P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

HerbClip™

File: ■ Saw Palmetto (*Serenoa repens*, Arecaceae)
■ Permixon®
■ Inflammation
■ Benign Prostatic Hyperplasia

HC 121553-546

Date: June 15, 2016

RE: Saw Palmetto Extract (Permixon®) Shows Anti-inflammatory Activity in Men with Benign Prostatic Hyperplasia for First Time in Clinical Trial

Latil A, Pétrissans M-T, Rouquet J, Robert G, de la Taille A. Effects of hexanic extract of *Serenoa repens* (Permixon® 160 mg) on inflammation biomarkers in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. *Prostate*. 2015;75(16):1857-1867.

Chronic prostatic inflammation (CPI) is a precursor to benign prostatic hyperplasia (BPH). CPI is characterized by nodules in the prostate that release mediators of inflammation and stimulate growth of the prostate. This ultimately leads to bladder outlet obstruction and the lower urinary tract symptoms (LUTS) associated with BPH. Permixon® (Pierre Fabre Médicament; Boulogne-Billancourt, France) is a hexanic extract of saw palmetto (*Serenoa repens*, Arecaceae) berries. In vitro and in vivo studies indicate that Permixon can modulate expression of several inflammation-related genes. Hence, the purpose of this randomized, double-blind, parallel-group, multicenter study was to evaluate the effect of Permixon on CPI biomarkers in men with BPH-related LUTS. The secondary objective was to evaluate the clinical efficacy of Permixon.

Men (n = 206, aged 45-85 years) with BPH-related LUTS for > 12 months participated in this study conducted at 36 centers in Spain, Portugal, Italy, and France. Inclusion criteria were as follows: International Prostate Symptom Score (I-PSS) ≥ 12; prostatic volume ≥ 30 cm^3 determined by transrectal ultrasound; maximum flow rate (Qmax) 5-15 mL/s for a voided volume 150-500 mL; total prostate-specific antigen (PSA) ≤ 4 ng/mL or ≤ 10 ng/mL with ratio PSA (free)/PSA (total) ≥ 25% or negative prostate biopsy; not taking anti-androgens or luteinizing hormone-releasing hormone (LH-RH) analog for ≥ 6 months; not taking 5-alpha-reductase inhibitors or plant extracts for ≥ 3 months; and not taking alpha-blockers or alpha/beta blockers for ≥ 1 month before screening. Patients taking the following oral medications at screening required a 2-week washout, and the medications were prohibited for the duration of the study: phosphodiesterase-5 inhibitors for BPH treatment, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antibiotics by systemic route, mepartricine, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, beta-blockers, diuretics, sympathomimetics,

antihistamines, antidepressants (anticholinergic), atropine, antispasmodic drugs, antiparkinsonism drugs, pseudoephedrine, chlorpheniramine, or spironolactone (if unstable dose or initiated ≤ 6 weeks prior to participation). Patients were excluded if they had a post-void residual urine volume (PVR) > 200 mL (by suprapubic ultrasound); previous urological history including urethral stricture disease and/or bladder neck disease; active, recent (< 3 months), or recurrent urinary tract infection; urinary retention; need for BPH surgery; stone in bladder or urethra; acute or chronic prostatitis; prostate or bladder cancer; interstitial cystitis; symptomatic active upper tract; surgery of the prostate, bladder neck, or pelvic region; any local and/or systemic inflammation disorders; orthostatic hypotension; any neurologic or psychiatric disease/disorder interfering with the detrusor or sphincter muscle; insulin-dependent diabetes mellitus; non-controlled non-insulin-dependent diabetes mellitus; chronic renal insufficiency; or history of severe hepatic failure or other severe underlying disease.

Following a 28- to 42-day washout, patients received either 320 mg/day Permixon or 0.4 mg/day tamsulosin LP for 90 days. Tamsulosin is a typical pharmaceutical treatment for BPH symptoms. Urine was collected, and messenger RNA (mRNA) was extracted from prostatic epithelial cells for quantification of 29 BPH inflammation biomarkers. Efficacy was evaluated with the following assessments: I-PSS, quality of life (QoL), sexual function (MSF-4), Qmax (uroflowmetry), PVR (suprapubic ultrasound), and prostate volume (transrectal ultrasound). Evaluations occurred at baseline, month 1, and month 3.

Both groups had similar demographics and baseline characteristics. Baseline LUTS were moderate to severe. At baseline, expression of 26 of the 29 genes (BPH inflammation biomarkers) was detected. At study end, mRNA expression decreased in 65.4% (17/26) of the markers in the Permixon group and 46.2% (12/26) of the tamsulosin group. Seven of the genes had decreased mRNA expression in both groups. When evaluating only the most frequently expressed markers (n = 15 genes), mRNA expression decreased in 80% (12/15) of the markers in the Permixon group and 33% (5/15) of the tamsulosin group. Also, when expression was upregulated, the Permixon group had fewer patients with upregulation compared with the tamsulosin group. Overall, Permixon had a more favorable effect on 73.3% of markers, while tamsulosin had a more favorable effect on 26.6% of markers. However, only 2 biomarkers were statistically significantly more favorable for Permixon ($P < 0.05$).

Three proteins (MCP-1/CCL2, IP-10/CXCL10, and MIF) were detected in the urine and evaluated over time. Protein expression decreased over time in the Permixon group and remained stable in the tamsulosin group. In particular, in the Permixon group, a higher percentage of patients had a downregulation of protein expression, and a lower percentage of patients had an upregulation of protein expression compared with the tamsulosin group.

At study end, both groups had improvement in I-PSS, QoL, Qmax, and prostate volume, and there was no statistical difference between groups. There was no association between mRNA expression, MCP-1/CCL2, or IP-10/CXCL10 and clinical outcomes. Patients in the Permixon group who overexpressed MIF protein had a greater improvement in I-PSS.

The frequency of adverse events (AEs) was similar between groups. In the Permixon group, 10.8% of patients had ≥ 1 treatment-emergent AE. The specific AEs were not

reported. A total of 7.8% of Permixon-treated patients and 3.0% of tamsulosin-treated patients had ≥ 1 AE leading to study discontinuation. AEs leading to discontinuation in the Permixon group were the following moderate AEs: palpitation, rash, dizziness, persistent tiredness, abdominal pain, dry mouth, insomnia, nightmare, joint swelling, and diarrhea; and the following mild AEs: stuffy nose, erectile dysfunction, groin pain, and hypertension. AEs leading to discontinuation in the tamsulosin group were moderate gynecomastia, moderate weight loss, mild epigastric pain, and mild anejaculation.

The authors conclude that although there was no significant difference between treatments, there was a trend in favor of Permixon in regard to the anti-inflammatory activity. The authors hypothesize that there was no relationship between mRNA expression and clinical outcomes because of both the high variability of gene expression at baseline and the population size. The authors conclude that this is the first study to show in humans that Permixon has anti-inflammatory activity in men with BPH-related LUTS. They hypothesize that Permixon may be useful as an early treatment to prevent the development of BPH in patients with CPI. This study had rigorous methodology, and the positive control group was a viable option to using placebo. The manufacturer of Permixon participated in the statistical analysis. Three of the authors (A. Latil, M-T Pétrissans, and J. Rouquet) are employed by Institut de Recherche Pierre Fabre (Toulouse, France).

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to include the original article.