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Efficacy and Safety of the Extract of *Serenoa repens* in the Treatment of Benign Prostatic Hyperplasia: Therapeutic Equivalence Between Twice and Once Daily Dosage Forms

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The efficacy and safety of two dosage forms (160 mg b.i.d. and 320 mg o.d.) of the extract of *Serenoa repens* were compared during a 1-year treatment in 132 patients suffering from benign prostatic hyperplasia (BPH). Both dosage forms induced a significant improvement in the efficacy variables: international prostate symptom score (60% after 1 year), quality of life score (85% of patients were satisfied after 1 year of treatment), prostatic volume (12% after 1 year), maximum flow rate (22% after 1 year), mean flow rate (17% after 1 year) and residual urinary volume (16% after 1 year). No significant differences were found between the two dosage forms. The percentage of patients or investigators evaluating that the treatment had a medium or bad tolerance was never superior to 4%. Nineteen side effects were observed in 16 patients (12.1%), 8 patients in each group. The majority of these side effects (at least 75%) were related to the natural evolution of the disease itself rather than to the medication. We conclude that the extract of *Serenoa repens* in its two dosage forms is a safe and effective treatment for the mictional problems associated with BPH. Consequently, it appears to offer a potential pharmacologic alternative capable of improving BPH symptoms in patients with mild-to-moderate disease.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) consists of an enlargement of the prostate to the extent that it produces obstruction of the urethra. It is an almost universal finding in aging men (Walsh, 1979; Denis, 1993). Its frequency above the age of 50 varies from 50% to 75% in most series (Rotkin, 1975).

Transurethral and open surgical prostactectomy are the most widely used treatments for BPH patients with severe symptoms. However, the incidence of complications such as blood loss, urinary tract infection, urethral stenosis, incontinence, impotence, and the need for reintervention is clinically significant after prostatic surgery, and thus excludes its use as routine treatment for all BPH patients (Mebust *et al*., 1989; Lepor and Rigaud, 1990). This has been an important motivating factor in the development of pharmacological treatment alternatives.

Phytotherapeutic drugs are used widely in Europe and a recent critical review has been devoted entirely to this subject (Lowe and Ku, 1996). Among phytotherapeutic agents, the extract of the fruit of the American dwarf palm tree, *Serenoa repens* (Prostaserene®) can be prepared according to an original procedure (Indena, European patent 0250953 B1) using a supercritical fluid extraction condition with carbon dioxide as solvent. Compared with existing methods, this procedure allows high-yield extraction of unaltered lipid components without contamination by residual solvents or nonvolatile agents frequently employed in industry (Bruhwyler, 1994). Di Silverio *et al*. (1992) demonstrated that the extract of *Serenoa repens* displayed an inhibitory effect on nuclear oestrogen receptors. It could also act as an antiinflammatory and antioedematous agent. *In vitro*, it was found to be a dual inhibitor of the cycloxygenase and 5-lipoxygenase pathway (Breu *et al*., 1992). Several *in vivo* models in the rat had already demonstrated this antiinflammatory and antioedematous potential (Tarayre *et al.*, 1983). In a model of transplantation of human BPH tissue into nude mice, a significant growth inhibiting effect of the extract of *Serenoa repens* has been demonstrated (Otto *et al.*, 1992). More recently, Weisser *et al.* (1996) have shown that the extract of *Serenoa repens* has an inhibitory effect on 5 alpha-reductase in the epithelium and stroma of human BPH. This inhibition was mainly due to the fatty acids contained in the saponifiable subfraction of the extract. An activation of the sodium/calcium exchanger, an interference with intracellular calcium mobilization possibly mediated by cAMP (Gutiérrez *et al*., 1996) and evan an antagonism on alpha adrenoceptors (Odenthal, 1996) have also been evoked to explain the spasmolytic and smooth muscle relaxing activities of the extract of *Serenoa repens.*

The efficacy and safety of the extract of *Serenoa repens*, administered at a dose of 160 mg twice a day, in the treatment of BPH have already been demonstrated in different studies (Champault *et al.*, 1984; Cukier *et al.*,

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1985; Romics *et al.*, 1993; Braeckman, 1994; Carraro *et al.*, 1996). The objective of this study was to demonstrate the therapeutic equivalence in terms of efficacy and safety between the twice a day 160 mg dosage form and a once daily 320 mg dosage form during a 1 year treatment.

PATIENTS AND METHODS

The study consists of a multicentre, single-blind, parallel, randomized, controlled design. One hundred and thirty-two patients suffering from a benign prostatic hyperplasia were randomized into two groups and received either the extract of *Serenoa repens* (Prostaserene®, capsule 160 mg p.o. twice a day, morning and evening) or the extract of *Serenoa repens* (Prostaserene®, capsule 320 mg p.o. once daily in the morning) and a placebo (capsule, p.o., once daily at evening) during 1 year. The size of 160 mg capsules and 320 capsules differed meaning that only the patient was unaware of the treatment. Medical visits were scheduled on day 0 and after 1, 3, 6, 9 and 12 months of treatment. The inclusion criteria were listed as follows: men aged a maximum of 75 years, suffering from a benign hyperplasia of the prostate (urgency, nocturia, pollakiuria, dysuria, decrease of urinary flow rate and terminal dribbling) confirmed by rectal examination and transrectal echography, maximal urinary flow rate superior or equal to 5 mL/s but inferior to 15 mL/s for a mictional volume of 150 mL, international prostate symptom score (I-PSS) situated between 12 and 24, residual volume inferior to 100 mL, serum prostate specific antigen (PSA) concentration inferior or equal to 10 ng/mL, written informed consent. The exclusion criteria were: indication for a surgical intervention, any malformation, tumour or infection of the genitourinary system, previous endoscopy of the lower urinary tract, renal and/or hepatic insufficiency. Obviously, any other treatment for prostatic hyperplasia (alpha blocking agent, finasteride or plant extracts) was excluded as well as any antibiotic or antiseptic treatment. The efficacy of treatments was evaluated using the following parameters: I-PSS score (7 questions, scored 0 to 35), quality of life score (1 question, scored 0 to 6), transrectal echographic prostatic volume determination using the following formula: volume = (antero-posterior diameter $\times$ (latero-lateral diameter)$^2 \times \Pi$)/6), urinary flow rates (mean and maximum) for mictional volumes superior or equal to 100 mL, residual volume and global evaluation of efficacy by the patient and the investigator (scored 0–3). The safety was also assessed using the following parameters: global evaluation by the patient and the investigator (scored 0–3), recording of side effects and blood and urine analyses. The compliance was measured by counting the number of capsules returned by the patient. The study was conducted in accordance with the Good Clinical Practice (GCP) guidelines as defined in the Helsinki Declaration. This study was approved by the Ethical Committee of University of Brussels (AZ-VUB). At baseline (day 0) the homogeneity between the two groups for continuous and discrete variables was measured using independent Student's *t*-tests and Mann–Whitney's tests respectively. The statistical analysis of efficacy and tolerance was conducted according to the 'intent-to-treat' (all patients included in the study) principle. The evolution of continuous varaibles was evaluated statistically using an analysis of variance for repeated measurements followed by appropriate *post-hoc t*-tests. The evolution of discrete variables was evaluated using the Mann–Whitney's test for inter-group comparisons and the Wilcoxon's test for intra-group comparisons. The global evaluation of efficacy and safety was analysed using a chi-square test comparing the observed distribution in four classes to a theoretical distribution of 25% in each class. The percentages of side effects were compared using the chi-square test. The results of the statistical analysis were audited and approved by an independent statistical centre (Data Investigation Company Europe, Brussels).

RESULTS

One hundred and thirty-two patients (65 in the 320 mg group and 67 in the 160 mg group) were recruited by ten Belgian urologists. Forty-eight patients (23 in the 320 mg group and 25 in the 160 mg group) did not fulfil all inclusion criteria. Of the 84 remaining patients (42 in both groups), 67 (33 in the 320 mg group and 34 in the 160 mg group) completed the study and participated in all visits. The demographic and baseline characteristics of patients are presented in Table 1. The two groups were homogeneous for all the variables and no statistical differences were measured between them.

Figure 1 shows the evolution of the I-PSS as a function of time and treatment according to the intent-to-treat analysis. The 'time–treatment' interaction was nonsignificant ($p > 0.05$) as well as the effect of treatment ($p > 0.05$) meaning that the evolution was comparable in both groups. The factor time was significant ($p < 0.0001$) meaning that both dosage forms produced a significant modification in the score. *Post-hoc* paired Student's *t*-tests revealed that the I-PSS decreased significantly ($p < 0.0001$) with both dosage forms from day 30 up to the end of the study. After 1 year of treatment the decrease was equal to 61.2% in the 320 mg o.d. group and 59.5% in the 160 mg b.i.d. group.

Table 2 shows the evolution of the prostatic volume, the maximum and mean flow rates and the residual volume as a function of time and treatment. To be sure that the flow rates were assessable, only the patients with a mictional volume superior or equal to 100 mL at each visit were taken into account. For these four parameters the 'time-treatment' interaction and the effect of the 'treatment' were non-significant ($p > 0.05$) meaning that the evolution was comparable in both groups. The effect of 'time' was significant ($p < 0.0001$ for the prostatic volume and maximal flow rate, $p < 0.01$ for the mean flow rate and the residual volume). *Post-hoc* paired Student's *t*-tests revealed that the prostatic volume was significantly ($p < 0.0001$) decreased in both groups from day 90 up to the end of the study. The percentage of increase after 1 year of treatment was equal to 14.7% in the 320 mg o.d. group and 9.7% in the 160 mg b.i.d. group. The maximum flow rate was significantly ($p < 0.0001$) increased in both groups from day 30 up to the end of the study. The percentage of increase after 1 year of treatment was equal to 21.4% in the 320 mg o.d. group and 23.8% in the 160 mg b.i.d. group. The mean flow rate was significantly ($p < 0.01$ on day 30 and 180; $p < 0.0001$ on day 90 and 360) increased in both groups from day 30 up to the end of the study. The percentage increase after 1 year of treatment was equal to 12.5% in the 320 mg o.d. group and 21.3% in the 160 mg b.i.d. group. The residual volume was significantly ($p < 0.05$ on day 360, $p < 0.01$ on day 180 and $p < 0.0001$ on day 30) decreased in both groups from day 30

Table 1. Demographic and baseline characteristics of the patient population ($n=132$)

Parameter	*Serenoa repens* 320 mg o.d. (mean ± SD or %)	*Serenoa repens* 160 mg b.i.d. (mean ± SD or %)	Statistical probability (p)
Age (years)	65.0 ± 6.9 ($n=64$)	65.1 ± 7.6 ($n=66$)	>0.05
Weight (kg)	74.9 ± 8.5 ($n=61$)	76.1 ± 9.6 ($n=64$)	>0.05
Height (cm)	172 ± 7 ($n=60$)	174 ± 6 ($n=64$)	>0.05
I-PSS	16.5 ± 3.3 ($N=65$)	17.3 ± 3.1 ($n=67$)	>0.05
Maximum flow rate (mL/s)	10.9 ± 2.9 ($n=65$)	10.9 ± 2.6 ($n=66$)	>0.05
Mean flow rate (mL/s)	6.1 ± 2.6 ($n=65$)	6.0 ± 2.1 ($n=65$)	>0.05
Mictional volume (mL)	225 ± 108 ($n=65$)	236 ± 108 ($n=66$)	>0.05
Residual volume (mL)	50 ± 32 ($n=63$)	44 ± 26 ($n=65$)	>0.05
Prostatic volume (mm^3)	45 599 ± 41 290 ($n=61$)	38 631 ± 20 206 ($n=63$)	>0.05
Quality of life score	($n=65$)	($n=67$)	
Delighted	0.0%	0.0%	>0.05
Happy	1.5%	3.0%	
Satisfied	15.4%	11.9%	
Mitigated	24.6%	16.4%	
Unsatisfied	47.7%	58.3%	
Unhappy	10.8%	10.4%	
Rectal examination	($n=65$)	($n=67$)	
<40 g	61.5%	68.7%	>0.05
40–60 g	30.8%	25.4%	
>60 g	7.7%	6.0%	

up to the end of the study (except on day 90). The percentage of decrease after 1 year of treatment was equal to 24.8% in the 320 mg o.d. group and 6.2% in the 160 mg b.i.d. group.

The evolution of the quality of life score is shown in Table 3. No significant ($p>0.05$) differences were found between the two groups using the Mann–Whitney's test. A significant ($p<0.0001$; Wilcoxon's tests) improvement was measured in both groups from day 30 up to day 360. After 1 year of treatment 88% and 83% of patients were satisfied, happy or delighted respectively in the 320 mg o.d. and 160 mg b.i.d. groups against 16% and 15% at the baseline.

A significant ($p<0.0001$, Chi-square tests) percentage of patients judged the treatment as effective and well tolerated from day 30 up to the end of the study (Table 4). The same conclusion applied to the judgment established by the investigators. After 1 year 86% and 75% of patients estimated that the treatment resulted in a slight or an important improvement respectively in the 320 mg o.d. and 160 mg b.i.d. groups. The percentages remained approximately the same when the evaluation was made by the investigators (88% and 75% respectively). After 1 year 100% of patients estimated that the treatment had a good or excellent tolerance. The same percentages were obtained in the evaluation made by the investigators. During the study the percentage of patients or investigators evaluating that the treatment had a medium or bad tolerance was never superior to 4%.

Globally, 19 side effects (Table 5) were observed in 16 patients (12.1%), 8 patients of the 320 mg o.d. group (12.3%) and 8 patients of the 160 mg b.i.d. group (11.9%). The difference between the two groups was nonsignificant ($p>0.05$, Chi-square). The majority of these side effects (75%) seemed more related to the natural evolution of the disease than to the medication itself. Side effects were responsible for stopping the treatment in two patients in both groups: 3.1% and 3.0% of patients in the 320 mg o.d. group and 160 mg b.i.d. group respectively. No significant

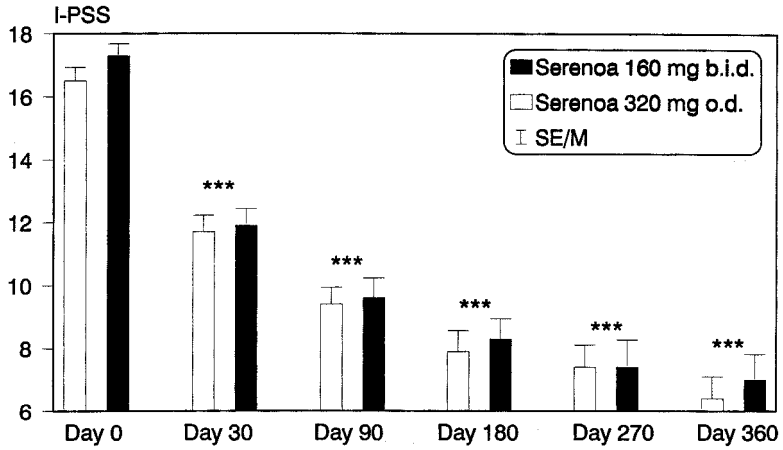

Figure 1. Evolution of the international prostate symptom score (I-PSS) as a function of time and treatment. In the 320 mg o.d. group $n=62$ on day 0 and 30, $n=60$ on day 90, $n=53$ on day 180, $n=52$ on day 270 and $n=51$ on day 360. In the 160 mg b.i.d. group $n=66$ on day 0, 30 and 90, $n=63$ on day 180, $n=54$ on day 270 and 360. SE/M: standard error on the mean, ***$p<0.0001$ paired Student's t-tests, comparisons versus baseline.

Table 2. Evolution of the prostatic volume, the flow rates and the residual volume as a function of time and treatment

Parameter	*Serenoa repens* 320 mg o.d. (mean ± SD)	*Serenoa repens* 160 mg b.i.d. (mean ± SD)	Probability (difference versus) baseline) (*p*)
Prostatic volume (mm^3)			
Day 0	46 421 ± 44 070 (*n*=53)	37 601 ± 17 596 (*n*=56)	
Day 90	40 624 ± 37 954 (*n*=53)	34 235 ± 17 257 (*n*=55)	<0.0001
Day 180	42 039 ± 36 476 (*n*=50)	31 514 ± 15 246 (*n*=55)	<0.0001
Day 360	39 676 ± 35 614 (*n*=49)	33 972 ± 26 937 (*n*=48)	<0.0001
Max flow rate (mL/s)			
Day 0	11.2 ± 2.9 (*n*=51)	10.9 ± 2.7 (*n*=51)	
Day 30	12.8 ± 3.6 (*n*=51)	12.4 ± 3.9 (*n*=51)	<0.0001
Day 90	12.6 ± 4.2 (*n*=48)	13.7 ± 4.9 (*n*=52)	<0.0001
Day 180	13.0 ± 3.9 (*n*=42)	12.9 ± 3.9 (*n*=51)	<0.0001
Day 360	13.6 ± 2.9 (*n*=42)	13.5 ± 3.6 (*n*=46)	<0.0001
Mean flow rate (mL/s)			
Day 0	6.4 ± 2.7 (*n*=51)	6.1 ± 2.2 (*n*=51)	
Day 30	7.0 ± 3.0 (*n*=51)	6.8 ± 2.7 (*n*=50)	<0.01
Day 90	6.8 ± 3.0 (*n*=48)	7.5 ± 3.1 (*n*=51)	<0.0001
Day 180	7.5 ± 3.4 (*n*=42)	7.2 ± 2.7 (*n*=49)	<0.01
Day 360	7.2 ± 2.6 (*n*=42)	7.4 ± 2.6 (*n*=45)	<0.0001
Residual volume (mL)			
Day 0	49.9 ± 32.3 (*n*=59)	43.8 ± 26.1 (*n*=62)	
Day 30	35.4 ± 31.1 (*n*=59)	37.7 ± 25.8 (*n*=60)	<0.0001
Day 90	41.6 ± 41.2 (*n*=58)	40.0 ± 44.1 (*n*=62)	>0.05
Day 180	39.1 ± 36.0 (*n*=56)	36.9 ± 41.0 (*n*=61)	<0.01
Day 360	37.5 ± 42.4 (*n*=48)	41.1 ± 47.5 (*n*=49)	<0.05

evolution was noted in blood and urine analyses in both groups during the whole study. A statistical significant ($p<0.05$) but clinically nonsignificant increase was measured in the PSA level in both groups after 6 months of treatment up to the end of the study without any difference between the two dosage forms.

DISCUSSION

The results of this study largely corroborate those previously obtained in randomized double-blind placebo-controlled (Champault *et al*., 1984; Cukier *et al*., 1985; Braeckman *et al*., submitted), reference-controlled (Carraro *et al*., 1996) and open trials (Romics *et al*., 1993; Braeckman, 1994; Braeckman *et al*., 1997) showing that the extract of *Serenoa repens* is an effective and well-tolerated drug for the treatment of the mictional troubles related to BPH. All the efficacy parameters (I-PSS, prostatic volume, flow rates, residual urinary volume and quality of life score) were significantly improved from administration day 30 (day 90 in the case of prostatic volume) up to the end of the treatment in both groups. The two groups, treated either with 160 mg b.i.d. or 320 mg o.d., developed in a similar way and did not show any significant difference. Although a therapeutic equivalence trial cannot be directly compared with a reference-controlled trial, it appears that the amplitude of improvement of efficacy parameters after 6 months of treatment in the present study are relatively comparable to that obtained during a 6 month treatment with the hexane extract of *Serenoa repens* (Permixon®) (Carraro *et al*., 1996). The IPSS decreased by 52% against 38%, the maximum flow rate increased by 17% against 25%, the mean flow rate increased by 18% against 15% and the prostate volume decreased by 13% against 6%, respectively in the present study and in the study of Carraro *et al*. (1996). As the present study was continued during 6 supplementary months it confirms that the improvement was maintained and even amplified. A large majority of patients reported benefit from the therapy on subjective evaluations, and this was corroborated by the evaluations of the doctors administering the treatment. In comparison with other available medications, the two main advantages of the extract of *Serenoa repens* are its rapidity of action (30 days) and its very safe profile.

We conclude that the extract of *Serenoa repens* in its two dosage forms, 160 mg administered twice daily and 320 mg

Table 3. Evolution of the quality of life score as a function of time and treatment

Quality of life (% patients)	Day 0		Day 30		Day 90		Day 180		Day 270		Day 360	
	320 mg	160 mg	320 mg	160 mg	320 mg	160 mg	320 mg	160 mg	320 mg	160 mg	320 mg	160 mg
Delighted	0	0	2	0	2	5	4	6	10	9	10	17
Happy	1	3	16	24	27	29	48	37	42	41	55	44
Satisfied	15	12	37	27	49	45	33	42	38	30	23	22
Mitigated	25	16	32	33	15	12	11	10	8	13	12	11
Unsatisfied	48	59	13	11	7	9	4	3	2	7	0	6
Unhappy	11	10	0	5	0	0	0	0	0	0	0	0
Hopeless	0	0	0	0	0	0	0	2	0	0	0	0

Table 4. Global evaluation of the efficacy and safety by the patient and by the investigator as a function of time and treatment

	Day 30		Day 90		Day 180		Day 270		Day 360	
	320 mg	160 mg	320 mg	160 mg	320 mg	160 mg	320 mg	160 mg	320 mg	160 mg
Efficacy evaluated by the investigator (%)										
Deterioration	3	5	7	3	2	3	2	4	4	2
Status quo	40	36	35	24	30	29	31	36	8	23
Slight improvement	43	48	43	57	48	49	46	42	61	41
Great improvement	14	11	15	16	20	19	21	18	27	34
Efficacy evaluated by the patient (%)										
Deterioration	0	3	5	3	2	2	0	7	0	4
Status quo	24	18	10	15	30	22	19	18	14	21
Slight improvement	53	51	57	45	31	33	46	42	40	34
Great improvement	23	28	28	37	37	43	35	33	46	41
Tolerance evaluated by the investigator (%)										
Bad	1	1	0	0	0	0	0	0	0	0
Medium	2	2	0	1	2	0	4	0	0	0
Good	11	7	7	3	5	6	6	7	15	9
Excellent	86	90	93	95	93	94	90	93	85	91
Tolerance evaluated by the patient (%)										
Bad	3	0	1	0	0	0	0	0	0	0
Medium	0	3	0	2	2	0	4	0	0	0
Good	13	6	7	3	11	6	6	7	15	9
Excellent	84	91	92	95	87	94	90	93	85	91

Table 5. Side effects

Type of side effect	*Serenoa repens* 320 mg o.d. (n=65)	*Serenoa repens* 160 mg b.i.d. (n=67)
Gastralgia	2	2 (1 Stop the treatment)
Infarctus	1	0
Dysuria	1	0
Bad breath	1	0
Headache	1	0
Nausea	1 (Stop the treatment)	0
Pulmonary disease	1 (Stop the treatment)	0
Allergy to chrome	1	0
Blood in sperm	1	0
Impotence	0	1
Haemorrhoids	0	1
Abdominal aneurism	0	1
Polyp ablation	0	1
Hernia	0	1
Hyperuricaemia	0	1
Residual volume >250 mL	0	1 (Stop the treatment)

administered once daily, is a safe and effective treatment for the mictional problems associated with BPH. Consequently, it appears to offer a potential pharmacologic alternative capable of improving BPH symptoms in patients with mild-to-moderate disease.

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REFERENCES

Braeckman, J. (1994). The extract of *Serenoa repens* in the treatment of benign prostatic hyperplasia: a multicenter open study. *Curr. Ther. Res.* **55**, 776–785.

Braeckman, J., Bruhwyler, J., Brichard, B., and Géczy, J. (1997). Efficacy and safety of the extract of *Serenoa repens* in the treatment of benign prostatic hyperplasia: an open multicentre study. *Eur. J. Clin. Res.* **9**, 1–11.

Braeckman, J., Denis, L., de Leval, J. *et al.* (in press). A double-blind, placebo-controlled study of the plant extract *Serenoa repens* in the treatment of benign hyperplasia of the prostate. *Eur. J. Clin. Res.*

Breu, W., Hagenlocher, M., Redl, K., Tittel, G., Stadler, F., and Wagner, H. (1992). Antiphlogistische Wirkung eines mit hyperkritischem Kohlendioxid gewonnenen Sabalfrucht-Extraktes. *Arzneimittelforsch./Drug Res.* **42**, 547–551.

Bruhwyler, J. (1994). Prostaserene. Purified extract of *Serenoa repens.* Treatment for BPH. *Drugs of the Future* **19**, 452–453.

Carraro, J. C., Raynaud, J. P., Koch, G. *et al.* (1996). Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1098 patients. *The Prostate* **29**, 231–240.

Champault, G., Patel, J. C., and Bonnard, A. M. (1984). A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia. *Br. J. Clin. Pharmacol.* **18**, 461–462.

Cukier, P. R., Ducassou, P., and Le Guillou, P. (1985). Permixon versus placebo. Résultats d'une étude multicentrique.

Comptes Rendus de Thérapeutique et de Pharmacologie Clinique **4**, 15–21.

Denis, L. J. (1993). Quantification and incidence of benign prostatic hyperplasia. *Drugs of Today* **29**, 328–333.

Di Silverio, F., D'Eramo, G., Lubrano, C. *et al.* (1992). Evidence that *Serenoa repens* extract displays an antiestrogenic activity in prostatic tissue of benign prostatic hypertrophy patients. *Eur. Urol.* **21**, 309–314.

Gutiérrez, M., Hidalgo, A., and Cantabrana, B. (1996). Spasmolytic activity of a lipidic extract from *Sabal serrulata* fruits: further study of the mechanisms underlying this activity. *Planta Med.* **62**, 507–511.

Lepor, H., and Rigaud, G. (1990). The efficacy of transurethral resection of the prostate in men with moderate symptoms of prostatism. *J. Urol.* **143**, 533–537.

Lowe, F. C., and Ku, J. C. (1996). Phytotherapy in treatment of benign prostatic hyperplasia: a critical review. *Urology* **48**, 12–20.

Mebust, W. K., Holtgrewe, H. L., Cockett, A. T. K.., Peters, P. C. and the Writing Committee (1989). Transurethral prostatectomy: Immediate and post operative complications. A cooperative study of 13 participating institutions evaluating 3885 patients. *J. Urol.* **141**, 243–247.

Odenthal, K. P. (1996). Phytotherapy of benign prostatic hyperplasia (BPH) with *Cucurbita, Hypoxis, Pygeum, Urtica* and *Sabal serrulata* (*Serenoa repens*). *Phytother. Res.* **10**, S141–S143.

Otto, U., Wagner, B., and Becker, H. (1992). Transplantation of human benign hyperplastic prostate tissue into nude mice: first results of systemic therapy. *Urol. Int.* **48**, 167–170.

Romics, I., Schmitz, H., and Frang, D. (1993). Experience in treating benign prostatic hypertrophy with *Sabal serrulata* for one year. *Int. Urol. Nephrol.* **25**, 565–569.

Rotkin, I. D. (1975). Epidemiology of benign prostatic hypertrophy: review and speculations. In, *Benign Prostatic Hyperplasia* ed. by T. Grayhack, D. Wilson and M. Sherkenske, pp. 105–116. DHEW Publication No. NIH 76-1113, NIH, New York.

Tarayre, J. P., Delhon, A., Lauressergues, H., and Stenger, A. (1983). Action anti-oedémateuse d'un extrait hexanique de drupes de *Serenoa repens. Ann. Pharm. Fr.* **41**, 559–570.

Walsh, P. C. (1979). Benign prostatic hyperplasia. In, *Campbell's Urology.* 4th edn, ed. by J. H. Harrison *et al.*, pp. 949–966. W. B. Saunders, Philadelphia.

Weisser, H., Tunn, S., Behnke, B., and Krieg, M. (1996). Effects of the *Sabal serrulata* extract IDS 89 and its subfractions on 5 alpha-reductase activity in human benign prostatic hyperplasia. *The Prostate* **28**, 300–306.

