Long-Term Clinical and Biologic Effects of the Lipidosterolic Extract of *Serenoa repens* in Patients With Symptomatic Benign Prostatic Hyperplasia

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ABSTRACT

Permixon®, the lipidosterolic extract of *Serenoa repens*, is widely used for the treatment of symptoms associated with benign prostatic hyperplasia (BPH). This open study assessed the efficacy and tolerability of Permixon 160 mg twice daily administered for 2 years. One hundred fifty-five men with clinically diagnosed BPH and complaints of prostatic symptoms were enrolled in the study. At 6, 12, 18, and 24 months, the International Prostate Symptom Score (I-PSS), quality of life, and sexual function score were recorded, and urodynamics and biologic values were measured. Adverse events were recorded every 3 months. I-PSS and quality of life improved significantly from baseline at each evaluation time point. At the end of the study and at each evaluation, maximum urinary flow also improved significantly. Prostate size decreased. Sexual function remained stable during the first year of treatment and significantly improved ($P = .001$) during

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the second year. Prostate-specific antigen was not affected, and no changes in plasma hormone levels were observed. Nine patients reported 10 adverse events, none related to treatment. Improvements in efficacy parameters began at 6 months and were maintained up to 24 months. These data demonstrate the long-term efficacy and tolerability of Permixon and support its use as a first-line medical therapy for uncomplicated symptomatic BPH.

Keywords: benign prostatic hyperplasia; *Serenoa repens*; lower urinary tract symptoms; phytotherapy

INTRODUCTION

The prevalence and incidence of benign prostatic hyperplasia (BPH) increase progressively with age, reaching 50% by age 50; by age 90, approximately 90% of men have histologic lesions. About half of affected men eventually experience macroscopic enlargement of the gland that in approximately 50% progresses to clinically symptomatic prostatism requiring treatment.[1]

Treatment with 5-alpha-reductase inhibitors or alpha-adrenergic-receptor blockers relieves symptoms or helps to postpone surgery,[2-4] although both classes induce undesirable side effects, including deterioration of sexual function and postural hypotension.[4-7]

Plant extracts afford symptomatic relief in BPH and are well tolerated.[8-10] The most extensively investigated extract of *Serenoa repens*, a widely used phytotherapeutic agent for the treatment of BPH, is a lipidosterolic extract (Permixon®*) available in more than 60 countries.

In addition to antiproliferative activity,[11] noncompetitive inhibition of 5-alpha-reductase types 1 and 2[12,13] and inflammatory mediators has been demonstrated for Permixon.

A recent meta-analysis[14] of clinical studies has demonstrated the superior efficacy of Permixon to placebo. In comparative studies, Permixon was equivalent to the 5-alpha-reductase inhibitor finasteride[6] and to the most commonly used alpha blocker, tamsulosin.[15] For uncomplicated BPH, Permixon was described as a first-line treatment, alleviating symptoms without causing sexual or cardiovascular dysfunction.[16] Up to now, however, no clinical trial had assessed its efficacy and safety beyond 12 months. The present study was designed to extend those evaluations to 24 months.

PATIENTS AND METHODS

Design

The primary objective of this open, three-center trial was to assess the long-term clinical efficacy and clinical and biologic safety of Permixon over 2 years.

This study was carried out in accordance with the provisions of the Declaration of Helsinki and good clinical practice guidelines. The protocol was approved by local ethics committees, and all patients gave their informed consent to participate.

*Trademark of Pierre Fabre Medicament, France.

Study visits occurred every 3 months to ensure close follow-up of patients and good compliance with Permixon, which was administered as one 160-mg capsule in the morning and one in the evening for 24 months following a 1-month run-in during which patients received an identically appearing placebo.

Patients

Eligible patients met the following criteria: age at least 50 years, symptomatic BPH for more than 6 months, International Prostate Symptom Score (I-PSS) greater than 6, maximum urinary flow rate (Q_{max}) between 5 and 15 mL/s, voided volume between 150 and 400 mL, postvoiding residual urine less than 150 mL, prostate volume exceeding 25 cm^3 on transrectal or abdominal ultrasonography, or both, and a prostate-specific antigen (PSA) level less than 4 ng/mL.

Reasons for exclusion were any history of bladder-neck or prostate surgery, prostate or bladder cancer, recurrent urinary tract infections, and use of a drug likely to alter the voiding pattern within the 3 months preceding entry in the study.

Assessments

Efficacy assessment was based on the evolution from baseline of BPH symptoms and quality of life. The severity of the symptoms was quantified by means of the Russian translation of the I-PSS.[17] The primary efficacy outcome was the absolute change from baseline in the I-PSS total score every 6 months. The impact of symptoms was assessed every 6 months by the quality-of-life question of the I-PSS. Urinary flow rates were determined by uroflowmetry before treatment at visit 0 and at visits 6, 12, 18, and 24. Postvoid residual urine was evaluated after each urodynamic measurement by suprapubic ultrasonography. Prostate volume was measured at each center by transrectal ultrasonography through the prolate spheroid method.[18]

Biologic and clinical safety was determined from all adverse events recorded during the study and from a validated questionnaire on male sexual function (MSF-4) completed by the patient.[19]

All serious or nonserious adverse events were reported, whether or not they were considered drug-related, including events possibly associated with an underlying condition. Adverse events were recorded every 3 months and classified by organ system and preferred term as defined by the World Health Organization Adverse Reaction Terminology Convention. Heart rate and blood pressure were also measured. Biologic safety was assessed by means of the following tests performed at baseline and every 6 months thereafter: routine blood and chemistry values, plasma PSA and hormones (testosterone, dihydrotestosterone, alpha-4-androstenedione, 3-alpha-5-alpha-androstanediol, androstanediol-glucuronide, estradiol, DHEA, DHEA-sulfate, TeBG, luteinizing hormone).

Statistical Analysis

The statistical significance level for two-sided tests was alpha = .05. Within-group analyses were performed as follows: quantitative variables—Wilcoxon or Student's paired tests by distribution, with the coherence of the response verified by the correlation test; qualitative variables—MacNemar's test of difference (post–pretreatment) or χ^2 paired test, with the coherence of the response verified.

RESULTS

Patients

Of the 155 patients who entered the study, 14 left before the last visit (3, insufficient response; 9, patient's decision; 1, adverse reaction; 1, lost to follow-up). Twenty-five patients (16%) were excluded from the per-protocol (PP) population for an absence of efficacy data (1 patient), a prostate volume smaller than 25 cm^3 (11 patients), a Q_{max} less than 5 or more than 15 mL/s (14), and a voided volume less than 120 or more than 500 mL (6).

One of these 25 patients had already been excluded from the intention-to-treat (ITT) population because of a failure to evaluate the main efficacy outcome.

Baseline Characteristics

The patients were white and ranged in age from 52 to 87 years (mean, 65.3 years). Most (71%) were nonsmokers, and only 6.5% were heavy smokers. Alcohol consumption was light in 61.9% of patients and nonexistent in 27.7%.

The mean I-PSS on inclusion was 12.8 (± 3.8), with a quality-of-life score of 3.2 (± 1.1). Other mean values were Q_{max} 11.8 mL/s (± 5.3), mean urinary flow 5.8 mL/s (± 2.4), prostate size 39.7 cm^3 (± 16.8), total PSA 2.5 ng/mL (± 1.6), MSF-4 9.6 (± 5.3). Blood pressure was 136.1 (± 13.4)/81.8 (± 7.8) mm Hg, and heart rate was 72.8 (± 6.6) beats per minute.

Efficacy

The I-PSS, the main efficacy criterion, was 12.8 ± 3.8 at baseline (n = 154) and 12.9 ± 3.9 at study end (n = 141) in the ITT population. Values were similar in the PP population.

The I-PSS decreased progressively over the 24 months of treatment. A statistically significant improvement was evident from the first evaluation at 6 months (P = .001) and was maintained and bettered up to 24 months (P = .001) (Table). The absolute changes corresponded to percent decreases of 31% at 6 months, 38.6% at 12 months, 40.6% at 18 months, and 41.4% at 24 months.

Those improvements are reflected in the classification of symptoms as "mild," "moderate," or "severe" (Fig 1). Indeed, half of the patients with moderate BPH symptomatology at enrollment described their symptoms as mild from month 12 of treatment. Most patients with scores in the severe range at baseline had moderate symptoms as early as the end of month 6. The percentage of patients with moderately symptomatic BPH decreased progressively during the first year of treatment and remained unchanged until the end of the trial. A concomitant increase was noted in the percentage of patients with mild symptoms.

From the sixth month, 46% to 69% of patients recorded improvements in obstructive and irritative symptoms (Fig 2).

Relative to baseline, a statistically significant improvement in quality of life was observed at 6 months (P<.001) and was maintained throughout the 2-year trial (see Table). The absolute changes corresponded to percent decreases of 24.6% at 6 months, 33.1% at 12 months, 36.2% at 18 months, and 40.2% at 24 months.

Fig 1. I-PSS for severity of BPH symptoms at each visit in the ITT efficacy population (n = 154).

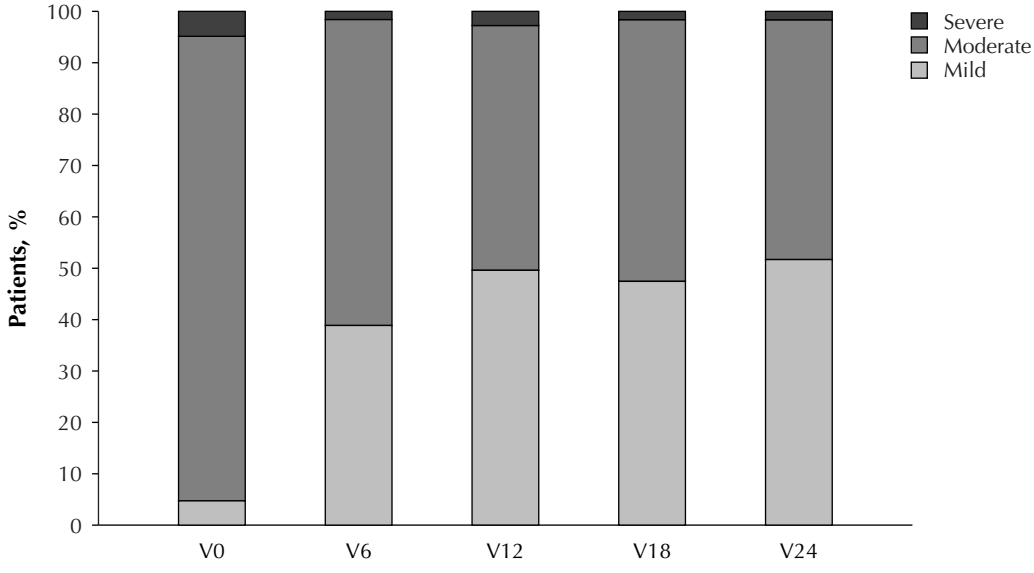
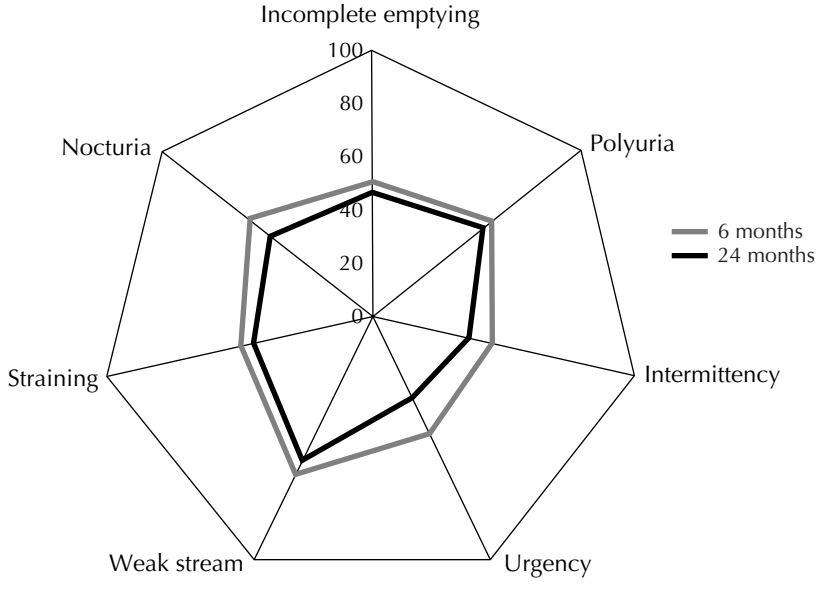


Fig 2. Percentage of patients with improvement on each I-PSS item in the ITT efficacy population (n = 154).



Mean Changes (±SD) in Health Outcomes and Biologic Measures at Each Evaluation Time—(ITT Efficacy Population)

	V0	V6		V12		V18		V24	
		Mean	Mean Change	Mean	Mean Change	Mean	Mean Change	Mean	Mean Change
I-PSS	12.83 (3.82)	8.85 (4.22)	–3.98 (3.62)	7.93 (4.46)	–4.98 (3.88)	7.65 (3.98)	–5.24 (4.0)	7.53 (4.5)	–5.33 (4.53)
Quality of life	3.25 (1.12)	2.45 (1.13)	–0.8 (0.97)	2.2 (1.04)	–1.09 (1.11)	2.10 (0.91)	–1.19 (0.96)	1.95 (0.82)	–1.31 (1.05)
Q_{max}, mL/s	11.75 (5.28)	15.82 (10.12)	4.08 (10.97)	15.06 (12.26)	3.22 (11.7)	12.76 (6.89)	0.94 (8.71)	12.99 (8.80)	1.13 (10.3)
Voided volume, mL	235.6 (77.0)	276.9 (120.7)	41.31 (132.1)	250.0 (107.3)	16.72 (129.0)	253.1 (122.3)	17.98 (141.3)	225.0 (93.4)	–11.7 (118.7)
Prostate size, cc	39.74 (16.82)	34.06 (14.84)	–5.68 (12.42)	33.47 (14.63)	–6.44 (13.68)	34.30 (15.60)	–6.06 (15.07)	34.47 (15.09)	–5.89 (14.96)
PSA, ng/mL	2.47 (1.56)	2.56 (1.93)	0.09 (1.65)	2.62 (1.79)	0.18 (1.47)	2.53 (1.62)	0.10 (1.41)	2.57 (2.33)	0.17 (2.18)
MSF-4*	9.64 (5.3)	9.35 (5.3)	–0.29 (1.9)	9.52 (5.3)	–0.35 (2.4)	8.71 (5.5)	–1.03 (3.4)	8.56 (5.5)	–1.21 (3.7)

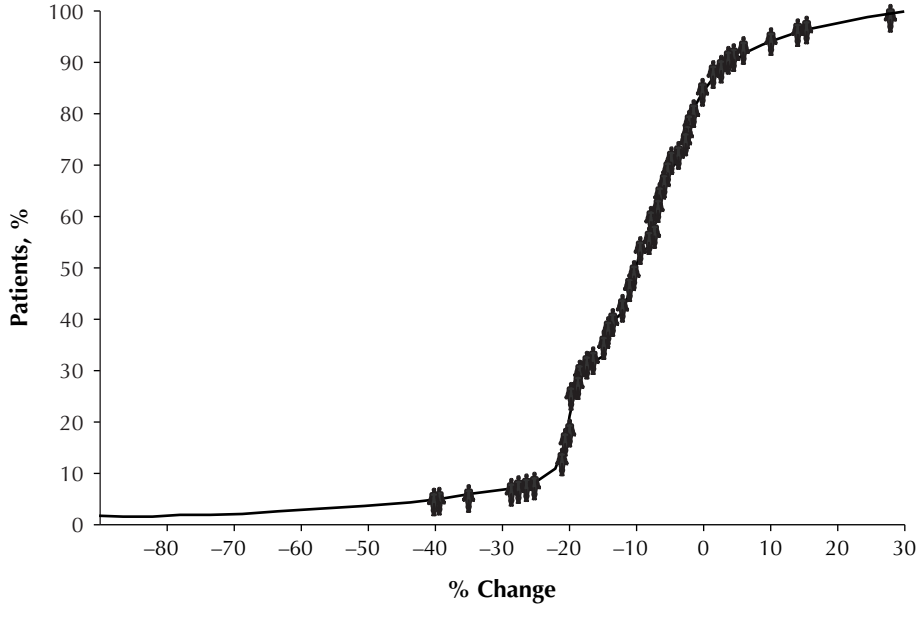
*n = 153; all others, n = 154.

Urodynamic results showed a significant improvement in Q_{max} at each assessment time compared with baseline. After a mean increase exceeding 3 mL/s during the first year of treatment, values remained higher than baseline until the end of the study. The absolute changes at the four evaluation timepoints corresponded to percent increases of 34.7%, 27.2%, 7.9%, and 9.5% (see Table). In the PP population, the observed change from baseline was 2.32 mL/s at 18 months and 2.8 mL/s at 24 months, compared with 0.9 mL/s and 1.1 mL/s in the ITT population.

After patients with aberrant values were excluded from the analysis, a statistically significant ($P = 0.006$) but clinically irrelevant increase in the voiding volume was seen at 6 months (see Table).

Prostate volume decreased by 14.6% after 6 months of treatment, and this reduction was maintained throughout the study (see Table). As demonstrated by the cumulative response curve, 80% of the patients experienced a decrease in prostate volume (Fig 3).

Fig 3. Change in prostate volume between visit 0 and visit 24 in the ITT efficacy population (n = 154).



Safety

The mean plasma level of PSA did not change significantly from baseline (see Table). In contrast, the MSF-4 score decreased progressively, corresponding to an improved sex life, throughout the 2-year trial. The changes were statistically significant at 18 and 24 months ($P<.001$).

Ten treatment-emergent events (appeared or worsened during the trial) were reported by nine patients (5.8% of the overall population). The most frequently cited adverse events were cardiovascular disorders (4/10). No specific adverse events were ascribed to Permixon.

Three adverse events/intercurrent illnesses/serious adverse events in three patients led to treatment discontinuation, but only one patient dropped out of the study. No deaths occurred during the trial.

Plasma hormone levels (testosterone, dihydrotestosterone, estradiol, luteinizing hormone, androstendione, E2) and vital signs remained unchanged. No clinically relevant changes from baseline in hematologic or biochemical values were observed at any timepoint.

DISCUSSION

This study assessed the long-term efficacy and tolerability of Permixon 160 mg twice daily in men suffering from lower urinary tract symptoms commonly associated with BPH. The patients' clinical and demographic characteristics were comparable to those in several clinical trials of BPH medications.[5,20-22]

Permixon relieved BPH symptoms, as shown by the progressive and sustained improvement in the main efficacy criterion, the I-PSS. From month 6 on, 46% to 69% of patients recorded improvements in most I-PSS items. Quality of life also improved significantly ($P<.001$), starting at 6 months and continuing throughout the 2-year trial. Between months 6 and 24, the percentage of patients who believed their quality of life had improved rose from 58.4% to 77.3%.

The I-PSS of 12.8 at baseline was slightly lower than that in recent clinical trials and reflects our inclusion score of more than 6, which resulted in only 4% of patients with severe BPH symptoms (I-PSS >19). The magnitude of I-PSS change during therapy is related to the baseline score: the higher the initial score, the greater the decrease.[23] The five-point decrease in this study is in line with the decreases in comparison studies of Permixon with finasteride (–6.0 points, from a baseline I-PSS of 15.9)[6] and with tamsulosin (–4.4 points, from a baseline I-PSS of 15.5).[16] In the present study, the 1-month run-in was used to differentiate as much as possible the well-known placebo effect usually observed in the medical treatment of BPH. The placebo effect is known to decrease as a function of time.[24] In our study, the beneficial changes observed with Permixon were maintained and even increased after 2 years of treatment.

The marked increase in Q_{max} during the early phase of treatment was moderated slightly during the second year of the trial. Again, the placebo effect was less dominant in this second phase, indicating that Permixon provided a clinically relevant benefit over at least 2 years and that the absence of a placebo arm did not jeopardize the evidence of a clinical response.

The absence of any effect of Permixon on the PSA level points to a lack of interference with the detection of prostate cancer that is consistent with early results[6,16,25] and has little or no effect on other androgen-dependent processes that rely on the binding of androgens to their receptor.[13]

In previous trials, prostate size decreased from 2%[16] to 7%[6] with Permixon. Our study noted a reduction in 80% of the patients.

A significant improvement of one point in quality of life ($P<.001$) and of one point in MSF-4 (measures sexual activity) was observed. Compared with finasteride,[6] with which sexual dysfunction is common, or with tamsulosin,[16] which induces ejaculation disorders, Permixon offers a marked advantage in sexual tolerability. Moreover, no changes were observed in plasma androgen levels.

In this study, Permixon had an excellent safety profile. Only four patients experienced serious adverse events, none related to treatment and none requiring its discontinuation. Of the 10 treatment-emergent adverse events reported, only 1 prompted discontinuation of Permixon. No clinically relevant changes from baseline occurred in hematologic or biochemical values. In a recent 3-year study of tamsulosin,[26] 76% of patients had at least one side effect, 26% of which were possibly or probably drug-related.

CONCLUSIONS

This long-term open study in BPH patients confirms that Permixon 160 mg twice daily for 2 years has a good clinical and biologic safety profile, does not interfere with plasma PSA concentrations, and has no effect on androgens. The sexual function score improved from baseline. By decreasing prostate volume, Permixon slows the natural progression of BPH.

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