PYCNOGENOL®

(French Maritime Pine Bark Extract)
Pinus pinaster Aiton subsp. *atlantica*
[Fam. Pinaceae]

OVERVIEW

This Clinical Overview is based on the full monograph covering the published scientific and clinical research on Pycnogenol®, a patented, proprietary extract made exclusively from French maritime pine bark (*Pinus pinaster,* manufactured by Horphag Research, Geneva, Switzerland). Pycnogenol extract is standardized to contain 70 ± 5% procyanidins in compliance with USP 28, compounds known for relatively significant antioxidant and anti-inflammatory activity, among other actions. Pycnogenol was ranked among the top 30 selling herbal dietary supplements in the United States in mainstream retail outlets (food, drug, and mass market stores) in 2008 in terms of dollar sales and had a total sales increase of nearly 34% over the previous year.

PRIMARY USE

Cardiovascular Health: Although there are many potential uses for Pycnogenol, the most well-studied use is for improving vascular health as a result of improved endothelial function and venous insufficiency. Controlled clinical trials have been published that demonstrate symptomatic improvement of blood circulation, blood pressure and platelet function normalization, and venous insufficiency. However, more studies with larger numbers of participants are needed to further establish these findings.

OTHER POTENTIAL USES

Controlled clinical trials have been published for the following indications: thrombosis, diabetes and its complications, hypertension and its complications, asthma, attention deficit hyperactivity disorder (ADHD), gynecology (endometriosis and dysmenorrhea), and osteoarthritis. None of these indications are supported by more than 1 or 2 well-designed published clinical trials.

Other potential uses with weaker research support include erectile dysfunction, retinopathy, gingivitis, melasma, and cramps and muscular pain.

PHARMACOLOGICAL ACTIONS

Pharmacological studies employing *in vitro*, animal, and human models have found that Pycnogenol has potent antioxidant activity, anti-inflammatory actions, improves endothelial function (produces vasodialation), reduces platelet aggregation, reduces alpha-glucosidase activity and blood glucose levels, promotes wound healing, alters neurotransmitter levels in children with ADHD, and improves reproductive health by improving sperm morphology and function.

DOSAGE AND DURATION OF ADMINISTRATION

The following doses were used in the clinical trials reported in the table in the full monograph. [Note: Some of the doses are based on single studies or uncontrolled studies.]

ADHD: 1 mg/kg of body weight/day
Asthma: 1 mg/lb of body weight/day
Cholesterol/dyslipidemia: 120-150 mg/day
Chronic Venous Insufficiency: 150-360 mg/day
Diabetes: 50-200 mg/day
Dysmenorrhea: 30-60 mg/day
Endometriosis: 60 mg/day
Erectile dysfunction: 120 mg/day
Hypertension: 100-200 mg/day
Melasma: 75 mg/day
Muscle cramps: 200 mg/day
Osteoarthritis: 100-150 mg/day
Perimenopause: 200 mg/day
Platelet function: 25-200 mg/day
Retinopathy: 20-160 mg/day

In the clinical trials the most common duration of use was 2-3 months; however, long-term use may be justified. There is no evidence from actual product use over several decades by millions of people that might warrant a limitation, and based on the published chemistry and pharmacology of Pycnogenol there are no data suggesting a limitation on duration of use. There are no long-term safety studies.

MANUFACTURER DOSE RECOMMENDATIONS:

According to the manufacturer, the dosage of Pycnogenol will depend on the nature of the desired health benefit. For example, the dose required for preventative effects is different from dose aimed at improving acute or chronic health problems.

As an antioxidant, Pycnogenol may be effective at any dose. The manufacturer states that in order to have measurable physiologic effects related to prevention of oxidative tissue damage the daily intake should be at least 20 mg.

When used as a preventative measure for cardiovascular health, 25 mg/day is recommended. Higher doses ranging from 50 to 100 mg are recommended for cardiovascular health risks such as hypertension, blood hyper-coagulation, and impaired blood circulation.

When using Pycnogenol for anti-edema effects, such as in venous insufficiency, the manufacturer recommends 50 mg/day. For more advanced stages the daily dosage should be higher, in the range of 100–150 mg for a limited period of time such as up to 4 weeks. Once edema and symptoms have improved, a daily maintenance dosage of 50 mg may be considered.

For lowering blood glucose in patients with diabetes the manufacturer recommends taking 50 mg once or twice daily.

Anti-inflammatory effects can be achieved with Pycnogenol doses ≥ 30 mg/day.

For dysmenorrhea, 30 mg once or twice daily is recommended.

For osteoarthritis or asthma, 100 mg/day is recommended.

CONTRAINDICATIONS AND PRECAUTIONS

There are no known contraindications for Pycnogenol.

Pregnancy and Lactation: As a general precaution, Pycnogenol should not be taken during the first 3 months of pregnancy. This precaution is based on general principles and a lack of any published data on pregnant women using Pycnogenol in the first trimester.

Safety trials have demonstrated absence of mutagenic and teratogenic effects, no perinatal toxicity, and no negative effects on fertility.

ADVERSE EFFECTS

Pycnogenol has been affirmed GRAS (generally recognized as safe) for use in conventional foods, based on the evaluation of clinical safety and pre-clinical toxicology data by an independent panel of toxicology experts contracted by the manufacturer in what is known as a GRAS self-affirmation process.

The safety of Pycnogenol is based on data obtained from 70 clinical studies (n =5723) including both healthy subjects and patients with a particular dysfunction or pathology. The mean daily Pycnogenol dose was 80 mg (range 30-450 mg/day, n = 4665). The global frequency rate of adverse effects (AEs) is 2.4%. However, in healthy subjects, the incidence rate of AEs is 0.19% (based on 2116 subjects in 31 clinical studies). An evaluation of the clinical studies revealed that the occurrence of AEs is unrelated to the dose or duration of use.

From what can be gleaned from the clinical trials, it appears that gastrointestinal (GI) discomfort is the most frequently occurring AE. This may be attributed to the astringent nature of Pycnogenol. The GI effects did not occur when Pycnogenol was taken with or after meals. Dizziness, headache, and nausea are the next most frequently reported AEs. Acne, diarrhea, and dysfunctional bleeding are the most frequent AEs in studies of women with premenstrual syndrome or dysmenorrhea. The majority of AEs observed were mild.

Analysis of clinical safety data obtained from 4 clinical studies (n =185) evaluating Pycnogenol's effect on blood pressure and heart rate in normo-tensive people did not reveal any significant changes on systolic or diastolic blood pressure or heart rate.

Post-marketing surveillance (spontaneous AE reporting) carried out between 2002 and 2005 in Europe and Asia revealed 6 case reports of AEs despite millions of Pycnogenol doses sold. There were 3 cases of urticaria, 1 case of headache, 1 case of nausea, and 1 case of eczema and diarrhea. According to the manufacturer, urticaria is a rare allergic reaction that could be due to the color component of the tablet.

There have been no reports of serious AEs in any clinical study or from commercial use of Pycnogenol since it was initially introduced into the market in Europe around 1970.

DRUG INTERACTIONS

Pycnogenol has been consumed by adult and elderly patients taking concomitant therapies. No information from spontaneous reporting is available on any interactions resulting from simultaneous intake of other drugs with Pycnogenol. Other interactions with alcohol consumption or nutrition habits have not been reported. Pycnogenol does not affect INR (International Normalization Ratio, a measurement of bleeding tendency) in patients taking aspirin. No other drug interaction studies have been performed with Pycnogenol.

CLINICAL REVIEW

As of June 2008 there are a total of 33 published human clinical trials on Pycnogenol as a monopreparation that have been published in English or translated to English. Due to space considerations, the authors and editors of the full Pycnogenol monograph decided to review only selected studies; however, most appear in the Published Clinical Studies Table. Studies included in the text of the Clinical Review section of the full monograph met the following criteria: human trial, any indication, any dose of Pycnogenol, English language or English translation, and any publication year. Exclusion criteria were: pilot study, no control group, untreated control group, or any other significant methodological limitation. Seventeen clinical trials met these criteria and are reviewed in the text in the full monograph. They evaluate chronic venous insufficiency and its complications, thrombosis, diabetes and its complications, hypertension and its complications, asthma, ADHD, gynecology (endometriosis and dysmenorrhea), and osteoarthritis.

To summarize the clinical findings, Pycnogenol may help decrease edema formation in the lower legs, such as in people with chronic venous insufficiency. Pycnogenol improves endothelial function resulting in improved blood circulation, lowered blood pressure in hypertension, and normalization of platelet coagulability. Pycnogenol has been shown to improve glycemic control in patients with type 2 diabetes and to improve treatment of diabetic ulcers. Preliminary studies suggest that Pycnogenol may be beneficial for children with ADHD and may be a useful adjunct therapy for patients with asthma. Pycnogenol may help reduce pain associated with menstrual disorders. Several clinical studies report that Pycnogenol may improve subjective symptoms of knee osteoarthritis.