

## **PRELOX<sup>®</sup> FOR IMPROVEMENT OF ERECTILE FUNCTION: A REVIEW**

Steven Lamm<sup>1</sup>, Frank Schönlau<sup>2</sup>, Peter Rohdewald<sup>2</sup>

<sup>1</sup>New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA

<sup>2</sup>Institute of Pharmaceutical Chemistry, University of Münster, Hittorf Strasse 58-62,  
48149 Münster, Germany.

### **ABSTRACT**

*Prelox<sup>®</sup> is a trademarked proprietary blend of French maritime pine bark extract, Pycnogenol<sup>®</sup>, and l-arginine aspartate<sup>1</sup>. This article reviews and discusses results of three clinical studies carried out with Prelox<sup>®</sup> for men with mild forms of erectile dysfunction. A first experimental study tested l-arginine aspartate (dosage 3 g a day) both alone as well as in combination with Pycnogenol<sup>®</sup> for recovery of erectile dysfunction in 40 men. Application of l-arginine aspartate alone for one month was effective in only 5% of men, while the addition of Pycnogenol<sup>®</sup> (80 mg a day) to the l-arginine aspartate regimen was effective during a second month's treatment in recovering erectile function in 80% of the cases ( $p < 0.01$ ). An increase of the daily Pycnogenol<sup>®</sup> dose to 120 mg further increased the number of men with restored sexual function to 92.5%.*

*Another clinical study extended these results by choosing ageing men as subjects who simultaneously suffered from erectile dysfunction as well as sub-fertility because of impaired sperm motility and morphology. Men were supplemented with*

*Prelox<sup>®</sup> over a period of one year. Again a statistical significant 80% of men experienced restored sexual function. The efficacy was sustained over the whole treatment period and no side effects occurred. Furthermore, Prelox<sup>®</sup> regimen had improved sperm parameters at the end of the one year treatment and 42% of the couples had achieved pregnancy. The improved sperm quality in sub-fertile men in response to Pycnogenol<sup>®</sup> supplementation had recently been discovered in US studies.*

*A third clinical study carried out in the US applied modern techniques, digital inflection rigidity (DIR) and the International Index of Erectile Function (IIEF) score, to substantiate the efficacy of Prelox<sup>®</sup> for 37 men with mild erectile dysfunction. After using Prelox<sup>®</sup> for 6 weeks 81.1% of men judged supplementation with Prelox<sup>®</sup> to be effective and 70.3% showed an increased IIEF score and a generally increased penile rigidity. 73% of the men reported easier initiation of erection and 70.3% reported it was easier to sustain the erection. 65% of the men reported to have increased morning erections. Data analysis revealed that Prelox<sup>®</sup> was particularly effective for milder forms of erectile dysfunction.*

*All three clinical studies uniformly showed that male sexual function was permanently restored during supplementation with Prelox<sup>®</sup>. Moreover, in none of the studies a side effect occurred and no cases of hyper-stimulation or priapism have been*

<sup>1</sup> Prelox<sup>®</sup> is a registered trademark of Horphag Research Ltd. Use of this product is protected by one or more of U.S. patents # 6,565,851 / #4,698,360 / #5,720,956 / #6,372,266 and other international patents.

reported. Prelox<sup>®</sup> is a safe and efficacious long-term regimen for aging men who wish to compensate for early signs of flawed sexual performance and regain the ability to respond spontaneously to sexual stimulation.

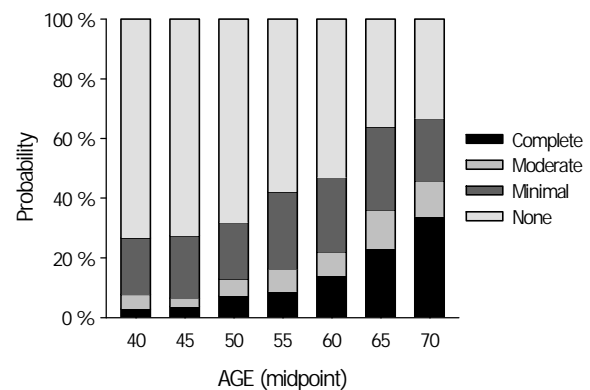
## INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to attain and/or maintain a penile erection sufficient to complete a satisfactory sexual intercourse (NIH, 1993). With increasing age erectile function deteriorates progressively (Montorsi *et al*, 2002). The association of aging and erectile dysfunction was shown in several epidemiological studies. The probably most comprehensive epidemiological study was the Massachusetts Male Aging Study (MMAS), which surveyed health and aging of more than thousand men including a questionnaire on sexual function and activity (Feldman *et al*, 1994). From this data a relationship between age and probability of erectile function was derived as shown in *Figure 1* (Kleinman *et al*, 2000).

During arousal, the aging man presents a lengthening of the excitement phase with a delayed erection, a lengthening of the plateau phase with a longer interval to ejaculation and decreased penile rigidity. During orgasm, a shorter ejaculation event with an increased incidence of resolution without ejaculation is common (Wespes, 2002).

Penile erection is a vascular phenomenon under psychological control. The initial sexual stimulus travels through the spinal cord to reach the corpora cavernosa. The terminal branches of the cavernous nerves release several neurotransmitters, the most important ones being nitric oxide (NO), acetylcholine and prostaglandins. These erectogenic neurotransmitters act in concert with vasodilators of the endothelium, predominantly NO. Increased blood flow through the penile arteries stimulates the en-

dothelium leading to further increase of NO (Simonsen *et al*, 2002). NO diffuses to smooth muscle layers to stimulate guanyl cyclase, followed by intra-cellular increases of cyclic guanosine monophosphate as second messenger which subsequently triggers muscle relaxation. Ultimately these processes allow enhanced inflow of blood into penile arteries and sinusoids, restriction of venous outflow and entrapment of pressurized blood in the corpora cavernosa.



*Figure 1.* Prevalence of erectile dysfunction: Massachusetts Male Aging Study, 1987-1989 (n = 1626), reproduced from McKinley 2000.

With normal aging physiological changes occur in male sexual activity, impairing erectile function. These changes largely comprise endocrinological (hormonal) and vascular abnormalities (Montorsi *et al*, 2002). Alterations in blood flow to and from the penis are thought to be the most frequent cause of male erectile dysfunction (Simonsen *et al*, 2001). Many alterations of penile arterial endothelial cell function relate to arterial risk factors such as atherosclerosis and hypertension which occur more frequently at higher age. A general age-related decline of endothelial function affects bioactivity and availability of NO (Carr and Frei, 2000). Thus, promising strategies to counteract impaired erectile function at higher age address the supply with NO

or prolong the bioactivity of NO's second messenger cyclic guanosine monophosphate.

### COMPOSITION AND PHARMACOLOGY OF PRELOX<sup>®</sup>

Prelox<sup>®</sup> is a branded, unique preparation of French maritime pine bark extract, Pycnogenol<sup>®</sup>, and L-arginyl aspartate, world-wide exclusively distributed by Horphag Research Ltd.

Pycnogenol<sup>®</sup> consists of phenolic substances chemically classified as flavonoids. Specifically, Pycnogenol<sup>®</sup> contains phenolic acids (p-hydroxy benzoic, protocatechuic, vanillic, gallic, p-cumaric, caffeic and ferulic acid) and taxifolin and catechin. The majority of Pycnogenol<sup>®</sup> consists of procyanidins: biopolymers of catechin units with a chain length of up to dodecamers (Rohdewald, 2002). Pycnogenol<sup>®</sup> has been demonstrated in various experimental settings to be an excellent antioxidant (Packer *et al*, 1999). In a great number of studies Pycnogenol<sup>®</sup> proved to have an extensive pharmacology. Clinical studies have established the benefits particularly for improvement of cardiovascular functions.

A central role of Pycnogenol<sup>®</sup> is its ability to enhance endothelial production of nitric oxide from the substrate L-arginyl aspartate by the enzyme nitric oxide synthase. A pharmacological study has shown that Pycnogenol<sup>®</sup> dose-dependently increases diameter of an adrenaline-constricted arterial blood vessel (Fitzpatrick *et al*, 1998). Pycnogenol<sup>®</sup> did not relax the artery in absence of endothelial cells or when NO-synthase was inhibited by N-methyl-L-arginine, an ineffective substrate for nitric oxide synthase. However, when the natural substrate L-arginyl aspartate was added, relaxation was restored. Unlike other antioxidants Pycnogenol<sup>®</sup> apparently does not act by merely extending the half-life of NO by preventing its oxidation to

inactive peroxyntirite by superoxide (Carr and Frei, 2000). Vasorelaxant activity of Pycnogenol<sup>®</sup> remained unaltered when peroxyntirite development was inhibited by presence of superoxide dismutase. These findings led to the proposition that Pycnogenol<sup>®</sup> stimulates production of NO from L-arginine by endothelial NO-synthase (Rohdewald, 2002).

As L-arginine is the pre-cursor of NO and its abundant availability is understood to support more efficient NO production. Indeed, pharmacologic studies with adult and aged male rats showed that oral supplementation with high doses of L-arginine statistically significantly increased maximal intracavernosal pressure and penile NOS activity was increased by almost 100% (Moody *et al*, 1997). It was postulated that L-arginine in the penis may be a substrate-limiting factor for NOS activity.

As Pycnogenol<sup>®</sup> was found to stimulate NOS to more efficiently produce NO, a more abundant L-arginine as precursor will be more effective. In Prelox<sup>®</sup> L-arginine is combined with Pycnogenol<sup>®</sup> as L-arginine aspartate. The ionic species is water-soluble and thus facilitates better absorption. L-aspartate plays a crucial role in the Krebs cycle (citrate cycle), the central biochemical cellular pathway for gaining energy and metabolite biosynthesis. Indeed, supplementation of rats with L-aspartate was shown to enhance physical performance (Lancha *et al*, 1995). Such a role of Prelox<sup>®</sup> is not intentional, yet might prove to be beneficial for certain individuals.

### CLINICAL STUDIES WITH PRELOX<sup>®</sup> DISCOVERY OF PRELOX<sup>®</sup> FOR IMPROVEMENT OF ERECTILE FUNCTION

At the Medical University of Sofia (Bulgaria) a group headed by Dr. Romil Stanislavov tested natural remedies for treatment of men with im-

paired erectile function (Stanislavov and Nikolova, 1993). Forty men participated in this study, aged between 25 and 45 years (mean age  $36.6 \pm 5.3$  years), suffering from an inability to achieve and sustain an adequate erection sufficient for successful intercourse. Men with organic causes for erectile dysfunction were excluded from the study. The erectile function before and after treatment was assessed using the questionnaire according to O'Leary (O'Leary *et al*, 1995). The O'Leary questionnaire was complemented by additional questions to assess the ratio of successful to unsuccessful attempts of erections for intercourse. Specific questions were raised regarding the nature of unsuccessful intercourse: too weak penile rigidity, delayed development of a sufficient erection, or erection was not sustained long enough. During the first three weeks run-in phase subjects did not receive medication to obtain reliable baseline values.

In a first treatment approach men received three portions of 1 g L-arginyl aspartate (dissolved in 5 ml water in ampoules) a day over a period of 1 month. As a result 2 men (5% of patients) experienced normal erections. During the following month subjects continued taking the same dosage of L-arginyl aspartate plus 40 mg Pycnogenol<sup>®</sup> twice a day. This led to a dramatic and statistical significant recovery of normal erectile function in 32 men (80% of patients). This successful result was the first discovery of a unique combination of Pycnogenol<sup>®</sup> with L-arginyl aspartate, denominated Prelox<sup>®</sup>.

The efficacy of the L-arginyl aspartate - Pycnogenol<sup>®</sup> combination, Prelox<sup>®</sup>, was further established by increasing the daily dosage of Pycnogenol<sup>®</sup> to 120 mg a day during another month's treatment. The number of men with restored normal erectile function was further increased to 37, equivalent to 92.5% of all subjects.

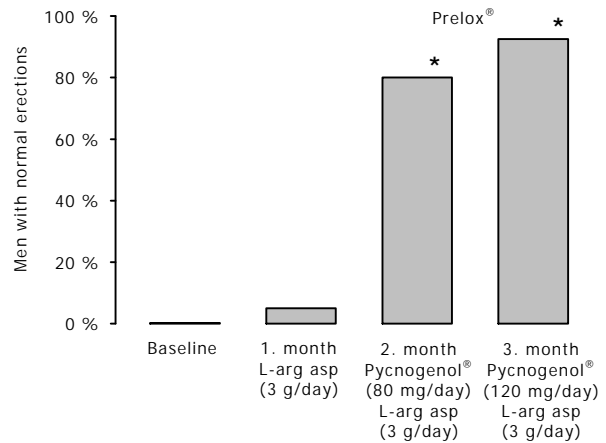


Figure 2. Restoration of normal erections of men with mild forms of erectile dysfunction. While supplementation with L-arginine aspartate (3 grams a day) only gave little effect, the combination of L-arg asp with 80 mg Pycnogenol<sup>®</sup> a day (= Prelox<sup>®</sup>) gave a statistical significant increase of men with restored erectile function. An increase of the Pycnogenol<sup>®</sup> dose further increased the benefit (Stanislavov and Nikolova, 1993).

In those patients who gained normal erectile function during treatment, Stanislavov and Nikolova estimated the time necessary to initiate penile erection as well as the period of time it sustained (Table 1). The two patients responding to L-arginine aspartate treatment required 10 min to achieve an erection. Again, the combination of L-arginine aspartate with Pycnogenol<sup>®</sup>, Prelox<sup>®</sup>, dramatically reduced the time for development of an erection. Moreover, the duration of the erection was prolonged. An increase of Pycnogenol<sup>®</sup> further improved these parameters.

The authors of the study reported that Prelox<sup>®</sup> was effective irrespective of the age of subjects. They found no side effects, and no signs of hyperstimulation or priapism were observed.

*Table 1.* The main characteristics of erectile response of patients who experienced restored erectile function. Given is the mean time (SEM) until erection developed in response to spontaneous sexual stimulation, as well as the duration of the erection.

	Baseline	L-arg asp (1. month)	L-arg asp + Pycnogenol <sup>®</sup> (80 mg/d) (2. month)	L-arg asp + Pycnogenol <sup>®</sup> (120 mg/d) (3. month)
Responders	0 (0%)	2 (5%)	32 (80%)	37 (92.5%)
Mean time until response emerges	-	10 ± 2 min	4 ± 1 min	2 ± 1 min
Mean time of duration	-	2 ± 1 min	4 ± 1 min	15 ± 3 min

### LONG TERM PRELOX<sup>®</sup> REGIMEN

The research group in Sofia, headed by Stanislavov extended their Prelox<sup>®</sup> research program to men, who do not only suffer from erectile dysfunction but furthermore have fertility problems (Stanislavov and Nikolova, 2002). Fifty aging men (>45 years) with diagnosed sub-fertile characteristics were enrolled for this study. These men had lowered volume of semen and sperms had reduced motility and showed morphological abnormalities. In addition to conventional sperm parameters the ability of sperms to penetrate ovulatory cervical mucous was measured. Furthermore, test were carried out to test vitality and chromatin condensation, acrosine proteolytical activity, as well as detailed spermatozoa motility. All the participants completed a questionnaire at baseline and after treatment addressing topics related to sexual drive, erectile function and overall sexual satisfaction.

As in their previous study Stanislavov and Nikolova started with a daily regimen of 3 g L-arginyl aspartate for 1 month. Again only a minority of 5 men (10%) responded favorably, experiencing a normal erection. In the following month the combination of L-arginyl aspartate (3 g per day) and

Pycnogenol<sup>®</sup> (80 mg per day), Prelox<sup>®</sup>, was administered. The treatment with Prelox<sup>®</sup> increased the number of men with restored sexual ability to 80%. The men continued taking Prelox<sup>®</sup> for a period of one year during which the number of men with restored erectile function remained constant. At the end of the trial particularly the motility of men's sperms had improved. Most convincing was the outcome that 21 couples (42%) had achieved pregnancy during the treatment period. No side effects occurred during the study.

The results showing improved sperm quality in response to Prelox<sup>®</sup> supplementation are in accordance to earlier studies carried out at the West Essex Center for Advanced Reproductive Endocrinology, West Essex, NJ (Roseff and Gulati, 1999; Roseff, 2002). Nineteen sub-fertile were supplemented with 200 mg Pycnogenol<sup>®</sup> over a period of nine months. The outcome showed improved sperm morphology and functionality. The method of action is most likely the pronounced antioxidant activity of Pycnogenol<sup>®</sup> which saves the abundant polyunsaturated fatty acids in sperm membranes from peroxidation. The study author concluded that Pycnogenol<sup>®</sup> supplementation may help couples to experience improved natural fertility rather than

having to rely on *in-vitro* fertilization.

### AMERICAN PRELOX<sup>®</sup> STUDY

Lamm and Couzens evaluated the efficacy of Prelox<sup>®</sup> for improving mild forms of erectile dysfunction (Lamm and Couzens, 2002). The widely accepted International Index of Erectile Function (IIEF) questionnaire was used for evaluation of men's erectile performance, which yields scores between 0 and 75 (Rosen *et al*, 1997). Furthermore, with digital inflection rigidity (DIR) using the instrument DIR H501 (UROAN21, Palma de Mallorca, Spain) the axial penile rigidity in grams was measured as an objective parameter for the efficacy of Prelox<sup>®</sup>.

Initially, 40 men were enrolled for the trial of which three, however, did not return for the second visit. The age-range of the 37 men who completed the trial was as follows:

30-39 years of age :	8
40-49 years of age :	14
50-59 years of age :	14
60 years of age/older :	1

Men with milder forms of erectile dysfunction were selected using the "Sexual Health Inventory for Men" (SHIM) questionnaire, which is an abbreviated version of the IIEF. The SHIM includes only five of the IIEF questions (questions 2,4,5,7 and 15) and is easier and faster to use at the recruitment level. The SHIM score ranges between 0 and 25. A value lower than 22 indicates abnormal erectile function. Men with a SHIM score lower than 22 and higher than 11 were selected, thus excluding men with more pronounced erectile dysfunction. The mean baseline SHIM score of men who completed the trial was  $18.05 \pm 2.49$ . At baseline subjects had to complete the IIEF score and

were provided a DIR to measure their penile rigidity during sexual arousal at home. Then they were equipped with a 6 weeks supply of Prelox<sup>®</sup> tablets. They were instructed to take 4 Prelox<sup>®</sup> tablets a day, each tablet containing 20 mg Pycnogenol<sup>®</sup> and 750 mg L-arginine aspartate, over a period of 6 weeks. Finally, they completed the IIEF questionnaire and measured penile rigidity again. Together with the second IIEF questionnaire 7 questions were added referring to the overall sexual satisfaction:

Since taking the pills,...

A: ...have you had an increase in morning erections?

B: ...have you had an increase in sexual dreams?

C: ...have you had an increase in sexual fantasies?

D: ...has it been easier to initiate erections?

E: ...has it been easier to sustain an erection?

F: ...has your partner noted any change in your sexual interest?

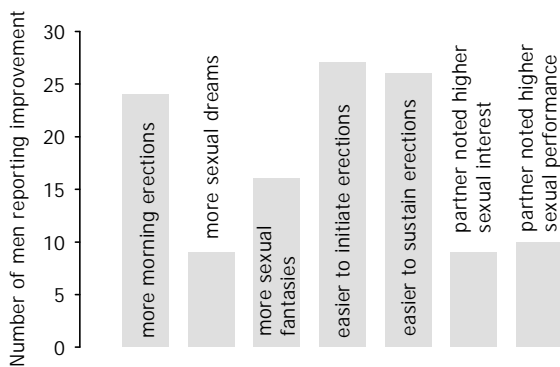
G: ...has your partner noted any change in your sexual performance?

The outcome of the study was a total of 30 men (81.1%) stating that treatment had improved their ability to engage in sexual activity. An increased IIEF score compared to baseline was found in 70.3% of subjects with a 10.2% mean IIEF score increase of all 37 men. Analysis of the erectile function domain of the IIEF (questions 1-5 and 15) shows a significant increase from baseline 73.7% to 81.7%. The additional questions at the end of the trial demonstrate a statistical significant improvement of erectile function. 73% of the subjects report that Prelox<sup>®</sup> supplementation made it easier to

initiate an erection, and 70.3% stated that Prelox<sup>®</sup> made it easier to sustain an erection (*Figure 3*).

81.1% of men judged Prelox <sup>®</sup> to be effective
70.3% showed an increased IIEF score
65% report increased morning erections
73% report erections are easier to initiate
70.3% report erections are easier to sustain

*Table 2.* Outcome of the Prelox<sup>®</sup> treatment of men with mild erectile dysfunction (Lamm and Couzens, 2002).

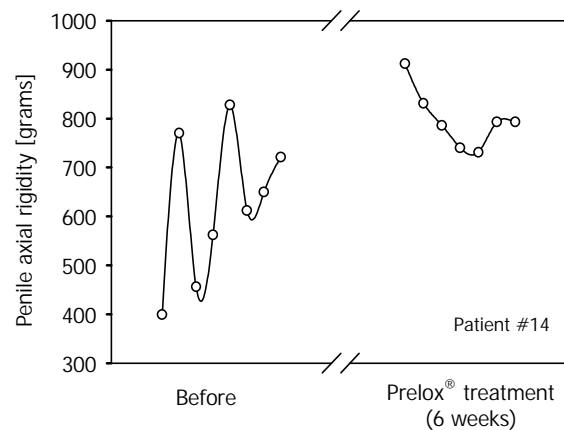


*Figure 3* Questions raised at the end of the Prelox<sup>®</sup> trial together with the IIEF questionnaire. Given are the absolute numbers of men reporting improvement of individual parameters (Lamm and Couzens, 2002).

The DIR readings clearly reflected the improvement showing higher penile rigidity values. However, during sexual excitement the penile rigidity varied considerably from one reading to another within the time frame of minutes. So values could not be evaluated for statistical analysis (*Figure 4*).

A closer examination of the data showed that Prelox<sup>®</sup> was particularly effective for those men

with milder forms of erectile dysfunction. Classification of men into three groups according to their ED severity, as taken from SHIM scores at baseline, reveals an increased efficacy of Prelox<sup>®</sup> particularly for moderate and milder ED (*Figure 5*). No side-effects were reported, all men tolerated Prelox<sup>®</sup> very well.



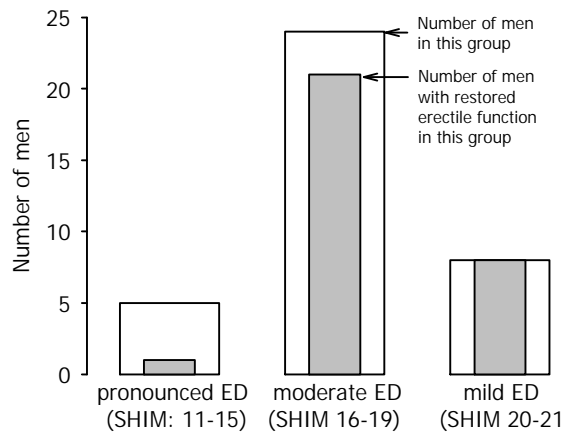
*Figure 4.* Results of digital inflection rigidometry (DIR) before and after Prelox<sup>®</sup> treatment of patient #14, representative for participating subjects. During sexual arousal the penis is held against the instrument to obtain momentary penile axial rigidity in grams. The penile axial rigidity necessary for vaginal penetration is 500 grams. The individual rigidity values obtained within minutes varies considerably. The values after Prelox<sup>®</sup> treatment are generally higher and consistently above the 500 grams level (Lamm and Couzens, 2002).

## DISCUSSION

Three clinical studies show that healthy male sexual function can be restored by continuous supplementation with Prelox<sup>®</sup>. Clinical experience made clear that a positive effect of Prelox<sup>®</sup> may not be expected in more severe conditions such as e.g. diabetes or advanced atherosclerosis. Prelox<sup>®</sup> is particularly effective in aging men experiencing first signs of reduced sexual performance. In fact, the study showed that 100% of men belonging to

the sub-group having the mildest forms of erectile dysfunction (SHIM score 20-21) experienced completely restored sexual function.

Unlike medications such as sildenafil, which are used in an “on-demand” fashion about 30 min before sexual intercourse, Prelox<sup>®</sup> restores sexual function permanently during supplementation. Thus, Prelox<sup>®</sup> enables men to spontaneously react towards sexual stimulation allowing to naturally interact with the partner.



**Figure 5.** The 37 men who completed the trial were separated into three groups of different erectile dysfunction (ED) severity at trial start according to their SHIM scores. While only one man out of five with more pronounced ED experienced an improved erectile function, the majority of men (87.5%) with moderate ED and all men with mild ED benefited from Prelox<sup>®</sup> supplementation (Lamm and Couzens, 2002).

Sildenafil acts by inhibiting phosphodiesterase type 5, preventing it from inactivating the second messenger, cyclic guanosine monophosphate (cGMP). This makes smaller amounts of NO more effective, prolonging the muscle relaxation effect and in consequence promoting enhanced penile rigidity.

These mechanisms raise an interesting question: What happens when Prelox<sup>®</sup> and sildenafil are taken in combination? In theory, Prelox<sup>®</sup> will stimulate enhanced NO production and subsequently enhance second messenger availability, while sildenafil ensures that every second messenger molecule is preserved for triggering muscle relaxation. Thus, the two mechanisms should work “hand-in-hand” for the benefit of better penile rigidity. Indeed, in the institute of Lamm individuals were observed who chose to take sildenafil while supplementing with Prelox<sup>®</sup>. These case reports indicate a dramatically enhanced effect when both products were taken in combination. Individuals reported that they could lower their sildenafil dose during supplementation with Prelox<sup>®</sup>. It might be interesting to investigate this phenomenon in more detail.

In none of the three clinical studies unwanted effects had been observed.

It can be concluded that Prelox<sup>®</sup> is effective for preserving a healthy sexual function in aging men experiencing first signs of lowered erectile performance. At higher age, Prelox<sup>®</sup> should be taken continuously to let first signs of sexual limitations vanish.

## REFERENCES

- Rossello Barbara M. A new harmless method for measuring accurately the axial penis rigidity. *J Urology*, submitted.
- Carr A, Frei B. The role of natural antioxidants in preserving the biological activity of endothelium-derived nitric oxide. *Free Rad Biol Med* 28: 1806-1814, 2000.
- Feldman HA, Goldstein I, Hatzichristou D, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. *J Urol* 151: 54-61, 1994.
- Fitzpatrick DF, Bing B, Rohdewald P. Endothelium-dependent vascular effects of Pycnogenol<sup>®</sup>. *Cardiovasc Pharmacol*

- 32: 509-515, 1998.
- Kleinman KP, Feldman HA, Johannes CB, McKinlay JB. A new surrogate variable for erectile dysfunction status in the Massachusetts Male Aging Study. *J Clin Epidemiol* 53: 78-88, 2000.
- Lamm S, Couzens GS. Prelox<sup>®</sup> for sexual satisfaction, a clinical trial. Study Report, 2002.
- Lancha AH, Recco MB, Abdalla DSP, Curi R. Effect of aspartate, arginine and carnitine supplementation in the diet on metabolism of skeletal muscle during a moderate exercise. *Physiol and Behaviour* 57: 367-371, 1995.
- McKinley JB. The worldwide prevalence and epidemiology of erectile dysfunction. *Int J Impot Res* 12 (suppl 4): S6-S11, 2000.
- Montorsi F, Salonia A, Deho F, Briganti A, Rigatti P. The ageing male and erectile dysfunction. *World J Urol* 20: 28-35, 2002.
- NIH consensus development panel on impotence. *JAMA* 270: 83-90, 1993.
- O'Leary MP, Fowler FJ, Lenderking WR, Barber B, Sagnier PP, Guess HA, Barry MJ. A brief male sexual function inventory for urology. *Urology* 46: 697-706, 1995.
- Packer L, Rimbach G, Virgili F. Antioxidant activity and biologic properties of a procyanidin-rich extract from pine (*Pinus maritima*) bark, Pycnogenol<sup>®</sup>. *Free Rad Biol and Med* 27: 704-724, 1999.
- Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol<sup>®</sup>), a herbal medication with a diverse clinical pharmacology. *Int J Clin Pharm and Ther* 40: 158-168, 2002.
- Roseff SJ. Improvement in sperm quality and function by French maritime pine tree bark extract. *J Reprod Med* 47: 821-824, 2002.
- Roseff SJ, Gulati R. Improvement of sperm quality by Pycnogenol<sup>®</sup>. *Eur Bull Drug Res* 7: 33-36, 1999.
- Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* 49: 822-830, 1997.
- Simonsen U, García Sacristán A, Prieto Dolores. Penile arteries and erection. *J Vasc Res* 39: 283-303, 2002.
- Stanislavov R, Nikolova V. Sexual and reproductive parameters in aging males after treatment with Pycnogenol<sup>®</sup> and L-arginine. *Int J Impot Res* 14 (suppl 4): S65, 2002.
- Stanislavov R, Nikolova V. Treatment of erectile dysfunction with Pycnogenol<sup>®</sup> and L-arginine. *J Sex Marital Ther* 29: 207-213, 2003.
- Wespes E. The ageing penis. *World J Urol* 20: 36-39, 2002.

**Prelox Blue \$47.95**  
**Free Shipping**  
**[www.lifemana.com](http://www.lifemana.com)**