



## PROSTATE SUPPORT:

### GRAMINEX Flower Pollen Extract

## A systematic review of Cernilton for the treatment of benign prostatic hyperplasia

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**Objective** To systematically review the evidence for the clinical effects and safety of the rye-grass pollen extract (Cernilton) in men with symptomatic benign prostatic hyperplasia (BPH).

**Methods** Trials were identified by searching Medline, specialized databases (EMBASE, Cochrane Library, Phytodok), bibliographies, and contacting relevant trialists and manufacturers. Randomized or controlled clinical trials were included if: men with symptomatic BPH were treated with Cernilton; a control group received either placebo or pharmacological therapy; the treatment duration was  $\geq 30$  days; and clinical outcomes were reported.

**Results** In all, 444 men were enrolled in two placebo controlled and two comparative trials lasting 12- 24 weeks. Three studies used a double-blind method although the concealment of treatment allocation was unclear in all. Cernilton improved 'self-rated urinary symptoms' (the proportion reporting satisfactory or improving symptoms) vs placebo and another plant product, Tadenan. The weighted mean (95% confidence interval) risk ratio (RR) for self-rated improvement vs placebo was 2.40

(1.21-4.75) and the weighted RR vs Tadenan was 1.42 (1.21-4.75). Cernilton reduced nocturia compared with placebo or Paraprost (a mixture of amino acids); against placebo, the weighted RR was 2.05 (1.41-3.00), and against Paraprost the weighted mean difference for nocturia was -0.40 times per evening (-0.73 to 0.07). Cernilton did not improve urinary flow rates, residual volume or prostate size compared with placebo or the comparative study agents. Adverse events were rare and mild; the withdrawal rate for Cernilton was 4.8%, compared with 2.7% for placebo and 5.2% for Paraprost.

**Conclusions** The Cernilton trials analyzed were limited by their short duration, limited number of enrollees, omissions in reported outcomes, and the unknown quality of the preparations used. The comparative trials had no confirmed active control. The available evidence suggests that Cernilton is well tolerated and modestly improves overall urological symptoms, including nocturia. Additional randomized placebo and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety of Cernilton.

**Key words:** Cernilton, plant extracts, benign prostatic hyperplasia, BPH, efficacy

### Introduction

The LUTS associated with BPH are common in ageing adult men [1]; in the USA, population studies show that the frequency of moderate to severe LUTS is 8-31% among men in their fifth decade and up to 44% among men in their

seventh decade [2]. The cost of managing BPH is >\$4 billion per year [3]. The primary aim of treatment in the vast majority of men is to relieve these bothersome obstructive and irritative symptoms.

Treatment options for symptomatic BPH include lifestyle change, medical, device or surgical therapy [4]. Phytotherapy, i.e. the use of plant extracts, is becoming widely used to manage BPH [5]; the use of phytotherapeutic agents is common in Europe and increasing in the Western hemisphere. In Germany, phytotherapy is the primary treatment for mild to moderate urinary obstructive symptoms and represents >90% of all drugs prescribed for treatment of BPH [6]. Phytotherapeutic agents are readily available in the USA as nonprescription dietary supplements and often recommended in 'natural health-food' stores or books for the self treatment of BPH symptoms [7].

Cernilton, prepared from the rye-grass pollen *Secale cereale*, is one of several phytotherapeutic agents available for the treatment of BPH. It is used by millions of men worldwide and is a registered pharmaceutical product throughout Western Europe, Japan, Korea and Argentina (data from the manufacturer, AB Cernelle, Engelholm, Sweden, 1999). In the USA, Cernilton is used as a nutritional supplement by ≈5000 men (D. Ruyan, Cernitin American, personal communication). One dose of Cernilton contains 60 mg of Cernitin T60, a water-soluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone-soluble pollen extract fraction (Cernelle AB). The acetone-soluble fraction contains  $\beta$ -sterols [8]. Several *in vitro* studies undertaken to investigate the mechanism of action suggest that Cernilton has antiandrogenic effects [9], may relax urethral smooth muscle tone and increase bladder muscle contraction [10], or may act on the  $\alpha$ -adrenergic receptors and relax the internal and external sphincter muscles [11].

Despite many studies showing *in vitro* activity [9-11], the clinical effectiveness of Cernilton for the treatment of LUTS remains unclear. The objective of the present study was to systematically review the existing evidence for the clinical effectiveness and safety of Cernilton. Specifically, we assessed whether Cernilton is more effective than placebo or as effective as other pharmacological therapies in improving the obstructive and irritative urinary symptoms associated with BPH.

## Methods

### *Inclusion criteria and the identification of relevant trials*

Randomized (RCTs) or controlled clinical trials (CCTs) were included if men had symptomatic BPH; the treatment intervention was Cernilton (Cernitin) or a preparation of *Secale cereale*; a control group received either placebo or pharmacological therapy for BPH; and the treatment duration was  $\geq 30$  days.

Medline (from 1966 to November 1998) was searched using a combination of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the medical subject headings 'prostatic hyperplasia', 'phytosterols', 'plant extracts', 'pollen', 'sitosterols', *Secale cereale*, 'Cernilton.tw', and 'Cernitin.tw' including all subheadings [12]. EMBASE was searched from 1974 to 1997 (performed in July 1997) in a similar approach to the one used for Medline. The private database Phytodok (Munich, Germany) and the Cochrane Library, including the database of the Cochrane Prostate Group and the Cochrane Field for Complementary Medicine, were also searched similarly. The reference lists of all trials found were searched for additional trials. We attempted to solicit trialists identified, asking them to identify any further published or unpublished trials; there were no language restrictions.

### *Data extraction and study appraisal*

Study characteristics, demographic information, enrolment criteria and outcomes were extracted independently by two reviewers. Authors or sponsors of the trials were petitioned for required missing or additional information. Extracted data were reviewed by the principal reviewer and discrepancies resolved by discussion. The number and age of enrollees, and dose and duration of treatment, were recorded. The main outcome was the efficacy of Cernilton vs placebo or control in improving urological symptom scores (e.g. the IPSS). The following secondary outcomes were also assessed: nocturia (times/evening); peak and mean urine flow; postvoid residual urine volume (PVR); and prostate size. One study used the Uroflow Index, a formula developed to examine urinary flow measurement based on maximum and mean flow [13]. The number of and reason for men withdrawing from the trial or being lost to follow-up were assessed, as were treatment-related side-effects.

The overall study quality was assessed according to the scale developed by Schulz *et*

al. [14]. The quality of the concealment of treatment allocation is assigned a score from 1 to 3, (1 for the poorest quality and 3 the best). Trials in which concealment was inadequate (e.g. alternation or reference to case-record numbers or to dates of birth) were given a score of 1. Trials in which the authors either did not report their approach to allocation concealment or reported an approach that did not fall into one of the other categories were given a score of 2. Trials deemed to have taken adequate measures to conceal allocation, e.g. central randomization, were scored as 3.

### Statistical methods

Summary treatment effect sizes were determined for Cernilton vs placebo and vs pharmacological therapies. Weighted mean differences (WMDs) and their 95% CI were calculated [15]. Heterogeneity was assessed using a chi-squared test; if there was evidence of heterogeneity then a random-effects model was used. For continuous measurements, a difference between treatment means and its correlated se of the difference were calculated using the methods of Lau [16] and Laird [17]. To assess the percentage of patients having an improvement in urological symptoms a modified intention-to-treat analysis was conducted (i.e. men who withdrew or were lost to follow-up were considered to have had worsening symptoms) [18]. Chi-square tests were used to analyze bivariate comparisons.

## Results

Four studies met the inclusion criteria from a total of six [19-24] identified through the combined search strategy. Two trials were excluded because they had no control groups [23,24]. The concealment of treatment allocation was rated as unclear in the four studies reviewed, although two indicated randomization [19,22]. Three trials reported using a double-blind method [19,20,22]. Two studies were placebo-controlled [19,20] and two were 'active controlled' trials. The 'active-controlled' trials included Tadenan, a phytotherapeutic extract from the African plum plant, *Pygeum africanum* [21], and Paraprost (Nikken Kagakusha, Japan), a pharmacological treatment for BPH used primarily in Japan, and containing 265 mg of L-glutamic acid, 100 mg of alanine and 45 mg of aminoacetic acid [22]. A total of 444 participants were enrolled in the four trials (163 in the placebo-controlled and 281 in the 'active controlled' trials). Table 1 describes the participants, intervention, follow-up period, number of participants randomized, number who withdrew or were lost to follow-up, double-blind method status, and adverse effects. The mean (range) age of the enrollees was 69 (42-89) years and the duration of the trials was 12-24 weeks. The overall mean (range) rate of reported withdrawals or losses to follow-up was 6.3 (0-11.7%) (n = 28).

Table 1 The description of the individual studies

Characteristic	Study			
	[19]	[20]	[21]	[22]
Participants	Symptomatic BPH Stage II-III (Vahlensieck) using authors' symptom scale; flow rate $\geq 150$ mL/s; US estimate of PVR and prostate size	Men with BOO from physician assessment; score; uroflowmetry; US of PVR and prostate size	Men with BPH; assessed symptom score (graded 0-3 for nocturia, dysuria, hesitancy, etc.) peak flow 10 mL/s ( $> 150$ mL); PVR $< 50$ mL	Men with BPH; global
Mean (range) age (years)	66.6 (not reported)	68.6 (59-89)	? (50-68)	70 (54-68)
Intervention	1. Cernilton 2 caps $\times 3$ /day; 2. Placebo	1. Cernilton 2 caps $\times 2$ /day; 2. Placebo	1. Cernilton 2 caps $\times 3$ /day for 2 weeks then 1 cap $\times 3$ /day; 2. Tadenan 2 tabs $\times 2$ /day	1. Cernilton (63 mg) 2 caps $\times 2$ /day; Paraprost 6 g tab 2/day
Follow-up (weeks)	12	24	16	12
No. enrolled (withdrawals)	103 (7)	60 (7)	89 (0)	192 (14)*
Quality scale score†	2	2	2	2
Double-blind method	Yes	Yes	No	Yes
Adverse events	Mild nausea (1)	None	None	None

\*Efficacy was studied in only 159 patients. †Based on Schulz *et al.* [14]. US, ultrasonography.

**Table 2** The summary of the outcome data

Mean (SD) variable†	Study							
	[19]		[20]		[21]		[22]	
	Cernilton	Control	Cernilton	Control	Cernilton	Control	Cernilton	Control
Symptom score or rating			'Overall improvement'		+ve response		11.5 (3.5)	11.4 (4.0)
Baseline	–	–					5.2 (2.5)	4.3 (2.7)
Follow-up	–	–	69%	29%†	78%	55%*	–6.3	–7.1
Difference	–	–						
Nocturia (times/night)			Improved		–	–	3.7 (0.5)	4.0 (0.8)
Baseline							2.8 (0.6)	3.2 (1.1)
Follow-up	'Improved' or symptom-free				–	–	–0.9	–0.8
Difference	69%	37%†	60%	30%	–	–		
Peak urinary flow rate (mL/s)								
Baseline	0.74 (0.27)	0.72 (0.34)	10.3 (5.2)	11.8 (6.4)	12.59 (3.0)	13.54 (3.2)	9.29 (4.99)	9.34 (4.86)
Follow-up	0.86 (0.25)	0.82 (0.31)	10.5 (5.1)	12.1 (5.1)	15.51 (4.3)	15.18 (4.5)	10.94 (5.09)	10.57 (4.82)
Difference	0.12	0.10	0.2	0.3	3.02	1.64	1.65	1.23
PVR (mL)								
Baseline	45.6 (30.4)	47.8 (32.8)	145.4 (107.5)	93.4 (91.4)	77.0 (15.7)	61.0 (14.1)	54.2 (78.84)	33.1 (40.06)
Follow-up	22.5 (20.9)	37.0 (28.9)	101.9 (87.3)	113.4 (87.3)	45.0 (21.0)	50.0 (15.8)	25.2 (28.22)	23.8 (28.59)
Difference	–23.1	–10.8*	–43.5	20.0*	–32.0	–11.0	–29.0	–9.26

\*P < 0.05; †P < 0.01, otherwise not significant. ‡Except for the values in [20], which are mean (sem).

Table 2 shows the summary of outcome data for urological symptoms scores, nocturia, peak urinary flow rate and PVR. Three studies reported symptom scores or measured the symptom improvement, nocturia was reported in three, peak urinary flow rate in four studies and four provided information related to PVR. Differences in the control agents and methods of reporting results did not permit all studies to be combined in a quantitative meta-analysis. However, the results from all studies were consistent with an improvement in symptoms and urinary flow measures, as described below.

*Mean differences in outcomes*

Cernilton was comparable with both Paraprost and Tadenan in improving urological symptoms based on the IPSS (Paraprost) and two undefined symptom scales evaluating obstructive or irritative symptoms. For the IPSS, the mean (95% CI) difference (MD) was 0.90 (-0.43 to 2.23), with a percentage improvement from baseline of 55% for Cernilton and 62% for Paraprost [22]. For the trial comparing Cernilton with Tadenan, the MD for the obstructive scale score was -0.70 (-1.78 to 0.40; % improvement from baseline, Cernilton 63%, Tadenan 46%) and for the irritative scale -0.90 (-2.26 to 0.46; % improvement from baseline, Cernilton 68%, Tadenan 40%) [21].

**Table 3** A comparison of Cernilton and placebo for nocturia and PVR in the two RCTs

Variable	Study		
	[19]	[20]	Total
Reported improvement in nocturia			
Cernilton (n/N)	33/48	17/31	50/79
Placebo (n/N)	16/48	7/26	23/74
Weight (%)	67.8	32.2	100
Relative risk (95% CI fixed)	2.06 (1.32–3.21)	2.04 (1.00–4.14)	2.05 (1.41–3.99)
PVR (mL)			
Cernilton (n)	48	28	76
Mean (SD)	22.5 (42.08)	101.9 (134.46)	–
Placebo (n)	48	24	72
Mean (SD)	37.0 (41.08)	113.4 (124.48)	–
Weight (%)	94.8	5.2	100
WMD (95% CI fixed)	–14.5 (–30.94 to 1.94)	–11.5 (–81.93 to 58.93)	–14.35 (–30.35 to 1.66)

Cernilton was better than placebo, Paraprost and Tadenan in the self-reported improvement of symptoms. The mean (95% CI) risk ratio (RR) vs placebo was 2.40 (1.21-4.75) (percentage of men reporting improvement, Cernilton 69%, placebo 29%) [20]. The RR vs Tadenan for a positive overall therapeutic response was 1.42 (1.21-4.75; % of patients who reported improvement, Cernilton 78%, Tadenan 55%). Cernilton reduced nocturia compared with the controls (Table 3; 30.8% absolute improvement) [19,20] and against Paraprost, the MD was -0.40 times per evening (-0.73 to -0.07).

Urinary flow measures were not significantly different between men treated with Cernilton and the placebo or active controls. The mean (95% CI) differences for peak urinary flow and the Uroflow Index were 1.60 ( -5.77 to 2.59) mL/s and 0.04 (-0.11 to 0.19) mL/s, respectively [19,20]. Against Paraprost, the MD was 0.37 (-1.90 to 2.64) mL/s for peak urinary flow rate (4.6% absolute improvement) and 0.39 (-0.80 to 1.58) mL/s for the mean flow rate [22]. Against Tadenan, the MD was 0.33 (-2.00 to 2.66) mL/s (8.7% absolute improvement) [21].

Cernilton modestly reduced the PVR in the two placebo controlled studies (Table 3; 36.5% absolute improvement vs placebo) [19,20]. Cernilton was comparable with the control agents; the MD was -5.00 (-14.98 to 4.98) mL vs Tadenan and 1.40 (-20.00 to 22.80) mL vs Paraprost [21,22]. No significant differences in prostate size were evident when compared with Tadenan, with a MD of -2.09 (-10.21 to 7.97) mL, and Paraprost, with a MD of -1.12 (-10.21 to 7.97) mL. One placebo-controlled study, reporting changes for three variables (circumference, transverse diameter and anteroposterior diameter) of the prostate, found a 'statistically significant reduction in the anteroposterior diameter' after treatment with Cernilton [20].

#### *Adverse effects*

In the short-term, Cernilton was well tolerated; the only reported adverse effect associated with the use of Cernilton was one case of mild nausea [20]. Withdrawal rates were Cernilton 4.8%, placebo 2.7% and Paraprost 5.2% (P = 0.26 for Cernilton vs placebo and P = 0.33 vs Paraprost).

#### **Discussion**

This is the first systematic review summarizing the evidence from RCTs or CCTs about the efficacy and safety of Cernilton; the results suggest that Cernilton improved subjective symptoms and nocturia compared with placebo, Paraprost and Tadenan. Cernilton produced a similar response to the comparative study agents in improving urinary symptoms when evaluated by symptom scores. Only one adverse effect was reported, indicating that Cernilton was well tolerated; the withdrawal rate was <5%.

In contrast to the modest improvement in subjective symptom outcomes, Cernilton did not significantly improve objective measures such as peak and mean urinary flow rates when compared with placebo and the control study agents. Although Cernilton was analogous to Paraprost and Tadenan in improving peak flow rates and reducing PVR and prostate size, these results were limited by the lack of confirmed active controls to validate the comparisons.

#### *Methodological issues*

Although the results suggest that Cernilton provides modest benefit to men with BPH, the studies assessed for this review were limited by several factors. The concealment of treatment allocation was deemed unclear in all four trials and may be indicative of the questionable methodological quality of the studies meeting the inclusion criteria. Two of the studies reported random allocation with no detail of the method of concealment and three reported using a double-blind method. One trial did not report random allocation or a double-blind method [21]. Inadequate concealment of randomization and blinding are known to affect the sizes of the outcomes [25].

The treatment duration was short, with no studies lasting longer than 24 weeks. Cernilton dosages were not reported in three studies and whether a standardized preparation was used is also unknown. Additionally, fewer than 500 men were evaluated. Therefore, the long-term efficacy and safety of Cernilton, and its effectiveness in preventing complications of BPH such as acute urinary retention or the need for surgical interventions, is unknown. Only one study reported results from a standardized and validated urological symptom scale, the IPSS [22], although a modified Boyarsky Scale was

used in one [20], the others reporting various outcome variables. Therefore, the effect sizes should be interpreted with caution until future RCTs are conducted [26].

Such RCTs should be of sufficient size and duration to detect important differences in outcome, including urological symptom scale scores (e.g. the IPSS), mean and peak urine flow, voided volume, prostate size, PVR, and the development of acute urinary retention or need for surgical intervention. Studies are needed to compare Cernilton,  $\alpha$ -blockers, 5 $\alpha$ -reductase inhibitors and other phytotherapeutic agents, e.g. extracts of *Serenoa repens* (saw palmetto) [5,27]. Studies should also use standardized doses of Cernilton products that have been analyzed for purity and potency by an independent laboratory to ensure the quality of the product.

Additionally, cost-effectiveness studies should be conducted to evaluate the long-term cumulative costs associated with plant extracts, including the potential need for surgical intervention. The cost of a 90-day supply of Cernilton (three tablets/day, suggested use 2-4 tablets daily) is  $\approx$ US \$40.00. In comparison, the cost of a 90-day supply of finasteride or terazosin (5 mg/day) is  $\approx$ \$200 and \$120, respectively. Alpha-blockers appear to be the preferred medical therapy for improving urological symptoms and urinary flow [28]. However, the costs of the initial medication may not reflect the total charges incurred for the treatment of BPH-related conditions. Finasteride has been shown to reduce the need for surgical intervention in about 6% of men who have large prostates and moderate to severe symptoms [29]. The comparative total cumulative costs of medical or surgical management alone, and a combination of medicine and surgery caused by any failure of the initial medical management (mixed therapies), has been shown to depend on the age of the patient at onset of therapy and the avoidance of mixed therapies [30]. Medical management (including phytotherapeutic agents such as Cernilton) in younger patients appears to be costly over time unless it can also reduce urinary retention or the need for surgery. In men with mild to moderate symptoms of BPH that do not interfere with lifestyle watchful waiting remains a good initial option [31].

In conclusion, additional randomized placebo and active-controlled studies are needed to

evaluate the clinical effectiveness of Cernilton. Until the results of such studies are available, the present systematic review provides the most complete assessment of the efficacy and safety of Cernilton in the treatment of mild to moderate BPH. The available evidence suggests that Cernilton is well tolerated and modestly improves subjective urological symptoms. Cernilton was not shown to improve urinary flow measures compared with placebo. The long-term effectiveness and safety of Cernilton, and its ability to prevent complications from BPH, are unknown.

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