 months	**No:** Pass to RPH; Deny (medical appropriateness)

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal?	**Yes:** Go to #2	**No:** Go to #3
2. Does the patient have documented response to therapy? Document response (e.g. improvement in FEV_1, weight gain, reduction in exacerbations or sweat test).	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Has the patient been compliant with therapy, as determined by refill claims history or as reported by requestor?	**Yes:** Go to #4	**No:** Pass to RPH; Deny
4. Is the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	**Yes:** Approve for 6 months	**No:** Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

• Ivacaftor is not effective in patients with Cystic Fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene.
• Ivacaftor has not been studied in other populations of patients with Cystic Fibrosis.

P &T Action: 6/28/12 (KS), 4/26/12 (MH/KS)
Revision(s): 5/29/2014
Initiated: