### SUMMARY OF CLINICAL STUDIES

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**Label**

Statements in this document have not been evaluated by the FDA.
This product is not intended to diagnose, treat, cure, or prevent any disease.
French Maritime Pine Supplementation to Support Healthy Circulation

Supplementation of French Maritime Pine Bark Extract (dosage at 100 to 300 mg Pycnogenol daily, divisible into multiple 50 mg doses) may support healthy circulation according to these clinical studies on humans:

- **Normalization of cardiovascular risk factors in peri-menopausal women with Pycnogenol®.** In 2017, this study found that French Maritime Pine supplementation “improved the quality of life of perimenopausal women and normalized a series of cardiovascular risk factors, especially factors connected to cardiovascular events”. Participants used 100 mg Pycnogenol daily for 8 weeks.

- **Management of Varicose Veins and Chronic Venous Insufficiency in a Comparative Registry with Nine Venoactive Products in Comparison with Stockings.** In 2017, this study compared French Maritime Pine supplementation with other interventions to support healthy circulation and found that “the best performers were [French Maritime Pine]” alone and in combination. Participants used 150 mg Pycnogenol daily for 12 months.

- **Preservation of muscular mass and strength in aged subjects with Pycnogenol® supplementation.** In 2016, this study found that “left ventricular ejection fraction (ultrasound) also had a significant improvement” with French Maritime Pine supplementation. Participants used 150 mg Pycnogenol daily for 2 months.

- **Effects of Pycnogenol® on endothelial dysfunction in borderline hypertensive, hyperlipidemic, and hyperglycemic individuals: the borderline study.** In 2015, this study found that French Maritime Pine supplementation “improves [endothelial function] in preclinical, borderline subjects”. Participants used 150 mg Pycnogenol daily for 12 weeks.
- **A Clinical Comparison of Pycnogenol, Antistax, and Stocking in Chronic Venous Insufficiency.** In 2015, this study compared French Maritime Pine supplementation with other interventions to support healthy circulation and found that “changes were more important with [French Maritime Pine]”. Participants used 100 mg Pycnogenol daily for 8 weeks.

- **Improvement in symptoms and cochlear flow with pycnogenol in patients with Meniere’s disease and tinnitus.** In 2014, this study found that blood “flow at cochlear level and tinnitus improved” with French Maritime Pine supplementation. Participants used 150 mg Pycnogenol daily for 6 months.

- **Postpartum Varicose Veins: Supplementation with Pycnogenol or Elastic Compression - A 12-Month Follow-Up.** In 2014, this study found that French Maritime Pine supplementation “improves signs/symptoms of postpartum [varicose veins], and venous function and shape seem to return faster to prepurtum, physiological pattern with its use”. Participants used 100 mg Pycnogenol daily for 6 months.

- **Improvements of venous tone with pycnogenol in chronic venous insufficiency: an ex vivo study on venous segments.** In 2014, this study found that French Maritime Pine supplementation “seems to decrease passive dilatation and stretching and gives vein walls a greater tonic recovery and elasticity that allows the vein to recover its original shape after dynamic stresses”. Participants used 150 mg Pycnogenol daily for 3 months.

- **Pycnogenol® in postpartum symptomatic hemorrhoids.** In 2014, this study found that French Maritime Pine supplementation “appears to positively affect hemorrhoid signs and symptoms”. Participants used 150 mg Pycnogenol daily for 6 months.

- **Pycnogenol® supplementation improves health risk factors in subjects with metabolic syndrome.** In 2013, this study found that French Maritime Pine supplementation “decreased waist circumference, [triglyceride] levels, blood pressure and increased the HDL cholesterol levels”. Participants used 150 mg Pycnogenol daily for 6 months.

- **Effects of Pycnogenol on endothelial function in patients with stable coronary artery disease: a double-blind, randomized, placebo-controlled, cross-over study.** In 2012, this study found that French Maritime Pine supplementation “was
associated with an improvement of [flow-mediated dilation]”. Participants used 200 mg Pycnogenol daily for 8 weeks.

- **Prevention of post thrombotic syndrome with Pycnogenol® in a twelve month study.** In 2011, this study found that French Maritime Pine supplementation “may have significant long-term protective efficacy for individuals following a thrombotic event”. Participants used Pycnogenol daily for 12 months.

- **Improvement in cochlear flow with Pycnogenol® in patients with tinnitus: a pilot evaluation.** In 2010, this study found that French Maritime Pine supplementation “is effective in a short period of time in relieving tinnitus symptoms by improving cochlear blood flow”. Participants used 100 mg or 150 mg Pycnogenol daily for 1 month.

- **Kidney function in metabolic syndrome may be improved with Pycnogenol®.** In 2010, this study found that French Maritime Pine supplementation “was more effective, improving cortical [blood] flow”. Participants used 150 mg Pycnogenol daily for 6 months.

- **Kidney flow and function in hypertension: protective effects of pycnogenol in hypertensive participants--a controlled study.** In 2010, this study found that French Maritime Pine supplementation “statistically significantly further enhanced kidney cortical flow velocities”. Participants used 150 mg Pycnogenol daily for 6 months.

- **Improvement of signs and symptoms of chronic venous insufficiency and microangiopathy with Pycnogenol: a prospective, controlled study.** In 2010, this study found “a significant clinical role for [French Maritime Pine] in the management, treatment and control of [venous insufficiency]”. Participants used 150 mg Pycnogenol daily for 8 weeks.

- **Pycnogenol treatment of acute hemorrhoidal episodes.** In 2010, this study found that French Maritime Pine supplementation “eases the management of acute hemorrhoidal attacks and help[s] avoid bleedings”. Participants used Pycnogenol daily for 7 days.

- **Reduction of cardiovascular risk factors in subjects with type 2 diabetes by Pycnogenol supplementation.** In 2008, this study found that French Maritime Pine supplementation “lowered [cardiovascular] risk factors, and reduced
antihypertensive medicine use”. Participants used 125 mg Pycnogenol daily for 12 weeks.

- **Pycnogenol, French maritime pine bark extract, augments endothelium-dependent vasodilation in humans.** In 2007, this study found that French Maritime Pine supplementation “augments endothelium-dependent vasodilation”. Participants used 180 mg Pycnogenol daily for 2 weeks.

- **Comparison of Pycnogenol and Daflon in treating chronic venous insufficiency: a prospective, controlled study.** In 2006, this study found “fast clinical efficacy of [French Maritime Pine] in patients with chronic venous insufficiency and venous microangiopathy”. Participants used 150 mg or 300 mg Pycnogenol daily for 8 weeks.

- **Rapid relief of signs/symptoms in chronic venous microangiopathy with pycnogenol: a prospective, controlled study.** In 2006, this study found “fast clinical efficacy of [French Maritime Pine] in patients with chronic venous insufficiency and venous microangiopathy”. Participants used 150 mg Pycnogenol daily for 8 weeks.

- **Diabetic ulcers: microcirculatory improvement and faster healing with pycnogenol.** In 2006, this study found that French Maritime Pine supplementation resulted in “better microcirculation”. Participants used 150 mg Pycnogenol daily for 6 weeks.

- **Pycnogenol, French maritime pine bark extract, improves endothelial function of hypertensive patients.** In 2004, this study found that “results support a supplementation with [French Maritime Pine] for mildly hypertensive patients”. Participants used 100 mg Pycnogenol daily for 12 weeks.

This clinical study reports divergent results:

- **No beneficial effects of pine bark extract on cardiovascular disease risk factors.** In 2010, this study (Drieling) found that French Maritime Pine supplementation “was not associated with improvement in cardiovascular disease risk factors” … “variations among participants, dosages, and chemical preparations could contribute to different findings compared with past studies”. Participants used 200 mg Flavangenol daily for 12 weeks.
This clinical study review challenges the study that reported divergent results, and confirms that supplementation of French Maritime Pine Bark Extract may support healthy circulation:

- **Effect of Pycnogenol Supplementation on Blood Pressure: A Systematic Review and Meta-analysis.** In 2018, this meta-analysis of 9 studies “demonstrated the favorable effects of [French Maritime Pine] supplementation on [blood pressure] reductions”. Regarding the Drieling study, it observed that “genetic background or a gene-diet interaction could be the sources of heterogeneity across studies. … Inclusion of various races in Drieling’s trial … possibly resulted in failure to observe the effect of the supplementation”.

**Garlic Supplementation to Support Healthy Cholesterol and Heart Function**

Supplementation of Garlic Bulb Extract (dosage standardized between 3 and 8 mg allicin daily) may support healthy cholesterol and heart function according to these clinical studies on humans:

- **Does Garlic Supplementation Control Blood Pressure in Patients with Severe Coronary Artery Disease? A Clinical Trial Study.** In 2016, this study found that “treatment with garlic-based drugs can be an effective treatment for controlling [blood pressure]”.

- **The effect of aged garlic extract on blood pressure and other cardiovascular risk factors in uncontrolled hypertensives: the AGE at Heart trial.** In 2016, this study found that Garlic supplementation “is effective in reducing peripheral and central blood pressure … and has the potential to improve arterial stiffness, inflammation, and other cardiovascular markers in patients with elevated levels”.

- **Aged garlic extract reduces blood pressure in hypertensives: a dose-response trial.** In 2013, this study found Garlic supplementation “to be an effective and tolerable treatment in uncontrolled hypertension, and may be considered as a safe adjunct treatment to conventional antihypertensive therapy”.

- **Aged garlic extract improves adiponectin levels in subjects with metabolic syndrome: a double-blind, placebo-controlled, randomized, crossover study.** In 2013, this study found that Garlic supplementation “might be a useful, novel, nonpharmacological therapeutic intervention to … prevent cardiovascular
complications”.

- **Effects of Allium sativum (garlic) on systolic and diastolic blood pressure in patients with essential hypertension.** In 2013, this study found that Garlic supplementation resulted in “significant decrease in both Systolic and Diastolic blood pressure”.

- **Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial.** In 2010, this study found that Garlic supplementation “is superior to placebo in lowering systolic blood pressure”.

- **The effects of time-released garlic powder tablets on multifunctional cardiovascular risk in patients with coronary artery disease.** In 2010, this study found that Garlic supplementation “results in the significant decrease of cardiovascular risk”.

- **Effects of garlic consumption on plasma and erythrocyte antioxidant parameters in elderly subjects.** In 2008, this study found that “LDL cholesterol was found to be significantly lower” with Garlic supplementation.

- **Lipid-lowering effects of time-released garlic powder tablets in double-blinded placebo-controlled randomized study.** In 2008, this study found “cardioprotective action of garlic preparations”.

- **Effects of anethum graveolens and garlic on lipid profile in hyperlipidemic patients.** In 2007, this study found that Garlic supplementation “has significant favorable effect on cholesterol, LDL-cholesterol, and HDL-cholesterol”.

- **Effect of garlic (Allium sativum) oil on exercise tolerance in patients with coronary artery disease.** In 2005, this study found that Garlic supplementation “reduced heart rate at peak exercise and also significantly reduced the work load upon the heart resulting in better exercise tolerance”.

- **Garlic supplementation prevents oxidative DNA damage in essential hypertension.** In 2005, this study found that Garlic supplementation resulted in “reducing blood pressure and counteracting oxidative stress, and thereby, offering cardioprotection”.

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Inhibiting progression of coronary calcification using Aged Garlic Extract in patients receiving statin therapy: a preliminary study. In 2004, this study found that Garlic supplementation may “inhibit the rate of progression of coronary calcification”.

These clinical study reviews confirm that supplementation of Garlic Bulb Extract may support healthy cholesterol and heart function:

- **Effect of garlic supplement in the management of type 2 diabetes mellitus (T2DM): a meta-analysis of randomized controlled trials.** In 2017, this meta-analysis of 9 studies observed that “garlic supplement plays positive and sustained roles in blood glucose, total cholesterol, and high/low density lipoprotein regulation”.

- **An umbrella review of garlic intake and risk of cardiovascular disease.** In 2016, this review of 9 meta-analyses observed that “garlic preparations as well as garlic exerted some positive effects on indicators and biomarkers of cardiovascular disease”.

- **Garlic Lowers Blood Pressure in Hypertensive Individuals, Regulates Serum Cholesterol, and Stimulates Immunity: An Updated Meta-analysis and Review.** In 2016, this meta-analysis of 20 studies observed that “garlic supplements have the potential to lower blood pressure in hypertensive individuals [and] to regulate slightly elevated cholesterol concentrations”.

- **A systematic review and metaanalysis on the effects of garlic preparations on blood pressure in individuals with hypertension.** In 2015, this meta-analysis of 9 studies observed that “garlic preparations may lower [blood pressure] in hypertensive individuals”.

- **Garlic powder intake and cardiovascular risk factors: a meta-analysis of randomized controlled clinical trials.** In 2014, this meta-analysis of 22 studies observed that “garlic powder intake reduces the [cardiovascular] risk factors of [total cholesterol], LDL-[cholesterol], [fasting blood glucose] and [blood pressure]”.

- **Effect of garlic on serum lipids: an updated meta-analysis.** In 2013, this meta-analysis of 38 studies observed that Garlic supplementation may be “effective in reducing total serum cholesterol … and low-density lipoprotein”.
cholesterol”.

This clinical study identifies allicin as the principal bioactive component in Garlic:

- **Allicin and allicin-derived garlic compounds increase breath acetone through allyl methyl sulfide: use in measuring allicin bioavailability.** In 2005, this study found that “allyl thiosulfimates (mainly allicin) are solely responsible for breath [allyl methyl sulfide] … a compound which stimulates the production of acetone and which can be used to measure the bioavailability of allicin and, hence, the ability of garlic supplements to represent fresh garlic”.

This clinical study confirms that the bioavailability of allicin in Garlic supplements may be as high as or higher than that of allicin from food sources. It also identifies standardization at 3 to 8 mg allicin daily as the dosage used in most studies, and recommends standardization at 7 to 16 mg allicin daily:

- **Allicin Bioavailability and Bioequivalence from Garlic Supplements and Garlic Foods.** In 2018, this study found that “bioavailability of allicin from garlic powder supplements containing alliin and active alliinase can be as high as that from an equivalent amount of crushed raw garlic”. It also observed that “almost all clinical trials with garlic powder supplements have used a daily dose standardized at 3.6–7.8 mg allicin potential” and proposed that “the minimum daily dose of a garlic powder supplement for possible health benefits should have high allicin bioavailability … by having an allicin potential of about 7-8 mg … and that the preferred dose for clinical trials should be two times this amount”.

**Omega 3 Supplementation to Support Healthy Triglycerides**

Supplementation of Omega 3 Docosahexaenoic Acid and Eicosapentaenoic Acid (dosage between 300 and 4200 mg, standardized at between 180 and 4050 mg EPA and between 120 and 2900 mg DHA, daily) may support healthy triglycerides according to these clinical studies on humans:

- **Fish oil supplementation alters circulating eicosanoid concentrations in young healthy men.** In 2013, this study found that Omega 3 supplementation “improved circulating triglyceride levels”. Participants used 3000 mg (2000 mg EPA and 1000 mg DHA) daily for 3 months.
- **Effect of fish oil supplementation on serum triglycerides, LDL cholesterol and LDL subfractions in hypertriglyceridemic adults.** In 2013, this study found “significant [triglyceride] lowering” with Omega 3 supplementation. Participants used 4000 mg daily for 12 weeks.

- **Effects of omega-3 fatty acids on postprandial triglycerides and monocyte activation.** In 2012, this study found that Omega 3 supplementation may “reduce fasting [triglycerides]”. Participants used 4000 mg daily for 3 weeks.

- **Docosahexaenoic acid supplementation decreases liver fat content in children with non-alcoholic fatty liver disease: double-blind randomised controlled clinical trial.** In 2011, this study found that “triglycerides decreased” with Omega 3 supplementation. Participants used 250 to 500 mg DHA daily for 6 months.

- **Moderate doses of EPA and DHA from re-esterified triacylglycerols but not from ethyl-esters lower fasting serum triacylglycerols in statin-treated dyslipidemic subjects: Results from a six month randomized controlled trial.** In 2011, this study found that “serum [triglyceride] levels were significantly lowered” with Omega 3 supplementation. Participants used 1680 mg (1010 mg EPA and 670 mg DHA) daily for 6 months.

- **Metabolic and endocrine effects of long-chain versus essential omega-3 polyunsaturated fatty acids in polycystic ovary syndrome.** In 2011, this study found that Omega 3 supplementation “lowered serum triglyceride”. Participants used 3600 mg (2148 mg EPA and 1452 mg DHA) daily for 6 weeks.

- **Dose-response effects of omega-3 fatty acids on triglycerides, inflammation, and endothelial function in healthy persons with moderate hypertriglyceridemia.** In 2011, this study found that Omega 3 supplementation “significantly lowered triglycerides”. Participants used 4000 mg (including 1944 mg EPA and 1686 mg DHA) daily for 8 weeks.

- **Treatment of rheumatoid arthritis with marine and botanical oils: influence on serum lipids.** In 2011, this study found that Omega 3 supplementation “significantly reduced ... triglycerides”. Participants used 3500 mg (2100 mg EPA and 1400 mg DHA) daily for 18 months.

- **Effects of prescription omega-3-acid ethyl esters on fasting lipid profile in subjects with primary hypercholesterolemia.** In 2011, this study found that, with
Omega 3 supplementation, “significant changes … were observed for … triglycerides”. Participants used 4000 mg daily for 6 weeks.

- **Prescription omega-3-acid ethyl esters reduce fasting and postprandial triglycerides and modestly reduce pancreatic β-cell response in subjects with primary hypertriglyceridemia.** In 2011, this study found that Omega 3 supplementation “resulted in significant lower mean fasting and postprandial [triglycerides]”. Participants used 1500 to 3000 mg (1100 to 2200 mg EPA and 400 to 800 mg DHA) daily for 6 weeks.

- **n-3 LC-PUFA-enriched dairy products are able to reduce cardiovascular risk factors: a double-blind, cross-over study.** In 2010, this study found that Omega 3 supplementation “resulted in a significant improvement of [triglycerides]”. Participants used 3000 mg daily for 15 weeks.

- **Effect of 6 Weeks of n-3 fatty-acid supplementation on oxidative stress in Judo athletes.** In 2010, this study found “significant interaction effect between supplementation and time on triglycerides … with values significantly lower” after Omega 3 supplementation. Participants used 1000 mg (600 mg EPA and 400 mg DHA) daily for 6 weeks.

- **The effects of low dose n-3 fatty acids on serum lipid profiles and insulin resistance of the elderly: a randomized controlled clinical trial.** In 2010, this study found that Omega 3 supplementation “could significantly protect … from a rise in serum triglycerides”. Participants used 300 mg (180 mg EPA and 120 mg DHA) daily for 6 months.

- **Fish oil supplementation improves endothelial function in normoglycemic offspring of patients with type 2 diabetes.** In 2009, this study found that Omega 3 supplementation “decreased plasma triglycerides”. Participants used 2000 mg (including approximately 950 mg EPA and 750 mg DHA) daily for 12 weeks.

- **Effect of fish oil (n-3 polyunsaturated fatty acids) on plasma lipids, lipoproteins and inflammatory markers in HIV-infected patients treated with antiretroviral therapy: a randomized, double-blind, placebo-controlled study.** In 2009, this study found that Omega 3 supplementation “slightly decreased plasma triglycerides”. Participants used 1800 mg (including 930 mg EPA and 750 mg DHA) daily for 12 weeks.
- **Effects of adding prescription omega-3 acid ethyl esters to simvastatin (20 mg/day) on lipids and lipoprotein particles in men and women with mixed dyslipidemia.** In 2008, this study found that, with Omega 3 supplementation, “favorable changes … were also observed for … triglyceride”. Participants used 4000 mg daily for 6 weeks.

- **Effects of omega-3 fatty acid supplements on serum lipids, apolipoproteins and malondialdehyde in type 2 diabetes patients.** In 2008, this study found that “fasting triglycerides decreased significantly” with Omega 3 supplementation. Participants used 2000 mg daily for 10 weeks.

- **Age- and dose-dependent effects of an eicosapentaenoic acid-rich oil on cardiovascular risk factors in healthy male subjects.** In 2007, this study found that Omega 3 supplementation “lowered plasma triacylglycerols”. Participants used 1350 to 4050 mg EPA daily for 12 weeks.

- **Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study.** In 2007, this study found that Omega 3 supplementation “improved … lipid and lipoprotein parameters”. Participants used 4000 mg daily for 8 weeks.

- **Additive benefits of long-chain n-3 polyunsaturated fatty acids and weight-loss in the management of cardiovascular disease risk in overweight hyperinsulinaemic women.** In 2006, this study found “some additional benefits of [Omega 3] on triglycerides”. Participants used 4200 mg (1300 mg EPA and 2900 mg DHA) daily for 24 weeks.

- **Microalgal docosahexaenoic acid decreases plasma triacylglycerol in normolipidaemic vegetarians: a randomised trial.** In 2006, this study found that Omega 3 “supplementation decreased plasma [triglycerides]”. Participants used 940 mg DHA daily for 8 weeks.

These studies report divergent results:

- **Omega-3 fatty acid supplementation improves vascular function and reduces inflammation in obese adolescents.** In 2010, this study found “no difference [in] triacylglycerol” but that Omega 3 supplementation “improves vascular function”. Participants used 1200 mg daily for 3 months.
• **Acute fish oil and soy isoflavone supplementation increase postprandial serum (n-3) polyunsaturated fatty acids and isoflavones but do not affect triacylglycerols or biomarkers of oxidative stress in overweight and obese hypertriglyceridemic men.** In 2009, this study found that “serum [triglycerides] ... did not differ” with Omega 3 supplementation. Participants used 4200 mg (2800 mg EPA and 1400 mg DHA) once.

• **Effects of moderate-dose omega-3 fish oil on cardiovascular risk factors and mood after ischemic stroke: a randomized, controlled trial.** In 2009, this study found “no effect … of treatment with moderate-dose fish oil supplements on cardiovascular biomarkers”. The study observed that “insufficient dose, short duration of treatment, and/or oxidation of the fish oils may have influenced these outcomes.” Participants used 1200 mg (including 700 mg DHA and 300 mg EPA) daily for 12 weeks.

• **Supplementation with omega3 polyunsaturated fatty acids and all-rac alpha-tocopherol alone and in combination failed to exert an anti-inflammatory effect in human volunteers.** In 2004, this study found that Omega 3 “supplementation resulted in no changes in plasma lipids”. Participants used 1500 mg daily for 12 weeks.

These clinical study reviews confirm that supplementation of Omega 3 Docosahexaenoic Acid and Eicosapentaenoic Acid may support healthy triglycerides:

• **A meta-analysis shows that docosahexaenoic acid from algal oil reduces serum triglycerides and increases HDL-cholesterol and LDL-cholesterol in persons without coronary heart disease.** In 2012, this meta-analysis of 11 studies observed that Omega 3 supplementation “may reduce serum [triglycerides]”.

• **Omega-3 fatty acids and hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy: systematic review and meta-analysis.** In 2011, this meta-analysis of 4 studies observed that Omega 3 supplements “significantly reduce triglycerides concentrations”.

• **Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis.** In 2011, this meta-analysis observed that “both EPA and DHA reduced triglycerides.”
Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. In 2009, this meta-analysis of 47 studies observed that Omega 3 supplementation “produces a clinically significant dose-dependent reduction of fasting blood [triglycerides]”. 