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### **Abbreviated Class Evaluation: Fat-Soluble Vitamins for the use of Cystic Fibrosis**

**Month/Year of Review:** May 2013

**End date of literature search:** April 2013

#### **Research Questions:**

- Is there evidence to support the use of fat-soluble vitamins for patients with Cystic Fibrosis (CF)?
- Are certain reformulations of fat-soluble vitamins more effective than safer than individual components or other formulations?

#### **Conclusions:**

- There is limited, low quality evidence to demonstrate a benefit or harm with fat-soluble vitamin supplementation in patients with CF.
- Therapy is guided by consensus recommendations and clinical practice guidelines which all recommend routine supplementation with vitamins A, D, E and K in patients who are pancreatic insufficient with CF.

#### **Recommendations:**

- Due to the consensus among CF practitioners of routine supplementation with fat-soluble vitamin preparations in patients with CF, compare and add appropriate formulations (Source CF®, Vitamax® or ADEK®) to the list of supplements that are included in the rebate policy.
- Further evaluate the vitamin and supplement policy for appropriate exclusions to the rebate list.
- Encourage CCO's to evaluate their CF vitamin utilization and adopt similar coverage guidelines.

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### Background:

Cystic fibrosis (CF) is the most common lethal genetic disease in white populations and is caused by a mutation in a gene that encodes cystic fibrosis transmembrane conductance regulator protein (CFTR).<sup>1</sup> Symptoms appear throughout life with variability in timing and severity. Short and long-term complications include failure to thrive, stunting, wasting, vitamin and mineral deficiencies, recurrent pulmonary infections, decreased lung function, and recurrent hospitalizations.<sup>2</sup> About 85-90% of infants with cystic fibrosis develop pancreatic insufficiency and leads to fat-soluble-vitamin deficiency and malnutrition. The use of pancreatic enzyme replacement therapy can help manage malnutrition; however, adequate caloric intake and fat-soluble-vitamin deficiencies are imperative in controlling disease.<sup>1</sup> Patients with CF also have malabsorption of bile acids, which are necessary for absorption of fat-soluble vitamins.<sup>3</sup> Poor absorption of the fat-soluble vitamins (A, D, E, and K) can lead to acrodermatitis, anemia, neuropathy, night blindness, osteoporosis, and bleeding disorders. Although there is limited evidence from randomized controlled trials, standard of care includes supplementation with fat-soluble-vitamins. Many clinical practice guidelines support this. There is a strong correlation between nutritional status and pulmonary function. Water-soluble vitamins are well absorbed and routine supplementation is not necessary.

After diagnosis, the goals of CF are to maintain normal growth and development and to delay onset of pulmonary disease. The goal of nutritional treatment of infants in the newborn period is normal growth.<sup>2</sup> Symptomatic vitamin A and vitamin E deficiency has been reported in patients with CF and many newly diagnosed infants have low levels of one or more fat-soluble vitamins.<sup>2</sup> Some particular groups are at a higher risk of having decreased levels. These include patients who are homozygous for F508del and those with hypoalbuminemia or elevated alkaline phosphatase. These vitamins are available as sole supplements as well as in combination form with other vitamins (either as liquid or a tablet). The availability of different formulations differs in different health services.

Currently, Cystic Fibrosis Medical Therapy is covered under the Oregon Health Plan prioritized list (Line 28) and there are no specific vitamin policies.

### **Methods:**

A Medline literature search ending February 2013 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) comparing fat-soluble vitamins in the use of CF was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

### **Efficacy Summary:**

#### Systematic Reviews:

Recently the Cochrane Collaboration completed systematic reviews for the supplementation of fat-soluble vitamins in the treatment of CF. Evidence was extremely limited for all vitamins and ultimately, authors found insufficient high quality evidence and recommended the guidelines be adhered to until further evidence is available. Guidelines from the Cystic Fibrosis Foundation, European Cystic Fibrosis Society, and the UK Cystic Fibrosis Trust currently exist.

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A recent Cochrane systematic review attempted to determine if vitamin A supplementation in children and adults with CF reduces the frequency of vitamin A deficiency disorders, improves general and respiratory health, or increases the frequency of vitamin A toxicity.<sup>5</sup> However, the authors only identified one study in their literature search. This was ultimately excluded because it was not placebo controlled. There were no randomized controlled trials identified and therefore authors could not draw any conclusions on the benefits or harms of regular administration of vitamin A in people with cystic fibrosis. They further described that until further data is available, country or region specific guidelines on the use and monitoring of vitamin A should be followed.

Another 2012 Cochrane systematic review evaluated vitamin D supplementation in children and adults with CF.<sup>6</sup> Three studies were included in the analysis, although only data from two were available. One study compared 800 IU of vitamin D and placebo for 12 months in pancreatic insufficient adults. The two studies showed no clear benefit or harm identified with short-term vitamin D supplementation compared to placebo (n=41). Only effects on bone mineral density (BMD) were evaluated; there were no data on the effects on growth and nutrition. No conclusions on the longer term effects could be drawn from the short term, limited data. Authors conclude there is insufficient evidence to determine a benefit or harm and adherence to relevant CF guidelines should be considered at this time.

A third systematic review from the Cochrane Collaboration assessed the effects of vitamin K supplementation in CF to determine the optimal dose and route of administration for routine and therapeutic use.<sup>4</sup> Only two trials were included in the review (n=32) and had a moderate risk of bias. Both trials were underpowered and of short duration. Patients were from 8 to 35 years old and all were pancreatic insufficient. Neither trial addressed outcomes of interest including coagulopathy, INR, and bone formation outcome measures. One trial demonstrated that serum vitamin K levels appeared to significantly ( $p < 0.001$ ) with supplementation. There was no statistically significant difference between the 5 mgd/day and 1 mg/day doses (MD -4.46, 95% CI -12.65 to 3.73). Based on these two trials, authors concluded that there is weak and limited evidence to support the use of vitamin K in patients with CF. However, no harm was seen and until further evidence is available, the present guidelines should be adhered to.

### Clinical Guidelines

#### Cystic Fibrosis Foundation:

The Cystic Fibrosis Foundation commissioned an evidence review to develop evidence-based guidelines for management of infants with CF.<sup>2</sup> Recommendations were graded using the United States Preventive Health Services Task Force (USPSTF) grading system and made consensus recommendations for topics not included in evidence reviews or for topics for which there was limited or no evidence for.

The CF Foundation gives the following recommendations:

- All infants with CF should receive standard, age-appropriate non-fat-soluble vitamins and vitamins A, D, E, and K as recommended in the CF Foundation Consensus Report on Nutrition for Pediatric Patients.
- For infants under 2 years of age, the Foundation recommends that multivitamins designed to provide at least the recommended levels of vitamins A,D,E and K for patients should be prescribed, beginning shortly after diagnosis (Low certainty, Moderate benefit, Consensus Recommendation)
- For infants under 2, the CF Foundation recommends that a trial of zinc supplementation (1 mg elemental zinc/kg/day in divided doses for 6 months) may be given to infants who are not adequately growing despite adequate caloric intake and pancreatic enzyme replacement therapy (Low Certainty, Moderate Benefit, Consensus Recommendation).
- There is insufficient evidence to recommend for or against supplementation with linoleic acid (Grade I)

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- There is insufficient evidence to recommend for or against supplementation with docosahexaenoic acid (Grade I)

The CF Foundation updated their Vitamin D guidelines in the treatment of CF due to insufficient prevention of vitamin D insufficiency due to insufficient prevention of vitamin D deficiency.<sup>7</sup> The foundation assembled a multidisciplinary committee with expertise in CF. A systematic review identified 36 articles for inclusion of review. The following recommendations are included:

- All individuals with CF have serum 25-hydroxyvitamin D measured to assess vitamin D status (Consensus Recommendation).
- All individuals with CF should maintain a serum 25-hydroxyvitamin D goal of at least 30 ng/ml.
- All individuals with CF be treated with vitamin D3 (Grade B).
- There was no evidence for the use of calcitriol or other or other analogs of vitamin D in CF patients.
- Although no evidence so support, consensus recommendation that all individuals with CF, from birth to 12 months of age, be treated with an initial dose of 400-500 IU vitamin D3 per day.

#### The European CF Society

The European CF Society Neonatal Screening Working Group also generated guideline statements from a core group of experts and reviewed then through a modified Delphi consensus process.<sup>8</sup> The goal was to produce guidelines on the management during the first year of life of infants with CF. The quality of identified literature was considered poor and were not reliable to provide clear guidance on management. The process resulted in 44 statements to guide management from over 86 CF specialists from 19 different countries. Therefore, general consensus statements were made and include the following:

- Fat-soluble vitamins need to be supplemented routinely in infants with pancreatic insufficiency.
- There is no agreement on the dose and preparation for Vitamin K supplementation. Recommendations for infants range from 0.3 to 1 mg daily dose.
- Suggested daily doses for fat-soluble vitamins in infants less than 1 year are
  - Vitamin A 1500 IU
  - Vitamin E 40-50 IU
  - Vitamin D 400-800 IU

#### The CF Trust

The Cystic Fibrosis Trust in the UK created recommendations for the nutritional management of CF.<sup>9</sup> This group describes what consensus groups consider to be best clinical practices. Recommendations were graded based on methods described by the Scottish Intercollegiate Guidelines Network. A Grade A recommendation is based on at least one RCT as part of overall good quality literature and addressing the specific recommendation. Grade B recommendations require well-conducted clinical studies but no RCTs. Level C recommendations required evidence from expert committee reports, opinions, and/or clinical experience of respected authorities. Recommendations from the trust include the following:

- Vitamin A, D and E supplements should be initiated on diagnosis in pancreatic insufficient patients (Grade B)
- In pancreatic sufficient patients, supplementation should be initiated when low levels are detected (Grade B)
- Vitamin K should be initiated if there is evidence of liver disease or prolonged prothrombin time (Grade B)
- Recommended dose of Vitamin A is:
  - < 1 year: 4,000 IU (1,200 mcg) daily
  - >1 year: 4,000 to 10,000 IU (1,200 to 3,000 mcg) daily
- Vitamin D recommendations:

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- Infants: 400 IU (10 mcg) daily
  - Children: 400 to 800 IU (10 to 20 mcg) daily
  - Adults: 800 to 2,000 IU (20 to 50 mcg) daily
  - Vitamin E recommendations:
    - Birth to 1 year: 10 to 50 mg daily
    - 1 year to 10 years: 50 to 100 mg daily
    - 10 years: 100 to 200 mg daily
  - Recommended dose of Vitamin K has not been established; suggested children and adults receive 10 mg daily (Grade C)

#### Randomized Controlled Trials

There were no RCT's identified from the literature search evaluating therapy. Only one poor quality, open-label, non-randomized study that evaluated the vitamin re-formulation of AquADEKs® softgels over 12 weeks to 14 patients with CF who were all recruited from the CF Center at the University of Denver was identified.<sup>10</sup>

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Appendix 1: Drug Specific Information

**AquADEKs Product Comparisons**

	<b>Amount per 2 Chewable tablets</b>		
Ingredient			
Calories	15		
Total Carbohydrate (g) Sugars (g)	2 2		
Vitamin A (IU)	18167		
Vitamin C (mg)	70		
Vitamin D (as cholecalciferol) (IU)	800		
Vitamin E (as d-alpha-tocopherol) (IU)	100		
Vitamin K1 (as phytonadione)	700		
Thiamin (Vitamin B1)(mg)	1.5		
Riboflavin (Vitamin B2) (mg)	1.7		
Niacin (as niacinamide) (mg)	10		
Vitamin B6 (mg)	1.9		
Folic Acid (mcg)	200		
Vitamin B12 (as cyanocobalamin)	12		
Biotin (mcg)	100		
Pantothenic Acid (mg)	12		
Zinc (mg)	10		
Selenium (mcg)	75		
Vitamin E (mg)	30		
Coenzyme Q10 (mg)	10		

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\*Daily value not established for these nutrients. †Percent Daily Values are based on a 2,000 calorie diet.

**AquADEKs Softgels (as sold in the US, international products may vary)**

Supplement Facts Serving Size: 1 softgel	Servings per container: 60	
	Amount per 1 softgel	%DV≥ 4yrs <sup>†</sup>
Calories	5	
Vitamin A (as 92% beta-carotene) (IU)	18167	363
Vitamin C (as sodium ascorbate) (mg)	75	125
Vitamin D (as cholecalciferol) (IU)	800	200
Vitamin E (as d-alpha-tocopherol) (IU)	150	500
Vitamin K1 (as phytonadione)	700	875
Thiamin (Vitamin B1) (as thiamin mononitrate) (mg)	1.5	100
Riboflavin (Vitamin B2) (mg)	1.7	100
Niacin (as niacinamide) (mg)	10	50
Vitamin B6 (as pyridoxine hydrochloride) (mg)	1.9	95
Folic Acid (mcg)	100	25
Vitamin B12 (as cyanocobalamin)	12	200
Biotin (mcg)	100	33
Pantothenic Acid (as calcium d-pantothenate) (mg)	12	120
Zinc (as zinc sulfate) (mg)	10	67
Selenium (as selenomethionine) (mcg)	75	107
Vitamin E (as other mixed tocopherols) (mg)	80	*
Coenzyme Q10 (mg)	10	*

\*Daily value not established for these nutrients. †Percent Daily Values are based on a 2,000 calorie diet.

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### AquADEKs Pediatric Liquid

Supplement Facts Serving Size: 1ml or 2 ml	Servings per container: 30 or 60			
	Amount per 1 ml	%DV Infants	Amount per 2 ml	%DV Infants
Vitamin A (liquid is 87% beta-carotene & 13% palmitate) (IU)	5751	383	11502	460
Vitamin C (as sodium ascorbate & ascorbic acid) (mg)	45	129	90	225
Vitamin D (as cholecalciferol) (IU)	400	100	800	200
Vitamin E (as d-alpha-tocopherol) (IU)	50	1000	100	1000
Thiamin (Vitamin B1) (as thiamin hydrochloride) (mg)	0.6	120	1.2	171
Riboflavin (Vitamin B2) (mg)	0.6	100	1.2	150
Niacin (as niacinamide) (mg)	6	75	12	133
Vitamin B6 (as pyridoxine hydrochloride) (mg)	0.6	150	1.2	171
Biotin (mcg)	15	30	30	20
Pantothenic Acid (as calcium d-pantothenate) (mg)	3	100	6	120
Zinc (as zinc gluconate) (mg)	5	100	10	125
Selenium (as selenomethionine) (mcg)	10	*	20	*
Vitamin E (as other mixed tocopherols) (mg)	15	*	30	*
Vitamin K1 (as phytonadione) (mcg)	400	*	800	*
Coenzyme Q10 (mg)	2	*	4	*
*Daily value not established for these nutrients.				

