



Supporting the Needs of "New CF"TM

Dietary Supplement

MVW Takes Multivitamins to a **New Level**

CFTR Modulators have been seen to affect fat-soluble vitamins levels in certain individuals on traditional CF-Specific Multivitamins, which can result in elevated serum vitamin A, D and E.

This novel formulation (PCT/US22/37053) combines patient tested and clinically studied absorption technologies, with new and innovative approaches, to better support multivitamin supplementation in individuals prescribed CFTR modulators who have elevated serum levels of A, D, or E.

Lower Preformed Vitamin A To Address The Higher Serum Vitamin A Levels Seen In Some Patients Prescribed Modulators

Preformed vitamin A is **insatiably absorbed**

- Brei et al¹ found that vitamin A exceeded the UL of intake in 69% of studied subjects
- Graham-Maar² found total preformed retinol intake exceeded the DRI tolerable upper intake level in 78% of the subjects

Today, due to the advances in care with modulators, and the potential for elevated serum retinol levels seen in some patients³, **this "New CF Multivitamin"TM provides lower amounts and intakes of preformed vitamin A**

Higher Pro-Vitamin A To Better Support An "Individualized Vitamin A Dosing Strategy"

Vitamin A status regulates beta carotene conversion to an active form (retinol)

- Beta carotene conversion cleavage efficiency and absorption is regulated via a negative feedback loop⁴
 - Following (preformed) vitamin A intake, intracellular concentrations of ATRA increase
 - Beta carotene is taken up by the enterocytes, and converted to retinol only as needed
- There is no set tolerable UL for beta carotene

Higher beta carotene content to better manage the variables affecting individuals' vitamin A serum levels

Higher Pro-Vitamin A To Address Conversion Efficiency Of Beta Carotene Due To Common Genetic Variants

BCMO1 variation has been reported to occur in 27-45%⁵ of the general population

- These individuals are called "poor converters"

Pro-vitamin A conversion, to an active form, is highly affected by variants in the BCMO1 gene⁶

- T allele on both rs12934922 and rs7501331 causes a **69% decreased conversion** of beta carotene to retinol
- Single T in the rs7501331 SNP causes a **decrease of 32%**
- Proteins encoded by the BCMO1 gene, called beta-carotene 15,15'-monooxygenase and beta-carotene 15,15'-dioxygenase, are responsible for converting beta-carotene into the active form of vitamin A

Today, with our knowledge and understanding of genetics, **CF-specific multivitamin supplements may benefit from higher pro-vitamin A (beta carotene) content.**



¹Brei et al, Clinical Nutrition 32 (2013) 805-810.

²Graham-Maar, Am J Clin Nutr 2006; 84: 174-82.

³Data on file: CF Global Services, LLC.

⁴Bohn et al, Proceedings of the Nutrition Society (2019), 78, 68-87.

⁵Leung et al, FASEB. 2009 Apr;23(4):1041-53.

⁶Genetic Lifehacks, February 21, 2020, by Debbie Moon.

Formulated with Lower Vitamin E

Meets CF Foundation recommendations for Vitamin E intake⁸

- Specifically formulated for individuals on modulators where Vitamin E levels are elevated when taking CF-specific multivitamins
- 50% reduction in total daily Vitamin E content to address elevated levels seen in some patients on modulators

A Novel Approach To Support The Absorption of Fat-Soluble Vitamins: A, D, E and K

Bile salt stimulator: Menta Piperata (Peppermint Oil)⁹

- Peppermint oil affects gall bladder physiology¹⁰
- Peppermint oil stimulates bile fluid secretion, potentially by upregulating CYP7A1 and FXR mRNA levels, a mechanism reported to be involved in bile acid synthesis¹¹
- Bile salts are important in solubilizing dietary fats by promoting micelle formation
- In CF, the bile pool is altered
- Peppermint oil is GRAS: FEMA 2848¹²

The addition of a solubilizer¹³: Polyoxymethylene sorbitan monolaurate (Polysorbate 20)

- Emulsifiers enable the suspension of oil in water, they are not water soluble
 - Results in large droplets suspended in an aqueous solution, like fats and fat-soluble vitamins in the small intestine
 - Emulsification is a critical part of digestion, promoting micelle formation in the presence of bile salts
 - Patient proven and clinically studied emulsifier TPGS
- **Solubilizers make otherwise insoluble materials – like fat-soluble vitamins – soluble in water**

Higher vitamin C content

- Vitamin C is a regulator of CFTR-mediated chloride secretion in the epithelia¹⁴
- While most focus has been directed to the airways, **high dose vitamin C may have the potential to induce the openings of CFTR chloride channels, reducing viscosity and stickiness of mucus and enhance absorption in the GI tract**



Softgels

Supplement Facts

Serving Size: 1 Softgel
Servings Per Container: 60

	Amount Per Serving	% Daily Value
Vitamin A (as 96.5% Beta Carotene and 3.5% Retinyl Palmitate)	6,000 mcg RAE	667%
Vitamin C (as Ascorbic Acid)	400 mg	444%
Vitamin D (as Cholecalciferol)	37.5 mcg	188%
Vitamin E (as d-Alpha Tocopheryl Acetate, d-Alpha Tocopheryl Polyethylene Glycol Succinate and Mixed Tocopherols)	80 mg	533%
Vitamin K (as Phytonadione)	800 mcg	667%
Zinc (from Zinc Oxide)	10 mg	90%

x - Percent daily value not established

Other Ingredients: Medium Chain Triglycerides, Gelatin, Glycerin, Polysorbate 20, Caramel (Color), Peppermint Oil, Purified Water.

REIMBURSEMENT CODE: 58204-0004-46

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MVW Modulator Formulation Multivitamin Supplement:

A novel formulation that combines patient tested and clinically studied absorption technologies, with new and innovative approaches, to better support multivitamin supplementation in individuals prescribed CFTR modulators who have elevated serum levels of A, D, or E.



Supporting the Needs of "New CF"TM

Manufactured for:

MVW Nutritionals, Inc., Huntsville, AL 35806

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1-855-236-8584 (CF-MULTI)

MF_DIETSUP_SFT_FL_12.5.22

⁷NH Office of Dietary Supplements noted that there may be an increased risk of lung cancers for smokers when taking 30mg of beta carotene plus 25,000 IU (7,500mcg RAE) retinyl palmitate daily. No other increased risk of cancer was noted. Among non-smokers there does not appear to be an increased risk. The RAE content of current CF-specific multivitamins and MF is less than the amounts and intake studied above.

⁸Borowitz et al, J Pediatr Gastroenterol Nutr, 35: 246-259 September 2002.

⁹Cohen, et al, FEMA GRAS assessment of natural flavor complexes. Food and Chemical Toxicology 135 (2020) 110870.

¹⁰Chumpitazi et al, Aliment Pharmacol Ther. 2018 March; 47(6): 738-752.

¹¹Zong et al, Journal of Digestive Diseases 2011; 12: 295-301.

¹²FEMA Expert Panel affirmation.

¹³Kalivianakis et al, Am J Clin Nutr 1999; 69: 127-34.

¹⁴Fischer et al, Proc Natl Acad Sci U.S.A. 2004 Mar 9; 101 (10): 3691-3696.