EZTREK[™] **Novel DFU Treatment**

- The Problem
- **EZTREK**™ Explained
- How **EZTREK**™ Works

The Problem: DFU Patient Statistics

>1.75 Million patients in US are annually diagnosed with a DFU (6% of all diabetics)^{1,2}

Lifetime: 12% - 25% of diabetics will develop DFU³

25% of DFUs never completely heal^{2,3,4}

40% Recurrence within 1 year after ulcer healing4

50% Recurrence after 3 years⁵

• Closure: 24% at 12 weeks³ / 30% at 20 weeks³

• Unhealed: 70% unhealed after 20 weeks⁶

46% of DFU Patients - Microvascular Complications⁷

65% of DFU Patients - Macrovascular Complications⁷

56% Become Infected8

28% 3-Year mortality9 / 42% 5-year mortality9

10% of Americans have diabetes and the number is increasing¹⁰

- 34 million Americans
- 88 million American adults approximately 1 in 3 have prediabetes

^{1.} Rice, JB, et al., "Burden of diabetic foot ulcers for Medicare and private insurers," Diabetes Care, Vol. 37, 2014, pages 651-658.

^{2.} Margolis D, et al., "Incidence of diabetic foot ulcer and lower extremity amputation among Medicare beneficiaries, 2006 to 2008. Data Points #2," January 2011. AHRQ Publication No. 10(11)-EHC009-1-EF.

^{3.} Game, FL, et al., "A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes," Diabetes/Metabolism Research and Reviews, 2012; 28 (Suppl 1): 119-141.

^{4.} Armstrong D, et al., "Diabetic foot ulcers and their recurrence," New England Journal of Medicine, 376:24, June 15, 2017.

^{5.} www.diabeticfootonline.com posted by David G. Armstrong, M.D., December 19, 2015. Ref.: "Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom," – Walsh – Diabetic Medicine – Wiley Online Library, January 2016.

^{6.} Wu, Stephanie, et al., "Foot ulcers in the diabetic patient, prevention and treatment," Vasc Health Risk Manag, 2007;3(1):65-76.

^{7.} Margolis D, et al., "Incidence of diabetic foot ulcer and lower extremity amputation among Medicare beneficiaries, 2006 to 2008. Data Points #2," January 2011. AHRQ Publication No. 10(11)-EHC009-1-EF.

^{8.} Boulton, Andrew, et al., "The global burden of diabetic foot disease," The Lancet, Vol. 366, No. 9498, p 1719-1724, 2005.

^{9.} Cook, JJ & Simonson, DC, "Epidemiology and health care cost of diabetic foot problems," Veves, (Diabetic series editor), "The Diabetic Foot: Medical and Surgical Management" (3rd edition), Springer, New York, NY, 2012.

^{10. &}quot;National Diabetes Statistics Report, 2020," https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html.

EZTREK™ **Explained**

Expedited DFU Healing — The New Patented Medical Food

It is well documented that diabetic patients have impaired delta-6 desaturase (D6D) metabolic pathways from impaired insulin production. 1,2,3 In particular, this metabolic defect causes a poor anti-inflammatory response in Type I patients. Even with insulin therapy, the pathway is still deficient. Type II patients also have significant impairment of D6D activity. Diabetic foot ulcer (DFU) wound healing is impaired.

This deficiency directly decreases PGE, output. Both a powerful anti-inflammatory and vasodilator, PGE, is critical to expedited DFU healing. Diabetic patients may possess only 42% of PGE,'s binding functionality — a 58% decrease compared with normal, non-diabetic patients. 6 Steroids (glucocorticoids) further impair the Δ -6 desaturase pathway.^{1,7} During hypoglycemic episodes, the hormone glucagon is produced, further impeding the Δ -6 desaturase pathway (by means of cAMP).^{1,8}

Compensating for impaired ∆-6 desaturase deficiency, the new medicament EZTREK™ —uniquely addresses underlying etiology — and simultaneously optimizes multiple metabolic pathways:

- 1. The Δ -6 desaturase metabolic pathway favors the omega-3 series. Alpha-linolenic acid is important for tissue structure and support. However, PGE, is produced exclusively from the omega-6 series. **EZTREK™** solves this issue by specific calibration of both omega-6 / -3 series and with specific modulation of their long-chain metabolites. 1,2,9,10
- 2. EZTREK™ further enhances patients' production of PGE, by calibration of gamma-linolenic acid with docosahexaenoic acid.7,11
- 3. Diabetic patients frequently consume (processed) foods that decrease the most fundamental substrate precursor of PGE₁—functional linoleic acid.^{1,2,12} Furthermore, the important cellular unfolded protein response (UPR) in secretory cells, such as the pancreas, is activated not only by unfolded proteins, but also by aberrant lipid composition (induced by the diet) of the ER membrane referred to as lipid bilayer stress. This response can trigger long-term stress (chronic inflammation) in cells.¹³ EZTREK™ calibrated EFA / eicosanoid modulating ratios are formulated to compensate for this and other obstacles that may impede the Δ -6 desaturase pathway.
- 4. Fibroblasts in the dermis important in allowing skin to regenerate connective tissue to recover from injury and maintain the extracellular matrix — are not maximized with Δ-6 desaturase deficiency.¹⁴

With continued EZTREK™ use, both acute and chronic DFUs heal faster.

Pathophysiology and Roles in Clinical Medicine, Wiley-Liss, NY, 1990, pages 505-511.

^{1.} Brenner, RR, "Hormonal modulation of Δ-6 and Δ-5 desaturases: case of diabetes," Prostaglandins, Leukotrienes, and Essential Fatty Acids, 68 (2003), 151-162.

^{2.} Das, UN, "Essential fatty acids: biochemistry, physiology and pathology," Biotechn., 2006, 1, 420-439.

^{3.} Mikhailidis DP, et al., "The effect of dihomogammalinolenic acid on platelet aggregation and prostaglandin release, erythrocyte membrane fatty acids and serum lipids: Evidence and defects in PGE1 synthesis, and Δ5-desaturase activity in insulin-dependent diabetics," Diabetes Research (1986), 3, 7-12.

^{4.} Brown JE, Lindsay RM, Riemersma RA, "Linoleic acid metabolism in the spontaneously diabetic rat: Δ-6 desaturase activity vs. product/precursor ratios," Lipids. 2000 Dec;35(12):1319-23.

^{5.} Huang M, et al., "FADS Gene Polymorphisms, Fatty Acid Desaturase Activities, and HDL-C in Type 2 Diabetes," Int. J. Environ. Res. Public Health, 2017, 14, 572. 6. Dutta-Roy, Asim, "Effect of Evening Primrose Oil Feeding on Erythrocyte Membrane Properties in Diabetes Mellitus," Omega-6 Essential Fatty Acids:

^{7.} Brenner, RR, "Nutritional and hormonal factors influencing desaturase of essential fatty acids," Prog Lipid Res., 1981;20:41-7.

^{8.} De Gomez Drumm, IT, de Alaniz, MT, Brenner, RR, "Effects of glucagon and dibutyryl adenosine 3'5'-cyclic monophosphate on oxidative desaturase of

fatty acids in the rat," J. Lipids Res., 16 (1975), 264-268.

9. Brenner, RR, "Inhibitory effect of docosa-4,7,10,13,16,19-hexaenoic acid upon the oxidative desaturation of linoleic into gamma-linolenic acid and of alpha-linolenic into octadeca-6,9,12,15-tetraenoic acid," Biochim. Biophys. Acta., 137 (1967), 184-186.

^{10.} Cho, HP, Nakamura, MT, Clarke, SD, "Cloning expression and regulation of human Δ-5 desaturase," J. Biol. Chem, 274 (1999), 37335-37339.

^{11.} Nassar, BA, et al., "The influence of dietary manipulation with n-3 and n-6 fatty acids on liver and plasma phospholipid fatty acids in rats," Lipids, 1986, Oct 21;10:652-

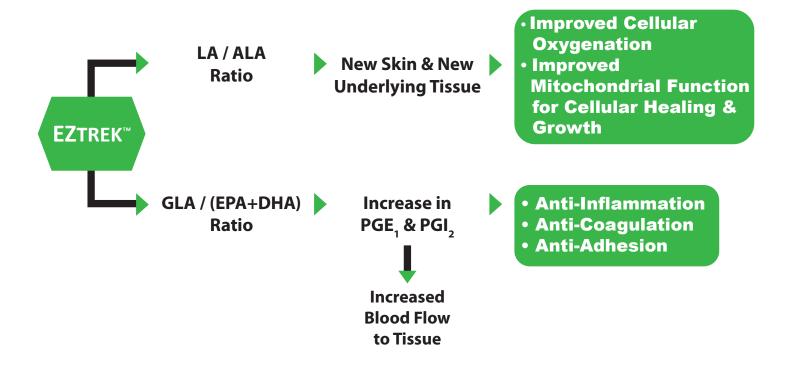
^{656;} Garg, ML, et al., "Δ-6 desaturase activity in liver microsomes of rats fed enriched with cholesterol and / or ω3 fatty acids," Biochem. J. (1988); 249:351–356.

12. Anton, SD, et al., "Differential effects of adulterated versus unadulterated forms of linoleic acid on cardiovascular health," J Integr Med, 2013; 11(1):2–10.

^{13.} Kristina Halbleib, et al., "Activation of the Unfolded Protein Response by Lipid Bilayer Stress," Molecular Cell (2017); "Molecularbiologists discover an active role of membrane lipids in health and disease," August 4, 2017 https://phys.org/news/2017-08-molecular-biologists-role-membrane-lipids.html 14. Willard, DE, et al., "Identification of a fatty acid Δ-6 desaturase deficiency in human skin fibroblasts," J. Lipids Res., 42, 2001, pages 501-508.

How EZTREK™ Works Uniquely Treating DFU

Utilizing Novel Mechanisms of Action



Lipids are the #1 (Modifiable) Variable in Tissue Composition with Potential to Impact Healing. 1,2

^{1.} E. Wainwright, Y. S. Huang, et al., "The effects of dietary n-3/n-6 ratio on brain development in the mouse: a dose response study with long- chain n-3 fatty acids," Lipids, vol. 27, no. 2, pp. 98–103, 1992; W. E. M. Lands, et al., "Quantitative effects of dietary polyunsaturated fats on the composition of fatty acids in rat tissues," Lipids, vol. 25, no. 9, pp. 505–516, 1990.

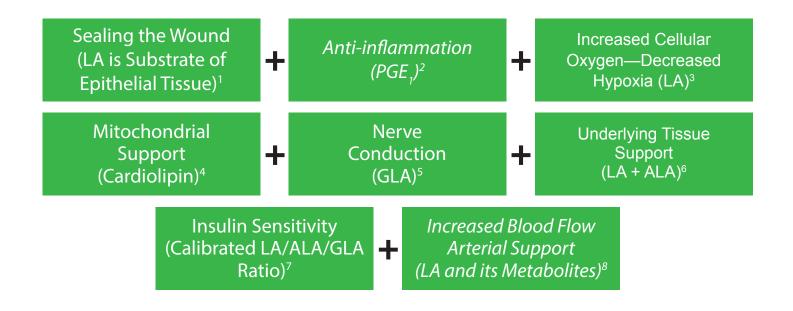
^{2.} C.V. Felton, et al., "Relation of Plaque Lipid Composition and Morphology to the Stability of Human Aortic Plaques," Arteriosclerosis, Thrombosis, and Vascular Biology," Vol. 17, No. 7, 1997, pp. 1337-1345.

Eicosanoid Optimization pg = prostaglandin tx = thromboxaneOmega-3 family It = leukotriene **Omega-6 family** linoleic acid α-linolenic acid 18:3 ω -3 $18:2 \omega - 6$ ∆6 desaturase Competition stearidonic acid γ-linolenic acid GLA 18:3 ω-6 18:4 ω-3 elongase **PGE** dihomo γ-linolenic acid eicosatetraenoic acid **Increases** DGLA 20:3 ω-6 $20:4 \omega - 3$ TXA. ∆5 desaturase PGI. Increases arachidonic acid eicosapentaenoic acid TXA, ΑΑ 20:4 ω-6 **Decreases** EPA 20:5 ω-3 LTB elongase Sprecher's Shunt docosapentaenoic acid docosatetraenoic acid DPA 22:5 ω-3 22:4 ω-6 Δ4 desaturase docosahexaenoic acid docosapentaenoic acid DHA 22:6 ω-3 $22:5 \omega - 6$

EZTREKTM, the new patented Medical Food — specifically and uniquely formulated for the DFU population. Positively impacts multiple metabolic pathways simultaneously. EZTREKTM distinctively compensates for impaired Δ -6 desaturase functionality — increasing PGE₁ output to expedite DFU wound healing.

With continued use, faster healing of both acute and chronic DFUs will occur.

Metabolic Pathways Required For Optimal Wound Healing



^{1.} Willard, DE, et al., "Identification of a fatty acid Δ -6 desaturase deficiency in human skin fibroblasts," The Journal of Lipid Research, 42, 2001, pages 501-508; Chapkin RS, Ziboh VA, Marcelo CL, Voorhees JJ. "Metabolism of essential fatty acids by human epidermal enzyme preparations: evidence of chain elongation." J Lipid Res 1986; 27:945-954; Anderson A, Sjödin A, Hedman A, Olsson R, Vessby B. "Fatty acid profile of skeletal muscle phospholipids in trained and untrained young men." Am J Physiol Endocrinol Metab 2000;279:E744-E751; Albina E et al, "Detrimental effect of an ω -3 fatty—acid enriched diet on wound healing." J Parenter Enteral Nutr. 1993;17(6):519—521: "Current results show that substituting ω -3 fatty acid [fish oil] for w-6 fatty acids in the diet is deleterious to the mechanical properties of wounds at 30 days."

^{2.} Libby P. "Inflammation in atherosclerosis." Nature. 2002 Dec 19–26;420(6917):868–874.

^{3.} Guo S, DiPietro LA. "Factors affecting wound healing." J Dent Res. 2010;89(3):219–229.

^{4.} Peskin BS. "Cancer and mitochondrial defects: New 21st century research," Townsend Letter, August/September 2009:87–90; Murray RK et al. Harper's Illustrated Biochemistry. 26th ed. New York: McGraw-Hill; 2003:97; Guyton AC, Hall JE. Textbook of Medical Physiology. 9th ed. W.B. Saunders Co.; 1996:16,861–862; Krebs, JJ, Hauser H, Carafoli E, "Asymmetric distribution of phospholipids in the inner membrane of beef heart mitochondria." J Biol Chem. 1979;254:5308–5316; Zhang M et al. "Gluing the respiratory chain together: cardiolipin is required for supercomplex formation in the inner mitochondrial membrane." J Biol Chem. 2002;277:43553–43556.
5. Dines KC, et al., "Effectiveness of natural oils as sources of gamma-linolenic acid to correct peripheral nerve conduction velocity abnormalities in diabetic rats: modulation by thromboxane A2 inhibition." Prostaglandins Leukot Essent Fatty Acids. 1996 Sep;55(3):159-65.
6. Alberts B et al. Molecular Biology of the Cell. 3rd ed. Garland Science; 1994:428.

^{7.} Asp ML et al. "Time-dependent effects of safflower oil [LA] to improve glycemia, inflammation and blood lipids in obese, post-menopausal women with type 2 diabetes: A randomized, double-masked, crossover study." Clin Nutr. 2011 Aug;30(4):443–449.; Kahleova H et al. "Vegetarian diet-induced increase in linoleic acid [LA] in serum phospholipids is associated with improved insulin sensitivity in subjects with type 2 diabetes." Nutr Diabetes 2013;3(6)e 75; Dutta-Roy A. "Effect of evening primrose oil feeding on erythrocyte membrane properties in d iabetes mellitus." In: Horrobin D, ed. Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine. New York: Wiley-Liss; 1990:505–511; Ray TK, Dutta-Roy AK, Sinha AK, "Regulation of insulin receptor activity of human erythrocyte membrane by prostaglandin E1," Biochim Biophys Acta. 1986; 856(3):421-427.

8. Das UN. "A defect in the activity of Δ-6 and D5 desaturases may be a factor in the initiation and progression of atherosclerosis."

Prostaglandins Leukot Essent Fatty Acids. 2007;76(5):251–268; "[O]mega-6 PUFAs also have powerful anti-inflammatory properties that counteract any proinflammatory activity,' say the advisory authors. 'It's incorrect to view the omega-6 fatty acids as "proinflammatory."' Ref.: Farvid MS et al. "Dietary linoleic acid [LA/ parent omega-6] and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies." Circulation. 2014;130:1568–1578; Terano T et al. "Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects." Atherosclerosis. 1983;46:321–331: Weiss, C., et al., "Hemostasis and fibrinolysis in patients with intermittent claudication: effects of prostaglandin E1, Prostaglandins, Leukotrienes and Essential Fatty Acids, Nov. 2000; 63(5):271–277; Lazaro, I, et al., "Linoleic Acid Status in Cell Membranes Inversely Relates to the Prevalence of Symptomatic Carotid Artery Disease," Stroke. 2021;52:703–706.

6-Week Progression of EZTREK™ in Chronic DFU Patient

Initial









Healing at 6-weeks of **EZTREK**™