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ADIS DRUG EVALUATION

Hexanic Extract of *Serenoa repens* (Permixon®): A Review in Symptomatic Benign Prostatic Hyperplasia

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Abstract

The hexanic extract (HE) of *Serenoa repens* (Permixon®) is indicated for the symptomatic treatment of benign prostatic hyperplasia (BPH). The drug is the n-hexane lipidosterolic extract of the American dwarf palm tree (also known as saw palmetto). The anti-inflammatory activity of HE *S. repens* has been demonstrated in vitro, in vivo and in men with prostatic inflammation. In randomized clinical trials, the efficacy of HE *S. repens* was similar to that of an α-blocker in terms of improving voiding and storage symptoms, increasing urinary flow rate and reducing prostate volume in men with BPH. HE *S. repens* was also as effective as 5α-reductase inhibitors and/or α-blockers at improving lower urinary tract symptoms (LUTS) and quality of life (QOL) in real-world observational studies. HE *S. repens* was generally well tolerated, with a lesser impact on male sexual function compared with other available therapies. Thus, HE *S. repens* is a useful option for the treatment of symptomatic BPH.

Plain Language Summary

BPH (enlargement of the prostate gland) compresses the urethra, leading to uncomfortable LUTS such as difficulty starting a urine stream, weak flow, incomplete bladder emptying, frequent urination, urgency, and waking at night to urinate. To avoid side effects often associated with other available treatments such as 5α-reductase inhibitors and α-blockers, plant extracts like HE *Serenoa repens* (Permixon®) are commonly used to treat the symptoms of BPH. HE *S. repens* is derived from a small palm tree native to America and has been shown to have anti-inflammatory effects in prostate inflammation. In clinical studies, HE *S. repens* was as effective as an α-blocker at improving urinary symptoms, increasing urinary flow rate and reducing prostate volume in men with BPH. In real-world studies, HE *S. repens* was as effective as 5α-reductase inhibitors and/or α-blockers at improving LUTS and QOL. European guidelines recommend HE *S. repens* as a treatment option for men with LUTS who want to avoid any potential side effects, especially those related to sexual function. HE *S. repens* was generally well tolerated, and is a useful option for the treatment of symptomatic BPH.

HE *S. repens*: clinical considerations in symptomatic BPH

- Hexanic lipidosterolic extract of the American dwarf palm tree with anti-inflammatory activity demonstrated in vitro, in vivo and in men with prostatic inflammation
- The only *S. repens* extract that is approved for use under EMA well-established use criteria
- Similar efficacy to 5α-reductase inhibitors and/or α-blockers in treating LUTS associated with BPH
- Recommended by European guidelines as a treatment option for men with LUTS who want to avoid any potential adverse events, especially those related to sexual function

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1 Introduction

Benign prostatic hyperplasia (BPH) is characterized by proliferation of stromal and epithelial cells in the prostate transition zone, leading to enlargement of the prostate gland [1]. This results in compression of the urethra, and is a common cause of lower urinary tract symptoms (LUTS) in men [1]. The pathogenesis of BPH is not completely understood but is likely to be multifactorial [2]. A persistent prostatic inflammatory status (PIS), also called chronic prostatic inflammation (CPI), has been shown to contribute to the development of BPH and increases the risk of (faster) disease progression. Therefore, inflammation is a key target of medical treatment for BPH [2].

LUTS are categorized as voiding symptoms (e.g. weak stream, hesitancy, straining, retention) and storage symptoms (e.g. frequency, urgency, nocturia) [3, 4]; these can lead to significant deterioration in quality of life (QOL) [2]. Available treatments such as 5α-reductase inhibitors and α_1-adrenergic receptor antagonists (α-blockers) are often associated with adverse events (AEs) including sexual dysfunction [4]. Moreover, evidence for a reduction in persistent PIS with 5α-reductase inhibitors and α-blockers is limited [2]. Phytotherapy is widely used in many regions for the treatment of LUTS [4]. Extracts of the American saw palmetto or dwarf palm tree, *Serenoa repens* [5], have been traditionally used for the relief of LUTS associated with BPH [6]. *S. repens* extracts are complex mixtures consisting mainly of free fatty acids [5]. There are three main types of *S. repens* extracts: hexanic, supercritical CO_2 and ethanolic [5, 7], each with differing phytochemical compositions [5].

The hexanic extract (HE) of *S. repens* (Permixon®) contains > 90% free fatty acids (lauric, oelic, myristic and palmitic acids) and 7% esterified fatty acids, while the rest is composed of phytosterols, flavonoids, alcohols and polyprenols [8]. HE *S. repens* was first approved for the treatment of BPH in 1981 [7], and efficacy similar to that of the 5α-reductase inhibitor finasteride was established in early clinical trials [9] (previously reviewed in *Drugs* [10]). HE *S. repens* is the only extract of *S. repens* that is approved for use under EMA well-established use criteria, because of the quality of data available [6]. Other (e.g. ethanolic) extracts have traditional use status [5, 6]. This article summarizes the pharmacological properties of HE *S. repens* and reviews more recent key clinical data relevant to its use in men with symptomatic BPH.

2 Pharmacodynamic Properties of HE *S. repens*

Several mechanisms of action have been proposed to explain the pharmacodynamic effects of HE *S. repens* on human prostatic tissue (Table 1), including anti-inflammatory activity (Sect. 2.1), anti-proliferative activity, and anti-androgenic activity.

2.1 Anti-inflammatory Activity

In vitro and in vivo studies have demonstrated that HE *S. repens* inhibits inflammatory cells and a range of inflammatory mediators and proteins, and was associated with down-regulation of genes that code markers of inflammation (Table 1) [2].

Importantly, HE *S. repens* also showed anti-inflammatory activity in a clinical trial in men with prostatic inflammation histologically confirmed by transrectal ultrasound-guided biopsy [11]. In this study, patients were randomized to receive HE *S. repens* 320 mg/day or no treatment (i.e. control), with biopsies performed at baseline and 6 months. Inflammation was graded according to Irani's scores for histological inflammation (extension of inflammatory cells; scores range from 0 to 3) and aggressiveness (effect of inflammatory cells on prostate tissue; scores range from 0 to 3). Among patients treated with HE *S. repens*, the mean inflammation and aggressiveness grading scores decreased significantly (both $p = 0.001$) from 1.55 for both at the first biopsy to 0.79 and 0.87 at the second biopsy. The mean reduction in inflammation grading (0.75 vs 0.21), aggressiveness grading (0.68 vs 0.20) and total Irani's score (1.43 vs 0.41) was significantly ($p \leq 0.009$) greater in the HE *S. repens* group compared with the control group. Immunohistochemical staining of biopsy samples for prostatic inflammation demonstrated significant ($p < 0.001$) reductions in the expression of antibodies specific for inflammatory cells (CD3, CD4, CD8, CD20 and CD163) after 6 months of treatment with HE *S. repens*, while there were no significant reductions in the expression of these antibodies in the control group [11].

As assessed using biomarkers of CPI, the anti-inflammatory activity of HE *S. repens* was more marked than that of tamsulosin in the exploratory phase IV PERMIN study in men with BPH-related LUTS [12] (Sect. 4.1.2). In this study, mRNA expression of the 29 most significant published BPH inflammation markers was quantified. Expression of each marker was normalized to KLK3, the gene that encodes prostate-specific antigen (PSA). Of the 29 genes investigated, 26 were detected at baseline. At day 90, there was a reduction in mean gene expression for 65% of markers in the HE *S. repens* group compared to 46% of markers in the tamsulosin group. When considering the 15 most commonly expressed genes, mean gene expression decreased for 80% of markers in the HE *S. repens* group and 33% of markers in the tamsulosin group [12].

Table 1 Overview of key pharmacodynamic properties of the hexanic extract of *Serenoa repens*

Anti-inflammatory activity
Inhibits phospholipase A2 activity, phospholipid hydrolysis, arachidonic acid release and prostaglandin E2 synthesis [34]
Inhibits production of 5-lipoxygenase metabolites [35]
Decreases expression of most inflammatory gene transcripts, downregulates phospholipase A2 and lipoxygenase pathways of the arachidonic acid cascade, downregulates expression of 17-β-hydroxysteroid dehydrogenase in vivo [36]
Reduces the number of B lymphocytes, reduces interleukin-1β and tumour necrosis factor-α levels in men with BPH [18]
Downregulates pro-inflammatory marker secretion or gene expression [37–40]
Reduces the number of CD45+ cell clusters and downregulates pro-inflammatory factors in a murine model of prostate hyperplasia [41]
Anti-proliferative and apoptotic activity
Inhibits cell proliferation, induces apoptosis [42, 43]
Increases Bax/Bcl-2 ratio (an apoptotic index), upregulates caspase-3 activity [44]
Anti-androgenic activity
Inhibits activity of both type 1 and type 2 isoforms of 5α-reductase (the enzyme that converts testosterone into DHT) [45, 46], without interfering with prostate-specific antigen expression [46]
Inhibits binding of DHT to cytosolic androgen receptors [10]
Decreases DHT and epidermal growth factor levels and increases testosterone levels ex vivo [47]
Anti-oestrogenic activity
Inhibits nuclear oestrogen receptors in vivo [10]

In vitro effects unless otherwise specified

Bax Bcl-2-associated X protein, *Bcl-2* B-cell lymphoma-2, *DHT* dihydrotestosterone

3 Pharmacokinetic Properties of HE *S. repens*

Because HE *S. repens* is a complex mixture of several compounds (Sect. 1), its pharmacokinetic profile cannot be fully evaluated.

Plasma concentrations of an unspecified component of HE *S. repens* were measured in healthy young male volunteers ($n = 12$) who received a single oral dose of HE *S. repens* 320 mg in the fasting state [7, 13]. The maximum plasma concentration (C_{max}) of 2.6 mg/L was achieved at 1.5 h post-dose [13]. The mean area under the concentration-time curve was 8.2 mg/L·h and the elimination half-life was 1.9 h [13]. In healthy volunteers ($n = 24$) who received a single dose of HE *S. repens* 160 mg containing 5 mg of radiolabeled lauric acid and myristic acid (active short-chain free fatty acids present in the extract), C_{max} was observed at ≈ 3 h postdose [14]. Tissue distribution of HE *S. repens* was assessed in rats after oral administration of the drug supplemented with radiolabeled oleic acid, lauric acid or β-sitosterol [15]. Uptake of radioactivity was higher in the prostate gland than in the bladder or seminal vesicles, or more remote sites (e.g. liver) [15].

HE *S. repens* has been shown to inhibit CYP2C9, CYP2D6 and CYP3A4 in vitro; however, the clinical relevance of this is unknown [7]. In healthy volunteers, HE *S. repens* did not appear to affect the pharmacokinetics of midazolam (a CYP3A4 substrate), caffeine (a CYP1A2 inducer), chlorzoxazone (a CYP2E1 inducer) or dextromethorphan (a CYP2D6 substrate) [7].

4 Therapeutic Efficacy of HE *S. repens*

The therapeutic efficacy of HE *S. repens* in men with symptomatic BPH was demonstrated in the randomized, double-blind, multicentre PERMAL [16] and PERMIN [12] studies comparing HE *S. repens* with the α-blocker tamsulosin (Sect. 4.1). Three open-label trials provide supportive evidence for the efficacy of HE *S. repens* in men with BPH. Briefly, in two small pilot studies, HE *S. repens* reduced infravesical obstruction and rapidly improved urodynamic parameters after 9 weeks of treatment [17] and improved clinical symptoms of BPH after 3 months of treatment [18]. The long-term clinical efficacy of HE *S. repens* was demonstrated in a 2-year study [19]. These open-label trials are not discussed further. The clinical efficacy of HE *S. repens* in real-world observational studies is discussed in Sect. 4.2.

4.1 Comparisons with Tamsulosin

4.1.1 PERMAL Study

HE *S. repens* was as effective as tamsulosin for the treatment of LUTS in men with BPH [16]. Patients enrolled in the PERMAL study were men aged 50–85 years (mean 65.5 years) with LUTS secondary to BPH. All patients had an International Prostate Symptom Score (I-PSS) of ≥ 10, a maximum urinary flow rate (Q_{max}) of 5–15 mL/s for a voided volume of ≥ 150 mL with a post-voiding volume of

< 150 mL, a prostate volume of ≥ 25 cm^3, and a serum PSA level of < 4 ng/mL (or 4–10 mg/mL with a free/total PSA ratio of ≥ 15%). Following a 4-week placebo run-in period, patients were randomized to receive oral HE *S. repens* 320 mg/day ($n = 350$) or tamsulosin 0.4 mg/day ($n = 354$). The primary endpoint was the change in I-PSS total score from baseline to endpoint (12 months) in the per-protocol population [16].

At 12 months, HE *S. repens* and tamsulosin produced similar reductions from baseline in I-PSS total score (Table 2) [16]. The two-sided 95% confidence interval (CI) for the difference between treatments in the mean absolute change in I-PSS at 12 months was − 0.894 to 0.895. The upper limit of the 95% CI did not exceed the non-inferiority criterion (+ 2), indicating that HE *S. repens* was non-inferior to tamsulosin. At 12 months, there was no significant difference between HE *S. repens* and tamsulosin in terms of the mean change from baseline in I-PSS irritative symptoms (− 1.7 vs − 1.5) and I-PSS obstructive symptoms (− 2.8 vs − 2.9). The I-PSS total score decreased in most (> 80%) patients in both groups. Overall, 67% of patients experienced a reduction of ≥ 3 points and 49% experienced a reduction of ≥ 5 points [16].

At 12 months, the change from baseline in Q_{max} was not significantly different between HE *S. repens* and tamsulosin (Table 2) [16]. Q_{max} improved by 20% in 49% of HE *S. repens* and 55% of tamsulosin recipients, and by 50% in 28% of HE *S. repens* and 31% of tamsulosin recipients. At 6 weeks, 3 months and 12 months, the proportion of patients with a Q_{max} improvement of ≥ 3 mL/s was 25, 34 and 34% with HE *S. repens* and 33, 35 and 37% with tamsulosin, respectively. At 12 months, the change from baseline in sexual function score, prostate volume and PSA level did not significantly differ between patients receiving HE *S. repens* and those receiving tamsulosin (Table 2) [16].

A subset analysis of the PERMAL study compared the efficacy of HE *S. repens* and tamsulosin in patients with severe LUTS (i.e. I-PSS > 19; $n = 124$) [20]. At 12 months, the mean improvement from baseline in I-PSS total score with HE *S. repens* versus that with tamsulosin approached statistical significance (Table 2). I-PSS irritative symptoms improved significantly ($p < 0.05$) more with HE *S. repens* than with tamsulosin (− 2.9 vs − 1.9), particularly among the most severely symptomatic patients (i.e. I-PSS > 21; $n = 61$). In terms of I-PSS obstructive symptoms, the change from baseline was − 4.9 with HE *S. repens* and − 3.9 with tamsulosin. The proportion of patients with an I-PSS response (i.e. ≥ 3-point reduction in I-PSS total score) was 80% with HE *S. repens* and 71% with tamsulosin. At 12 months, changes from baseline in Q_{max}, prostate volume and sexual function score were not significantly different between HE *S. repens* and tamsulosin (Table 2) [20].

Table 2 Efficacy of the hexanic extract of *Serenoa repens* versus tamsulosin in the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia in the PERMAL and PERMIN studies

Study	Treatment (no. of pts)	Mean change from BL[a] [mean BL value]				
		I-PSS total score[b,c]	Q_{max} (mL/s)	MSF-4 score[d]	Prostate volume (cm^3)	Serum PSA (ng/mL)
PERMAL						
All patients [16]	HESr 320 mg/day (266–269)	− 4.4[e] [15.3]	1.9 [10.9]	0.5 [8.3]	− 0.9 [48.0]	0.3 [2.5]
	TAM 0.4 mg/day (265–273)	− 4.4 [15.4]	1.8 [11.2]	0.4 [7.7]	0.2 [48.0]	0.2 [2.7]
Severe LUTS[f] [20]	HESr 320 mg/day (65)	− 7.8* [22.3]	1.2 [10.7]	1.0 [8.9]	− 2.2 [48.5]	NR
	TAM 0.4 mg/day (59)	− 5.8 [23.2]	1.7 [10.3]	0.2 [8.0]	− 0.9 [47.7]	NR
PERMIN [12]	HESr 320 mg/day (102)	− 4.3 [17.7]	1.8 [10.9]	0.4 [7.4]	− 0.99 [48.8]	NR
	TAM 0.4 mg/day (101)	− 6.6 [16.8]	2.1 [10.6]	0.6 [6.9]	− 0.53 [46.3]	NR

BL baseline, *HESr* hexanic extract of *Serenoa repens*, *I-PSS* International Prostate Symptom Score, *MSF-4* Male Sexual Function 4-item, *NR* not reported, *PSA* prostate-specific antigen, Q_{max} maximum urinary flow rate, *TAM* tamsulosin

*$p = 0.051$ vs TAM 0.4 mg/day

[a]At 90 days (PERMIN) or 12 months (PERMAL)

[b]Primary endpoint in PERMAL

[c]I-PSS total scores range from 0 to 35, with higher scores indicating worsening symptoms

[d]MSF-4 item scores range from 0 (best) to 5 (worst)

[e]HESr was non-inferior to TAM

[f]Defined as I-PSS total score of > 19 at BL

4.1.2 PERMIN Study

The exploratory phase IV PERMIN study enrolled men aged 45–85 years with a > 12-month history of BPH-related LUTS [12]. Other inclusion criteria included an I-PSS of ≥ 12, a prostate volume of ≥ 30 cm^3 as determined by transrectal ultrasound, a Q_{max} of 5–15 mL/s for a voided volume of 150–500 mL, and a total PSA level of ≤ 4 ng/mL (or ≤ 10 mg/mL with a free/total PSA ratio of ≥ 25%). Following a 28- to 42-day washout period, patients were randomized to receive oral HE *S. repens* 320 mg/day ($n = 102$) or tamsulosin 0.4 mg/day ($n = 104$). The primary endpoint was mRNA expression associated with selected genes encoding biomarkers of prostate inflammation at day 90 (Sect. 2.1). Both HE *S. repens* and tamsulosin were associated with improvements in the secondary endpoints of I-PSS, Q_{max}, sexual function score and prostate volume (Table 2). There was no relationship between the change in clinical symptoms and the change in mRNA expression level. At day 90, the mean change from baseline in I-PSS total score with HE *S. repens* was − 6.4 in the subgroup of patients who overexpressed macrophage migration inhibitory factor (MIF) protein at baseline (> 3rd quartile), compared with − 4.5 in patients who did not overexpress MIF; this difference was not seen in the tamsulosin group (− 6.5 vs − 6.3) [12].

4.2 Observational Studies

Several observational studies in Europe have confirmed the efficacy of HE *S. repens* for the treatment of LUTS in men with BPH. For example, in two prospective, longitudinal studies conducted in real-life practice in Spain (QUALIPROST [21]) and France (PERSAT [22]), HE *S. repens* demonstrated similar efficacy to α-blockers [21, 22] and 5α-reductase inhibitors [21] in men aged ≥ 40 years with LUTS associated with BPH.

In the QUALIPROST study ($n = 1713$), 70% of patients received monotherapy with phytotherapy (of which 95% was HE *S. repens*), α-blockers (most commonly tamsulosin) or 5α-reductase inhibitors (most commonly dutasteride), 20% received combination therapy and 9% did not receive treatment (watchful waiting) [21]. At 6 months, improvements in QOL and urinary symptoms were not significantly different between medical treatment groups (Table 3). Among patients with moderate-high baseline symptoms, all three monotherapies were associated with significantly greater improvements in QOL [assessed using the Benign Prostatic Hyperplasia Impact Index (BII)] than watchful waiting (Table 3). In terms of compliance, most (≈ 90%) patients in each medical treatment group took the medication with no difficulty [21]. In a subset analysis, the efficacy of HE *S. repens* was similar to that of tamsulosin in men with moderate to severe LUTS associated with BPH [23]. In patients

Table 3 Effect of the hexanic extract of *Serenoa repens* on quality of life and lower urinary tract symptoms in patients with benign prostatic hyperplasia in the real-world QUALIPROST study [21]

Endpoint (mean change from BL at 6 months)	WW	AB	5ARI	HESr[a]	AB + 5ARI	AB + HESr
Moderate-low BL symptoms (I-PSS 8–13)	**(*n* = 64)**	**(*n* = 87)**		**(*n* = 269)**		**(*n* = 32)**
BII score[b]	− 0.3	− 1.7	NA	− 1.2	NA	− 2.2
I-PSS total score[c]	− 0.5	− 2.4	NA	− 1.7	NA	− 2.8
Moderate-high BL symptoms (I-PSS 14–19)	**(*n* = 46)**	**(*n* = 171)**	**(*n* = 34)**	**(*n* = 256)**	**(*n* = 25)**	**(*n* = 84)**
BII score[c]	− 1.1	− 2.5*	− 2.1*	− 2.0*	− 2.3	− 2.9
I-PSS total score[c]	− 3.0	− 4.6	− 5.2	− 4.2*	− 4.4	− 5.0
Severe BL symptoms (I-PSS ≥ 20)		**(*n* = 118)**	**(*n* = 45)**	**(*n* = 106)**	**(*n* = 58)**	**(*n* = 86)**
BII score[c]	NA	− 2.8	− 3.0	− 2.9	− 3.7	− 3.7
I-PSS total score[c]	NA	− 7.6	− 9.0	− 7.9	− 9.8	− 9.5

Groups of $n < 25$ were excluded from the analysis due to small sample size

5ARI 5α-reductase inhibitors, *AB* α-blockers, *BII* Benign Prostatic Hyperplasia Impact Index, *BL* baseline, *HESr* hexanic extract of *Serenoa repens*, *I-PSS* International Prostate Symptom Score, *NA* not applicable, *QOL* quality of life, *WW* watchful waiting (no treatment)

*$p < 0.05$ vs WW

[a]95% of patients in this group received HESr

[b]BII scores range from 0 (best QOL) to 13 (worst QOL) on a self-administered questionnaire

[c]I-PSS total scores range from 0 to 35, with higher scores indicating more severe symptoms and a change of ≥ 3.1 corresponding to a clinically meaningful change in patients' global feeling of urination

who received monotherapy with HE *S. repens* 320 mg/day ($n = 384$) or tamsulosin 0.4 mg/day ($n = 353$), changes from baseline to 6 months in I-PSS total score, Q_{max}, prostate volume and PSA were not significantly different between treatment groups. Improvements in QOL (assessed using the BII and I-PSS 8) were also similar in both treatment groups [23].

In the PERSAT study ($n = 759$ evaluable), 50% of patients were treated with phytotherapy (of which 98% was HE *S. repens*) and 50% received an α-blocker (most commonly silodosin) [22]. After 6 months, the proportion of patients with a ≥ 3-point reduction in total I-PSS score (primary endpoint) was 93% with phytotherapy and 94% with α-blockers. Overall, the mean change in total I-PSS score was − 10.0 points, with no significant difference between treatment groups. In terms of QOL, the proportion of patients bothered by their LUTS (i.e. I-PSS-QoL score of ≥ 4) decreased from 86% at baseline to 6% at 6 months in the phytotherapy group, and from 91% at baseline to 7% at 6 months in the α-blockers group. Overall, 93% of patients were satisfied with their prescribed treatment (95% with phytotherapy and 91% with α-blockers) [22]. Similar results were seen among the subpopulation of patients who had no changes to their treatment during the study ($n = 633$) [24].

HE *S. repens* was also effective in patients with chronic benign prostate diseases with associated inflammation [25]. A study conducted as part of routine clinical practice in Italy included 591 men aged 35–65 years with a clinical diagnosis of BPH or chronic prostatitis without infection, non-acute irritative dysuria symptoms, an I-PSS score of ≥ 13, a National Institute of Health-Chronic Prostatitis Symptom Index (NHI-CPSI) score of ≥ 2, a Q_{max} of < 12 mL/s, a post-voiding volume of < 150 mL, a digital rectal examination not suggestive of prostate cancer, and a total PSA of ≤ 4 ng/mL. HE *S. repens* improved bladder emptying and LUTS at 6 months, as evidenced by a significant ($p < 0.001$) increase from baseline in Q_{max} (from 10.7 to 13.7 mL/s) and significantly ($p < 0.0001$) improved scores on the I-PSS (from 17.8 to 12.2) and the NHI-CPSI (from 13.3 to 8.2). HE *S. repens* was also associated with an improvement in erectile function, as demonstrated by a significant ($p < 0.0055$) increase in International Index of Erectile Function-5 score (from 17.6 to 18.1) [25].

5 Tolerability of HE *S. repens*

HE *S. repens* was generally well tolerated in men with symptomatic BPH. In clinical trials, the most common adverse events (AEs) were headache and abdominal pain [6]. Less common AEs included nausea, skin rash, reversible gynaecomastia, increased γ-glutamyltransferase and increased transaminases [6].

In the PERMAL study, AEs occurred in 66% of HE *S. repens* recipients and 67% of tamsulosin recipients [16]. The most common (incidence ≥ 3% in any treatment group) AEs were rhinitis (9% with HE *S. repens* vs 12% with tamsulosin), headache (8 vs 11%), dizziness (3 vs 2%) and ejaculation disorders (1 vs 4%; $p = 0.001$). Rates of possibly treatment-related AEs (TRAEs; 22 vs 24%), serious AEs (8 vs 9%) and discontinuations due to AEs (8 vs 8%) were similar across both treatment groups [16]. In the PERMIN study, the overall incidence of AEs was 29% with HE *S. repens* and 31% with tamsulosin [12]. The most common (incidence > 2%) treatment-emergent AEs were retrograde ejaculation (4%), constipation (3%) and back pain (3%) with tamsulosin, while no AEs occurred in > 2% of HE *S. repens* recipients. AEs leading to treatment discontinuation (all of which were mild or moderate in severity) occurred in 8% of patients receiving HE *S. repens* and 3% of those receiving tamsulosin [12].

HE *S. repens* was better tolerated than α-blockers [21, 22] and 5α-reductase inhibitors [21] in the real-world QUALIPROST and PERSAT studies. In QUALIPROST, the overall incidence of AEs was 1% with HE *S. repens*, 16% with α-blockers and 14% with 5α-reductase inhibitors [21]. For combination therapies, the incidence of AEs was 17% with HE *S. repens* + 5α-reductase inhibitors, 14% with HE *S. repens* + α-blockers, and 31% with α-blockers + 5α-reductase inhibitors [21]. In PERSAT, potentially TRAEs were reported in 6% of phytotherapy recipients and 12% of patients receiving α-blockers; the most common TRAEs were ejaculation disorders (1 vs 4%) and asthenia (1 vs 3%) [22].

6 Dosage and Administration of HE *S. repens*

HE *S. repens* is approved under well-established use criteria in the EU for the symptomatic treatment of BPH [6]. The recommended dosage is 320 mg once daily or 160 mg twice daily, administered orally. Long-term use is possible [6]. Local prescribing information should be consulted for detailed information regarding contraindications, warnings and precautions, and drug interactions.

7 Place of HE *S. repens* in the Management of Symptomatic BPH

The main goals in the management of BPH are to relieve bothersome LUTS, improve QOL, and reduce disease progression and the development of complications [1]. Therefore, management options for BPH are determined by symptom severity and the impact these symptoms have

on QOL [26]. They often consist of watchful waiting for patients with mild or non-bothersome LUTS and pharmacological treatment for patients with more severe symptoms [1, 27].

Pharmacotherapies for BPH-related LUTS include 5α-reductase inhibitors (e.g. dutasteride, finasteride), α-blockers (e.g. doxazosin, silodosin, tamsulosin) and phosphodiesterase type 5 inhibitors (e.g. tadalafil) [1, 3]. Muscarinic receptor antagonists (e.g. oxybutynin, tolterodine) are also strongly recommended by the European Association of Urology (EAU) as a treatment option for men with moderate to severe LUTS who mainly have bladder storage symptoms [27]. However, the efficacy and tolerability of these pharmacological agents varies [1, 3]. There is ongoing interest in the use of phytotherapeutic agents, of which *S. repens* extracts are the most commonly prescribed and extensively studied [2, 28]. Recently updated EAU guidelines conclude that HE *S. repens* improves Q_{max} and nocturia, and now recommend HE *S. repens* as a treatment option for men with LUTS who want to avoid any potential AEs, especially those related to sexual function [27].

HE *S. repens* appears to have multiple mechanisms of action, including anti-inflammatory, anti-proliferative and anti-androgenic activity (Sect. 2). The effects of HE *S. repens* on inflammation (Sect. 2.1) are clinically relevant, given the known association between prostatic inflammation and the development/progression of BPH (Sect. 1). Indeed, the anti-inflammatory activity of HE *S. repens* has been demonstrated in vitro, in vivo, and in randomized clinical trials (Sect. 2.1).

Experience in randomized clinical trials has established the therapeutic efficacy of HE *S. repens* for the treatment of symptomatic BPH (Sect. 4.1). In the PERMAL and PERMIN studies, HE *S. repens* was as effective as tamsulosin in terms of improving voiding and storage symptoms, increasing urinary flow rate and reducing prostate volume in men with BPH (Sect. 4.1). The greater degree of improvement in urinary symptoms with HE *S. repens* in patients who overexpressed MIF protein at baseline versus those who did not (Sect. 4.1.2) suggests that patients with higher CPI and greater MIF expression may benefit most from treatment with HE *S. repens* [12]. Additional studies to further investigate this finding would be of interest.

Data from several European observational studies were generally consistent with those seen in clinical trials (Sect. 4.2). In the real-world QUALIPROST and PERSAT studies, improvements in QOL observed with HE *S. repens* were similar to those observed with 5α-reductase inhibitors and/or α-blockers (Sect. 4.2). Despite their inherent limitations, such observational studies offer a better representation of real-life clinical practice than prospective clinical trials [21], confirming the efficacy of HE *S. repens* for the treatment of LUTS in men with BPH.

The clinical efficacy of HE *S. repens* in men with BPH-related LUTS has also been confirmed in various systematic reviews and network meta-analyses [29–31]. Generally, HE *S. repens* was associated with greater clinical benefits than placebo [29–31] and demonstrated similar efficacy to α-blockers and 5α-reductase inhibitors [30, 31]. However, the results of these indirect comparisons require cautious interpretation given the heterogeneity of the studies and patient populations assessed.

HE *S. repens* was generally well tolerated in clinical trials, with the most frequent AEs being headache, dizziness and ejaculation disorders (Sect. 5). However, it should be noted that the incidence of ejaculation disorders was significantly lower with HE *S. repens* than with tamsulosin (Sect. 5). Men with BPH are often dissatisfied with α-blocker and 5α-reductase inhibitor therapy due to ejaculation disorders and sexual dysfunction, respectively [28] and, in a real-world setting, the most common reason for prescribing HE *S. repens* was to avoid sexual dysfunction and ejaculation disorders (Sect. 4.2). Results of a sexual function questionnaire used in the PERMAL and PERMIN studies showed no significant differences between HE *S. repens* and tamsulosin (Sect. 4.1). However, pooled data from three randomized, double-blind studies (including PERMAL) demonstrated that HE *S. repens* had no negative impact on male sexual function in terms of interest in sex, quality of erection, achievement of orgasm and ejaculation, while tamsulosin and finasteride had a slight negative impact on sexual function (particularly ejaculation) [32]. Moreover, in systematic reviews and meta-analyses, HE *S. repens* was associated with a significantly lower incidence of ejaculation disorders ($p = 0.001$) [31] and ejaculatory dysfunction (0.5 vs 4%; $p = 0.007$) [30] than tamsulosin, and numerically lower rates of decreased libido (2.2 vs 3%) and impotence (1.5 vs 2.8%) than finasteride [30].

Another key factor influencing physicians' prescription of HE *S. repens* was patient acceptability (Sect. 4.2), the role of which is gaining greater importance in clinical decision-making [33]. In the Adelphi Real World Permixon Study, which collected prescribing data from 200 physicians in France and Spain for 1197 patients with BPH, the main reasons for prescribing HE *S. repens* monotherapy aside from relief of urinary symptoms (including voiding and storage symptoms) were the avoidance of sexual dysfunction and ejaculation disorders, patient acceptability, value for money, familiarity with the drug, and reduction of inflammation [33]. In the observational PERSAT study, almost all patients receiving HE *S. repens* were satisfied with their prescribed treatment (Sect. 4.2). According to current EAU guidelines for LUTS, the choice of treatment should always take into account factors such as patient values and preferences [27].

In conclusion, HE *S. repens* is an effective and generally well-tolerated treatment that is a useful option for men with symptomatic BPH.

Data Selection Hexanic Extract of *Serenoa repens*: 325 records identified	
Duplicates removed	44
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	166
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	68
Cited efficacy/tolerability articles	13
Cited articles not efficacy/tolerability	34
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Permixon, *Serenoa repens*, saw palmetto extract, LUTS, benign prostatic hyperplasia, prostatic hypertrophy. Records were limited to those in English language. Searches last updated 7 February 2022	

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