EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Serenoa repens* (W. Bartram) Small, fructus

Final

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Serenoa repens (W. Bartram) Small, fructus*
Herbal preparation(s)	**Well-established use (WEU)** Soft extract (DER 7-11:1), extraction solvent hexane **Traditional use (TU)** Soft extract (DER 7.5-14.3:1), extraction solvent: ethanol 90% to 96% m/m
Pharmaceutical forms	Herbal preparations in solid dosage form for oral use.
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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Dried ripe fruit of *Serenoa repens* (W. Bartram) Small, *Serenoa repens* containing minimum 11% of total fatty acids in the dried material. Synonyms of the plant include *Sabal serrulata* (Mich.) Nutall ex Schult and *Serenoa serrulata* Hook (Eur. Pharm 2012; Hänsel *et al*. 1994; Sweetman 2009).

The plant is a bush with leaves having 18 to 24 sharp-ending segments. The flowers are on short branches; the fruit is an ovoid or subspherical drupe dark brown or blackish up to 2.5 cm long and 1.5 cm in diameter. Confusion with *Sabal minor* (Jacq.) Pers. seldom occurs. *Serenoa repens* is found in costal environments of southern states of the USA, tropical Middle and South-America. The plant grows on dunes and pine forests (Hänsel *et al*., 1994).

The fruit contains primary and secondary metabolites (Hänsel *et al*., 1994; Barnes *et al*., 2007):

Carbohydrates

Polysaccharides (MM about 10,000) with an acid character: galactose (38.4%), arabinose (18.7%), uronic acid (14%). Invert sugar (28.2%) and mannitol.

Sterols

Beta-sitosterol, beta-sitosterol-3-*O*-beta-D-glycoside, beta-sitosterol-3-*O*-beta-D-diglycoside and several esters of beta-sitosterol with saturated fatty acids; campestrol and stigmasterol.

Flavonoids

Isoquercitrin, rutin, kaempferol-3-*O*-beta-D-glucoside and rhoifolin

Triglycerides and fatty acids

Capric acid, caproic acid, caprylic acid, lauric acid, myristic acid, oleic acid(s) (oleic acid and myristoleic acid) and palmitic acid: free form, ethylic esters or in triglycerides.

There may be a variation in qualitative and quantitative composition. Habib & Willie 2004 reported a free acid content variation from 41 to 81% of the total lipid content, while glycerides are reported to vary between 7 and 52% of the total lipid content. Some marketed products contain olive oil, which can lead to confusion with regard to the lipid composition (Habib & Willie 2004).

CH3-(CH2)8-COOH	capric acid
CH3-(CH2)4-COOH	caproic acid
CH3-(CH2)6-COOH	caprylic acid
CH3-(CH2)10-COOH	lauric acid
CH3-(CH2)12-COOH	myristic acid
CH3-(CH2)6-CH=CH-(CH2)6-COOH	oleic acid
CH3-(CH2)2-CH=CH-(CH2)6-COOH	myristoleic acid
CH3-(CH2)14-COOH	palmitic acid

Figure 1: fatty acids identified in *Serenoa repens products*

Other substances

Volatile oil, anthranilic acid, carotene, resin, tannin.

- Herbal preparation(s)

Extracts of the fruits are mainly prepared with hexane, ethanol or supercritical CO_2 (Hänsel, 1994).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Bulgaria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Croatia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Only combinations
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Estonia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Finland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
France	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Greece	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☒MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Luxemburg	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food supplements
The Netherlands	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	TRAD registration
Norway	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	TRAD registration
Poland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Portugal	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Slovenia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
Spain	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Registered products
Sweden	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Authorised products
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	TRAD registration

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

For clinical articles a search was initiated using the ESCOP monograph (2003) and the most recent Cochrane Collaboration Review (2012). All individual studies within the Cochrane review are separately discussed within this Assessment Report.

A complementary literature search was conducted in PubMed, using the following key words and restrictions: *Serenoa (repens), Sabal, Serenoa repens*, clinical, review.

The ESCOP monograph (2003) was used as an additive source for botanical, phytochemical and preclinical data.

The following reference books were used:

Barnes J, Anderson LA, Phillipson JD. Herbal Medicines 3rd Ed., Pharmaceutical Press, London 2007.

Delfosse M. Drogues végétales et plantes médicinales. APB Brussels, 1998.

Hänsel R, Keller K, Rimpler H, Schneider G. Hagers Handbuch der Pharmazeutischen Praxis, Drogen P-Z, Springer-Verlag, Berlin 1994.

Schulz V, Rietbrock N, Roots I, Loew D (edit.). Phytopharmaka VII, Steinkopff, Darmstandt 1995 (cited as Koch 1995).

Loew D, Rietbrock N (edit). Phytopharmaka in Forschung und klinischer Anwendung, Steinkopff, Darmstadt 1999.

Sweetman SC. Martindale: the Complete Drug Reference 36th Edition, London 2009.

Van Hellemont J. Fytotherapeutisch Compendium, APB Brussels, 1985.

Williamson E, Driver S, Baxter K. editors: Stockley's Herbal Medicines Interactions. A guide to the interactions of herbal medicines. 2nd Ed. The Pharmaceutical Press, 2013 London.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

General

The use of *Serenoa repens* originates from America where the Native Americans used it in cases of infertility and impotence. The use of the whole berries as a tonic was later adopted by colonists. The first reports in the literature about use in urinary complaints date from the beginning of the 20th century (Verhelst, 2010).

Serenoa repens has been traditionally used as water and ethanol extracts. It is stated to possess diuretic, urinary antiseptic, endocrinological and anabolic properties. Traditionally it has been used for chronic or sub-acute cystitis, catarrh of the genitourinary tract, testicular atrophy, sex hormone disorders and most specifically for prostatic enlargement. Inflammation of lactic glands in the breast, eczema, bronchial pathology and cough are also mentioned as indications in traditional medicine. It has been deemed to enhance sexual desire. There is no scientific support for these traditional applications (Barnes *et al*., 2007; Hänsel *et al*., 1994).

The main interest in *Serenoa repens* has focused on its use in the treatment of symptoms of benign prostatic hyperplasia (BPH), in particular, grade I to III (Vahlensieck; see Table 7). Preparations are used to alleviate micturition disorders such as, dysuria, pollakisuria, nocturia and urine retention (Barnes *et al*., 2007; Hänsel *et al*., 1994; Van Hellemont, 1985; ESCOP, 2003).

Practice

Data on the following preparations are reported using standard sources.
Serenoae repentis mother tincture (Ø): 3 x 5 drops per day (Van Hellemont, 1985; Delfosse, 1998). Other sources recommend 3 x 25 drops a day (Verhelst, 2010).
Dried fruit: 0.5 to 1.0 g as a decoction 3 x per day (Barnes *et al*., 2007; ESCOP, 2003). For preventive use 2-3 x 200 mg is recommended (Verhelst, 2010).
The preparations are not further documented in this report.

2.2. Information on traditional/current indications and specified substances/preparations

Austria

Product 1 (WEU)
Preparation: dry extract of *Serenoa repens* , fructus: 160 mg per capsule
Extraction solvent hexane standardised to 85-95% fatty acids (free and esterified); 1.8-3.5% non-saponifiable fraction, containing 0.15-0.25% and 0.15-0.4% long chain fatty alcohols
Since when on the market: 1994
Pharmaceutical form: soft capsule
Posology: 2 capsules daily for 4-8 weeks
Therapeutic indication: Prostatic hypertrophia and prostatic adenoma at an early stage (stage I or II). In case of contraindication of a surgery also in severe cases (WEU).

Product 2 (WEU)
Preparation: dry extract of *Serenoa repens* , fructus 320 mg per capsule
DER 8.0-9.52:1, extraction solvent ethanol 90% m/m
Since when on the market: 1999
Pharmaceutical form: soft capsule
Posology: 1 capsule daily
Therapeutic indication: supportive treatment of mild complaints of urination in men, like pollakisuria, dysuria, dribbling (WEU)

Product 3 (WEU)
Preparation: dry extract of *Serenoa repens*, fructus 160 mg per capsule
DER 9-12:1, extraction solvent ethanol 96% V/V
Since when on the market: 2007
Pharmaceutical form: capsule
Posology: 1 capsule daily for 4-8 weeks
Therapeutic indication: supportive treatment of mild complaints of urination in men, such as pollakisuria, dysuria, dribbling (WEU)

Product 4 (WEU)
Preparation: dry extract of *Serenoa repens*, fructus 320 mg per capsule.
DER 9-11:1, extraction solvent ethanol 96% V/V
Since when on the market: 2006
Pharmaceutical form: capsule
Posology: 1 capsule daily
Therapeutic indication: to be mentioned (WEU)

Combination products are also available.

Belgium

Product 1 WEU

Preparation: dry extract of *Serenoa repens*, *fructus* (6.5–9:1): 320 mg per capsule. Extraction fluid: supercritical CO_2

Since when on the market: 1996

Pharmaceutical form: soft capsules

Posology: 1 capsule per day in the morning with food

Therapeutic indication: symptomatic treatment of urinary retention due to benign prostate hyperplasia, after exclusion of serious complications (WEU)

Other information: Pyrosis and gastic pain were reported when taken on an empty stomach. The frequency is not known.

Product 2 TU

Preparation: lipophilic extract of *Serenoa repens*, *fructus* (no DEV given). Extraction solvent: ethanol 90%: 320 mg per capsule

Since when on the market: 1996

Pharmaceutical form: soft capsules

Posology: 1 capsule per day by preference during a meal

Therapeutic indication: Used as an adjuvant in case of urinary retention due to benign prostate hyperplasia, after exclusion of serious pathologies (TU).

Other information: gastro-intestinal side effects when taken on an empty stomach. Allergic reactions. The frequency of both side effects is seldom.

Product 3 TU

Preparation: *Serenoa repens*, fructus, dry extract DER 9.0-12.0:1, extraction solvent ethanol 94% m/m: 320 mg per capsule

Since when on the market: 2013

Pharmaceutical form: soft capsules

Posology: 1 capsule per day by preference during a meal

Therapeutic indication: "Traditional herbal medicine to alleviate symptoms of the lower urinary tract in men after the diagnosis of benign prostate hyperplasia (BPH) has been confirmed. Before starting to use this traditional herbal medicine, all serious conditions should be excluded by a medical doctor."

Combination products are also available

Bulgaria

Preparation: extract (solvent: hexane) (DER 7-11:1) (MA). Containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part: 160 mg per capsule

Since when on the market: not specified

Pharmaceutical form: hard capsule

Posology: 1 capsule 2 times daily

Therapeutic indication: treatment in micturition moderate disorders connected with BHP (WEU).

Other information: gastro-intestinal disorders (nausea, abdominal painful) may occur. Frequency is not known. Rare skin rash and oedema have been reported very rare. Reversible gynecomastia cases have been observed.

Croatia

Only combination products are available.

Czech Republic

Product 1 (WEU)
Preparation: Serenoae extractum 7-11:1, extraction solvent hexane - 160 mg/capsule.
Since when on the market: 1996
Pharmaceutical form: hard capsules
Posology: 1 capsule per day
Therapeutic indication: in men in functional disorders (such as the frequent urination especially at night, weak or interrupted urinary flow, or the feeling of not being able to empty the bladder completely) associated with early stages of benign prostatic hyperplasia (WEU).
Contraindication: hypersensitivity to the active substance
Adverse effects: nausea and pyrosis when used before meal, frequency is not known

Product 2 (WEU)
Preparation: Serenoae extractum 8.0-9.52:1, extraction solvent ethanol 90% (V/V)-320 mg/capsule
Since when on the market: 1999
Pharmaceutical form: soft capsules
Posology: 1 capsule /day
Therapeutic indication: micturation disorders associated with benign prostatic hyperplasia (WEU)
Contraindication: hypersensitivity to the active substance
Special warning: regular control by urologist is needed

Product 3 (WEU)
Preparation: Serenoae extractum 9-11:1, extraction solvent ethanol 96 % (V/V) – 320 mg/capsule
Since when on the market: 2000
Pharmaceutical form: soft capsules
Posology: 1 capsule daily
Therapeutic indication: micturation disorders associated with benign prostatic hyperplasia stage I and II according to Alken (WEU)
Contraindication: hypersensitivity to the active substance
Adverse effects: rarely nausea, eructation and pyrosis

Product 4 (WEU)
Preparation: Serenoae extractum 9-11:1, extraction solvent ethanol 96% (V/V) – 160 mg/cps
Since when on the market: 1999
Pharmaceutical form: soft capsules
Posology: 1 capsule 2 x daily
Therapeutic indication: micturation disorders associated with benign prostatic hyperplasia stage I and II (WEU)
Special warning: regular control by urologist is needed
Adverse effects: rarely gastric and intestinal disorders

Product 5 (WEU)
Preparation: Serenoae extractum 9-11:1, extraction solvent ethanol 96% (V/V) – 320 mg/cps
Since when on the market: 1999
Pharmaceutical form: soft capsules
Posology: 1 capsule daily
Therapeutic indication: micturation disorders associated with benign prostatic hyperplasia stage I and II (WEU).
Special warning: regular control by urologist is needed
Adverse effects: rarely gastric and intestinal disorders

Product 6 (WEU)

Preparation: Serenoae extractum 10–14.3:1, extraction solvent ethanol 90% (w/w) -160 mg/cps
Since when on the market: 1999
Pharmaceutical form: soft capsules
Posology: 1 capsule 2 x daily
Therapeutic indication: in men in functional disorders (such as the frequent urination especially at night, weak or interrupted urinary flow, or the feeling of not being able to empty the bladder completely) associated with benign prostatic hyperplasia stage I and II (WEU)
Contraindication: hypersensitivity to the active substance
Adverse effects: nausea and pyrosis when used before meal, frequency is not known

Combination products are also available.

Denmark

Product 1 (WEU)

Preparation: fruit extract 320 mg (ethanol 96% extract) corresponding to 2.88 to 3.84 mg *Serenoa repens* fruit.
Since when on the market: 1997
Pharmaceutical form: soft capsules
Posology: 1 capsule daily
Therapeutic indication: Herbal medicinal product to relief of urinary difficulties due to minor benign prostate hyperplasia when a medical doctor has excluded other reasons for the disease (WEU).
Other information: Patients are advised to contact a doctor if symptoms worsen or if no relief is seen within 3 months.

Product 2 (WEU)

Preparation: *Serenoa repens* fruit extract 320 mg (ethanol 96% extract) corresponding to 2.9 to 3.5 mg *Serenoa repens* fruit
Since when on the market: 2007
Pharmaceutical form: soft capsules
Posology: 1 capsule daily
Therapeutic indication: Herbal medicinal product to relief of urinary difficulties due to minor benign prostate hyperplasia when a medical doctor has excluded other reasons to the disease (WEU).
Other information: Patients are advised to contact a doctor if symptoms worsen or if no relief is seen within 3 months.

Estonia

Product (WEU)

Preparation: Each soft capsule contains an extract of *Serenoa repens* berries (9-11:1) 320 mg, Extraction agent: ethanol 96% per capsule
Since when on the market: 2000
Pharmaceutical form: soft capsules
Posology: 1 soft capsule is taken daily at the same time of each day
Therapeutic indication: used in the treatment of voiding difficulties in benign enlargement of the prostate gland (benign prostatic hyperplasia, BPH)(WEU)
Other information: side effects: gastrointestinal disorders (rare: stomach discomfort)

Finland

Product 1 (WEU)
Preparation: *Serenoae repentis* fruct. extr. spir. oleos. (9-11:1) 320 mg per capsule
Since when on the market: 2004
Pharmaceutical form: soft capsules
Posology: 1 capsule x 1 for men
Therapeutic indication: herbal medicinal product for mild prostate complaints for men (WEU)
Other information: Not for children. Gastric complaints may occur rarely.

Product 2 (WEU)
Preparation: *Serenoae repens* (syn.Sabal. serrulatae) fruct.extr.spir.oleos. (9-12:1). 320 mg
Since when on the market: 1999
Pharmaceutical form: soft capsules
Posology: 1 capsule x 1 for men
Therapeutic indication: herbal medicinal product for mild prostate complaints for men (WEU)
Other information: Not for children. Gastric complaints may occur rarely.

Product 3 (WEU)
Preparation: *Serenoae repentis* fruct. extr. oleos. (6.5-9:1) 160 mg
Since when on the market: 2007
Pharmaceutical form: soft capsules
Posology: 1 capsule x 2 for men
Therapeutic indication: herbal medicinal product for mild prostate complaints for men (WEU)
Other information: Not for children. Gastric complaints may occur rarely.

France

Product 1 (WEU)
Preparation: extract (solvent: hexane) (DER 7-11:1) containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part: 80 mg per tablet
Since when on the market: 1981
Pharmaceutical form: coated tablet
Posology: 4 tablets daily
Therapeutic indication: Functional symptoms connected with BHP (WEU)
Other information: not applicable

Product 2 (WEU)
Preparation: extract (solvent: hexane) (DER: 7-11:1). Containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part: 160 mg per capsule
Since when on the market: 1982
Pharmaceutical form: hard capsule
Posology: 1 capsule 2 times daily
Therapeutic indication: treatment in micturition moderate disorders connected with BHP (WEU)
Other information: Gastro-intestinal disorders such as abdominal pain (≥1/100 to <1/10): frequency common. Nausea (≥1/1000 to <1/100): Frequency uncommon
Increase of transaminase or gamma-glutamyltransferase has been reported (≥1/1000 to <1/100): Frequency uncommon. Skin rash has been reported (≥1/1000 to <1/100): frequency uncommon.
Reversible gynecomastia cases have been reported (≥1/1000 to <1/100): frequency uncommon.
Headache has been reported (≥1/100 to <1/10): Frequency common
Oedema has been reported. The frequency is unknown.

Product 3 (WEU)

Preparation: dry extract (solvent: CO_2), (DER: 6.5-9:1)

Since when on the market: 2010

Pharmaceutical form: hard capsule

Posology: 1 capsule 2 times daily (1 capsule contains 160 mg)

Therapeutic indication: treatment in micturition moderate disorders connected with BHP.

Other information: gastro-intestinal disorders (nausea, abdominal painful) may occur. Frequency is not known. Rare skin rash and oedema have been reported. Very rarely reversible gynecomastia cases have been observed.

Germany

Preparations on the market:

1, 5, 8, 16, 17, 18, 22, 23, 24, 28, 29, 32, 33)	soft extract (9-11:1), extraction solvent: ethanol 96% V/V
2, 3)	soft extract (9-11:1), extraction solvent: ethanol 90% V/V
4, 6, 27)	soft extract (9-11:1), extraction solvent: ethanol 96% V/V
7, 14, 15, 34, 39, 40)	soft extract (10-14.3:1), extraction solvent: ethanol 90% m/m
9, 10, 19, 20, 25, 26, 31)	soft extract (7.5-12.5:1), extraction solvent: ethanol 90% m/m
11)	soft extract (8-13:1), extraction solvent: ethanol 90% m/m
12, 36, 37, 38, 41)	soft extract (10-14.3:1), extraction solvent: ethanol 90% m/m
13)	soft extract (9-12:1), extraction solvent: ethanol 96% V/V
21, 35)	soft extract (8.0-9.52:1), extraction solvent: ethanol 90% m/m
30)	soft extract (8-13:1), extraction solvent: ethanol 90% m/m
42)	soft extract (10-14:1), extraction solvent: ethanol 90% m/m

Since when on the market:

1, 6, 18, 24, 27, 33)	1997
2, 3)	2000
4, 7, 8, 14, 15, 34, 39, 40)	1995
5, 9, 10, 13, 16, 17, 21, 22, 23, 28, 29, 32, 35)	1998
11, 19, 20, 25, 30)	1999
12)	1994
36, 37, 38)	2008
26, 31, 41, 42)	at least since 1976

Pharmaceutical form:

All soft capsules

Posologies

All for oral use in male adults

1, 5, 8, 16, 22, 29, 32, 33)	1 x daily 1 containing 320 mg soft extract
2, 3)	1 x daily 1 containing 320 mg soft extract
4, 6)	2 x daily 1 containing 160 mg soft extract
7, 14, 15, 34, 39, 40)	1 x daily 1 containing 320 mg soft extract
9, 20)	2 x daily 1 containing 160 mg soft extract
10, 19, 25, 26, 31)	1 x daily 1 containing 320 mg soft extract
11)	1 x daily 1 containing 320 mg soft extract
12, 36, 37, 38)	2 x daily 1 containing 160 mg soft extract

13)	1 x daily 1 containing 320 mg soft extract
17, 18, 23, 24, 28)	2 x daily 1 containing 160 mg soft extract
21)	2 x daily 1 containing 160 mg soft extract
27)	1 x daily 1 containing 320 mg soft extract
30)	1 x daily 1 containing 320 mg soft extract
35)	1 x daily 1 containing 320 mg soft extract
41)	1 x daily 1 containing 320 mg soft extract
42)	2 x daily 1 containing 160 mg soft extract

Therapeutic indications:

1, 2, 4, 5, 6, 9, 10, 13,16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 37, 38, 42) urinary complaints related to benign prostate enlargement (alken-stage I to II).

3, 7, 8, 14, 15, 34, 39, 40, 41) urinary complaints related to benign prostate enlargement (alken-stage I to II).

11) urinary complaints related to benign prostate enlargement (alken-stage I to II).

12) urinary complaints related to benign prostate enlargement (alken-stage I to II).

Other information:

Gastro-intestinal

Uncommon: gastro-intestinal complaints (nausea, vomiting, diarrhoea, stomach ache, abdominal pain)

Vascular

Uncommon: rise in blood pressure

Frequency not known: bleeding when taken together with other medicinal products (Phenprocoumon, Warfarin, Clopidogrel, Acetylsalicyl acid, NSAR)

Immune system

Frequency not known: allergic or hypersensitivity reactions

Eye:

Frequency not known: intra-operative floppy iris syndrome

Greece

Preparation: extract (solvent: hexane) (DER 7-11:1) (MA). Containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part: 160 mg per capsule

Since when on the market: not specified

Pharmaceutical form: hard capsule

Posology: 1 capsule 2 times daily

Therapeutic indication: treatment in micturition moderate disorders connected with BHP (WEU).

Other information: gastro-intestinal disorders (nausea, abdominal painful) may occur. Frequency is not known. Rare skin rash and oedema have been reported very rare. Reversible gynecomastia cases have been observed.

Hungary

Product 1 (WEU)

Preparation: Extractum *Serenoa repens* fructus (DER: 8-9.52:1)

Extraction solvent: ethanol 90%(m/m): 320 mg/capsule

Since when on the market: 2004

Pharmaceutical form: soft capsule

Posology: one capsule daily

Therapeutic indication: in the early stages of benign prostatic hyperplasia (according to Alken I. and II. phase, moreover according to the Vahlensieck II. and III. phase) for the treatment of terminal dribbling (WEU)
Other information: Rare: Gastrointestinal symptoms may occur.

Product 2 (WEU)
Preparation: sabalis serulatae extractum (DER: 7.5-12.5:1). Extraction solvent: ethanol 96% (m/m)
Since when on the market: 1997
Pharmaceutical form: soft capsule
Posology: one capsule daily in the same time, taking after meals with plenty amount of water.
Therapeutic indication: For the treatment of urinary symptoms related to benign prostatic hyperplasia. (BPH according to Alken I and II, according to Vahlensieck II and III phase).
The product reduces the urinary symptoms without ending the enlargement so the patient's condition requires constant control (WEU)
Other information:
Gastrointestinal tract: very rare (0.1-1%) gastro-intestinal symptoms
Skin: hypersensitivity reactions very rare (‹0.01%)- allergic reaction
Nervous system: very rarely dizziness

Product 3 (WEU)
Preparation: sabalis serulatae extractum (DER: 9-11:1). Extraction solvent: ethanol 96%(V/V): 320 mg per capsule
Since when on the market: 1999
Pharmaceutical form: soft capsule
Posology: one capsule daily, swallowed after meals with plenty amount of water in a whole
Therapeutic indication: for the symptomatic treatment of urinary problems in benign prostatic hyperplasia according to Alken I. and II. Phase (WEU)
Other information: rare: abdominal discomfort, nausea, diarrhoea

Product 4 (WEU)
Preparation: sabalis serulatae extractum (DER: 9-11:1). Extraction solvent: ethanol 96%(V/V): 320 mg per capsule
Since when on the market: 2002
Pharmaceutical form: soft capsule
Posology: one capsule daily, taken with plenty amount of water
Therapeutic indication: For the treatment of urinary symptoms related to benign prostatic hyperplasia (BPH according to Alken I and II, according to Vahlensieck II and III phase) (WEU)
Other information: in rare cases, gastrointestinal side effects

Product 5 (WEU)
Preparation: 160 mg per capsule (no further details given on the extract)
Since when on the market: 2001
Pharmaceutical form: soft capsule
Posology: one capsule twice daily
Therapeutic indication: For the treatment of prostatic hyperplasia reported urination disorders (benign prostatic hyperplasia associated with urinary disorders according to I. and II. Phase).
The product improves emptying the bladder, reducing the urge to urinate, reduces the too frequent and too weak emptying of the bladder, relieves the painful related to urination and increases the amount of excreted urine (WEU).
Other information: rarely: gastro-intestinal complaints

Combination products are also available.

Italy

Product 1 (Authorised product)

Preparation: *Serenoa repens* dry ripe fruit; DER 7-11:1, extraction solvent: mixture of hexanes, cyclohexane and methylcyclopentane with specific acceptance criteria: 99%

Since when on the market: 1984

Pharmaceutical form: soft capsules

Posology: 320 mg 1-2 times daily depending on the severity of BPH (during meals)

The treatment should be continued for not less than 30 days. The cycles may be repeated.

Therapeutic indication: Functional disorders of BPH. It is used on symptoms of BPH such as: pollakiuria, disuria, decrease in volume and strength of urination, sensation of incomplete emptying of bladder and of painful perineal tension. The administration facilitates the surgery therapy, because it ameliorates the patient's clinical conditions.

Other information:

a) *Gastrointestinal pathologies*: nausea, gastrointestinal complaints abdominal pains. Frequency: unknown.
b) *Skin pathologies and subcutaneous tissue:* cutaneous rash, edema. Frequency: unknown.
c) *Reproductive system and mammary pathologies:* gynecomastia. Frequency: unknown.

Product 2 (Authorised product)

Preparation: *Serenoa repens* fruit; DER 9-12:1; extraction solvent ethanol 93%

Since when on the market: 1993

Pharmaceutical form: soft capsules

Posology:

160 mg 2 times daily: (The posology may vary) according to the medical prescription.

320 mg 1-2 times daily, depending on the severity of BPH (during meals).

The treatment should be continued for not less than 30 days. The cycles may be repeated.

Therapeutic indication: Functional disorders of BPH.

Other information: Occasionally nausea, particularly when the medicine has been taken on an empty stomach.

Product 3 (Authorised product)

Preparation: *Serenoa repens* fruit; DER 9-12:1; extraction solvent ethanol 96%

Since when on the market: 1993 (160 mg) and 1996 (320 mg)

Pharmaceutical form: soft capsules

Posology: 160 mg 2 times daily: (The posology may vary) according to the medical prescription

The treatment should be continued for not less than 30 days. The cycles may be repeated

Therapeutic indication: Functional disorders of BPH. It is used on symptoms of BPH such as: pollakiuria, nicturia, disuria, decrease in volume and strength of urination, sensation of incomplete emptying of bladder and of painful perineal tension. The clinical testing results have confirmed, in a large part of the study population, the improvement of symptoms at the beginning of the disease and for uncomplicated cases. In more advanced states of the disease, the administration may be useful to relief the symptoms and to ameliorate the patient's clinical conditions before the surgery.

Other information: Occasionally gastrointestinal pathologies: nausea, gastrointestinal complaints, epigastric pains, headache, vertigo, sleepiness, insomnia, cutaneous rash, itching.

Product 4 (Authorised product)

Preparation: *Serenoa repens* dry ripe fruit; DER 6.5-9:1, extraction solvent CO_2

Since when on the market: 1993

Pharmaceutical form: soft capsules

Posology: 160 mg 2 times daily: The posology may vary according to the medical prescription.

The treatment should be continued for not less than 30 days. The cycles may be repeated.
Therapeutic indication: Functional disorders of BPH
Other information: Occasionally nausea, particularly when the medicine has been taken on an empty stomach

Product 5 (Authorised product)
Preparation: *Serenoa repens* fruit; DER 9-12:1; extraction solvent ethanol 96%
Since when on the market: 1994
Pharmaceutical form: soft capsules
Posology: 160 mg 2 times daily to take with water
Therapeutic indication: Functional disorders of BPH
Other information: Occasionally nausea, particularly when the medicine has been taken on an empty stomach

Product 6 (Authorised product)
Preparation: *Serenoa repens* fruit; DER 10-14; 3:1; extraction solvent ethanol 90%
Since when on the market: 2000
Pharmaceutical form: soft capsules
Posology: 320 mg 1-2 times daily, depending on the severity of BPH (during meals)
The treatment should be continued for not less than 30 days. The cycles may be repeated.
Therapeutic indication: Urinary disorders (nicturia, pollakiuria, polyuria), in case of BPH I and/ or II Alken stadium
Other information: (rarely seen) Occasionally gastrointestinal pathologies: nausea, gastrointestinal complaints, diarrhea particularly when the medicine has been taken on an empty stomach. Cutaneous and subcutaneous disorders: allergic reaction such as cutaneous rash, itching and exanthema

Combination products are also available.

Latvia

Product (WEU)
Preparation: *Serenoae repentis fructus extractum spissum* (9–11:1), extraction solvent: ethanol 96%: 320 mg per capsule
Since when on the market: 1999
Pharmaceutical form: soft capsules
Posology: 320 mg of extract (1 capsule) per day
Therapeutic indication: disturbed urination in I and II stages of benign prostate gland hypertrophy (WEU)

Lithuania

Product 1 (WEU)
Preparation: lipido-sterolic extract: 160 mg/capsule
Since when on the market: 1997
Pharmaceutical form: capsules
Posology: two capsules daily (320 mg) with meals
Therapeutic indication: Symptomatic treatment of benign prostatic hyperplasia
Other information: May lead to gastrointestinal problems, such as nausea and abdominal pain. Rare skin reactions and swelling may occur. Very rarely seen gynecomastia, which disappeared after stopping the medicine (WEU).

Product 2 (WEU)
Preparation: extractum spissum 9.0-11.0:1; ethanol 96%: 320 mg/capsule
Since when on the market: 1999
Pharmaceutical form: capsules
Posology: one capsule daily
Therapeutic indication: Symptomatic treatment of benign prostatic hyperplasia (WEU).

Product 3 (WEU)
Preparation: extr. fruct. *Serenoa repens* seu Sabali serrulatae spissum (10-14.3:1); ethanol 90% m/m: 320 mg/capsule
Since when on the market: 1999
Pharmaceutical form: capsules
Posology: one capsule daily
Therapeutic indication: Symptomatic treatment of benign prostatic hyperplasia (WEU).
Other information: In rare cases gastrointestinal problems may occur.

Luxemburg

Preparation: extract (solvent:hexane) (DER 7-11:1) (MA). Containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part: 160 mg per capsule
Since when on the market: not specified
Pharmaceutical form: hard capsule
Posology: 1 capsule 2 times daily
Therapeutic indication: treatment in micturition moderate disorders connected with BHP (WEU)
Other information: gastro-intestinal disorders (nausea, abdominal painful) may occur. Frequency is not known. Rare skin rash and oedema have been reported very rare. Reversible gynecomastia cases have been observed.

Malta

Preparations classified as food supplements.

Netherlands

Product (TU)
Preparation: Ethanolic extract of *Serenoa repens* (Betram). Extraction solvent: ethanol 96% (V/V) DER 9-12:1.
Since when on the market: 2009
Pharmaceutical form: capsule
Posology: oral, once daily
Therapeutic indication: Traditional herbal medicinal product used for the relief of urinary complaints such as the need to urinate frequently and weak or interrupted urinary flow in men who have confirmed diagnosis of a benign enlarged prostate (benign prostatic hypertrophy). The use is based on traditional use only, not on clinical evidence" (Pharmacy only)(TU).
Other information: Gastro-intestinal complaints (>1/10.000, <1/1.000)

Additional information
The product in the present composition has been available since 1998 on the Dutch market. Comparable product has been available since 1964 on the market. The product has been registered as traditional use medicinal product in October 2009.

Norway

Product 1 (TU)

Preparation: 1 capsule contains: 320 mg soft extract of *Serenoa repens* (Bartram) Small, fructus (equivalent to 2.9-3.5 g dried *Serenoa repens* fruit)
Extration with ethanol 96% (V/V)
Therapeutic indication: Traditionally used for the relief of lower urinary tract symptoms such as frequent and nightly urination in men who have a confirmed diagnosis of benign prostatic hypertrophy (BPH) based on traditional use only. Prior to treatment other serious conditions should have been ruled out by a doctor (TU).
Posology: *Adult men:* 1 capsule daily.
Marketing authorisation: 27.6.2011.

Product 2 (WEU)

Preparation: 1 capsule contains 60 mg extract (as soft extract) from *Serenoa repens* (Bartram) Small, fructus (equivalent to 1.04–1.44 g dried *Serenoa repens* fruit)
Extraction: with supercritical CO_2
Posology: For oral use: *Adult and elderly men:* 1 capsule in the morning and evening
Therapeutic indication: for the relief of lower urinary tract symptoms in men with benign prostatic hypertrophy (BPH) such as frequent and nightly urination
Marketing authorisation: 23.8.2011

Product 3 (TU)

Preparation: *Serenoa repens* fruit extr. soft extract from *Serenoa repens* (Bartram) Small equivalent to 1.04-1.44 g dried *Serenoa repens* fruit: 160 mg per capsule
No data about the date of registration, the pharmaceutical form and the posology
Therapeutic indication: traditionally used for the relief of lower urinary tract symptoms in men who have a confirmed diagnosis of benign prostatic hypertrophy (BPH), based on traditional use only. Prior to treatment other serious conditions should have been ruled out by a doctor (TU).

Poland

Product 1 (WEU)

Preparation: *Serenoae repentis fructus* extractum spissum (9-11:1); extraction solvent – ethanol 96% (V/V)
Since when on the market: 1995
Pharmaceutical form: soft capsules
Posology: 1 capsule (320 mg) daily
Therapeutic indication: Micturition disorders in mild benign prostatic hyperplasia stages I and II such as: pollakisuria, nocturia, decrease of urine stream
Other information: Sporadic gastrointestinal complaints

Product 2 (WEU)

Preparation: *Serenoae repentis fructus* extractum spissum (9-11:1); extraction solvent – ethanol 96% (V/V)
Since when on the market: 2000
Pharmaceutical form: soft capsules
Posology: 1 capsule (320 mg) daily
Therapeutic indication: Micturition disorders in benign prostatic hyperplasia such as: decrease of urine stream, urgency, pollakisuria, nocturia
Other information: Gastrointestinal disorders

Product 3 (TU)

Preparation: *Serenoae repentis fructus* extractum (6.5-9:1); extraction solvent – supercritical carbon dioxide
Since when on the market: 2007
Pharmaceutical form: soft capsules
Posology: 1 capsule (160 mg) 2 times daily
Therapeutic indication: Functional disorders in mild benign prostatic hyperplasia such as: nocturia, decrease of urine stream, urine retention, pain complaints
Other information: Sporadic nausea

Product 4 (TU)

Preparation: *Serenoae repentis fructus* extractum (9-12:1); extraction solvent – ethanol 96% (V/V)
Since when on the market: 2004
Pharmaceutical form: soft capsules
Posology: 1 capsule (320 mg) daily
Therapeutic indication: Mild benign prostatic hyperplasia symptoms such as: nocturia, pollakisuria, urine retention, decrease of urine stream
Other information: Minor gastrointestinal complaints

Combination products are also available.

Portugal

Preparation: extract (solvent: hexane) (DER 7-11:1) (MA). Containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part: 160 mg per capsule
Since when on the market: 1982
Pharmaceutical form: hard capsule
Posology: 1 capsule 2 times daily
Therapeutic indication: treatment in micturition moderate disorders connected with BHP (WEU)
Other information: gastro-intestinal disorders (nausea, abdominal painful) may occur. Frequency is not known. Rare skin rash and oedema have been reported very rare. Reversible gynecomastia cases have been observed.

Romania

Product 1 (WEU)

Preparation : lipophilic hexane extract of *Serenoa repens*, fructus, containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part; 160 mg per capsule
Since when on the market: 1998
Pharmaceutical form: hard capsules
Posology: 1 capsule 2 times daily, by preference during meal
Therapeutic indication: treatment in micturition moderate disorders connected with BHP
Contraindication: hypersensitivity to the active substance
Adverse effects: gastro-intestinal disorders (nausea, abdominal painful) may occur. Skin rash and oedema have been reported very rare. Reversible gynecomastia cases have been observed.

Product 2 (WEU)

Preparation: Serenoae repentis fructus extractum spissum; DER 9-11:1; extraction solvent ethanol 96 (V/V); 320 mg per capsule
Since when on the market: 2001
Pharmaceutical form: soft capsules
Posology: one capsule per day taking with plenty amount of water

Therapeutic indication: Urinary complaints related to benign prostate enlargement (alken-stage I to II). The product reduces the urinary symptoms without ending the enlargement so the patient's condition requires constant control.
Adverse effects: Occasionally nausea, particularly when the medicine has been taken on an empty stomach.

Slovakia

Product (WEU)
Preparation: Serenoae extractum concentratum (9-11:1), extraction solvent: ethanol (96%): 320 mg
Since when on the market: 2000
Pharmaceutical form: soft capsule
Posology: oral, 1 capsule daily
Therapeutic indication: Urinary disorders in benign prostatic hypertrophy in the I and II phase of the disease (WEU)
Other information: rarely gastro-intestinal problems like nausea, vomiting

Slovenia

Product (WEU)
Preparation: extract (as soft extract) from *Serenoa repens* fruit (*Serenoa repens* (Bartram) Small fructus) (9-12:1). Extraction solvent: Ethanol 96% V/V: 320 mg per capsule
Since when on the market: 2008
Pharmaceutical form: soft capsules
Posology: Adults and the elderly: One capsule daily
Children and adolescents less than 18 years old: This product is not indicated in patients less than 18 years.
Therapeutic indication: Herbal medicinal products for relief of micturition disorders (disuria, pollakisuria, nocturia, urine retention) linked with benign prostatic hyperplasia (at stages I and II as defined by Alken or stages II and III as defined by Vahlensieck) which has been medically diagnosed (WEU).
Prior to treatment other serious conditions should have been ruled out by a doctor.

Spain

Product (MA)
Preparation: n-hexane lipidosterolic extract
Since when on the market: 1985
Pharmaceutical form: hard capsule (160 mg)
Posology: 160 mg 2 x daily
Therapeutic indication: relief of lower urinary tract symptoms associated with BPH
Other information:
- Uncommon gastrointestinal effects, such as nausea and abdominal pain, pyrosis, diarrhoea
- Rare cases of cutaneous reactions.
- Very rare cases of transitory modification of the hepatic enzymes, headache and vertigo, as well as gynecomastia.

Combination products are also available.

Sweden

Product 1 (WEU)

Preparation: 320 mg soft extract from *Serenoa repens* (Bartram) Small, fructus (9-11:1). Extraction solvent is ethanol 96%

Since when on the market: Since 2006-03-23 as a natural remedy, re-classified 2010-05-12 as a HMP according to Directive 2001/83 EC

Pharmaceutical form: soft capsules

Posology: oral 1 capsule daily

Therapeutic indication: G04CX02 : Herbal medicinal product used in case of mild micturition problems caused by benign prostatic hyperplasia e.g. nocturia (WEU).

Other information: A few cases of suspected interactions with warfarin have been reported. Increased INR-values have been described in these cases. The mechanism for this possible interaction is not clear (section 4.5 of the SmPC). Cases of gastrointestinal disturbances have been reported. The frequency is not known (section 4.8 of the SmPC).

Product 2 (WEU)

Preparation: 160 mg Soft extract from *Serenoa repens* (Bartram) Small, fructus (9-11:1). Extraction solvent is ethanol 96% (WEU)

Since when on the market: Since 2006-03-06 as a natural remedy, re-classified 2010-05-27 as a HMP according to Directive 2001/83 EC

Pharmaceutical form: soft capsules

Posology: oral 2 capsules daily

Therapeutic indication: G04CX02: Herbal medicinal product used in case of mild micturition problems caused by benign prostatic hyperplasia e.g. nocturia (WEU).

Other information:

A few cases of suspected interactions with warfarin have been reported. Increased INR-values have been described in these cases. The mechanism for this possible interaction is not clear (section 4.5 of the SmPC).

Cases of gastrointestinal disturbances have been reported. The frequency is not known (section 4.8 of the SmPC).

Product 3 (WEU)

Preparation: 320 mg soft extract from *Serenoa repens* (Bartram) Small, fructus (9-12:1). Extraction solvent is ethanol 96%

Since when on the market: Since 2004-06-29 as a natural remedy, re-classified 2011-10-30 as a HMP according to Directive 2001/83 EC

Pharmaceutical form: capsule

Posology: oral 1 capsule daily

Therapeutic indication: G04CX02: Herbal medicinal product used in case of mild micturition problems caused by benign prostatic hyperplasia e.g. nocturia (WEU)

Other information:

A few cases of suspected interactions with warfarin have been reported. Increased INR-values have been described in these cases. The mechanism for this possible interaction is not clear (section 4.5 of the SmPC).

Cases of gastrointestinal disturbances have been reported. The frequency is not known (section 4.8 of the SmPC).

Combination products are also available.

2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications

Table 1: Overview of extracts, posology and marketing data of within EU. Complete overview per country

Austria		
Extraction solvent hexane standardised to 85-95% fatty acids (free and esterified)	2 x 160 mg per day	Since 1994
Extraction solvent 90% ethanol (V/V) DER 8.0-9.52:1	1 x 320 mg per day	Since 1999
Extraction solvent 96% ethanol (V/V) DER 9-12:1	1 x 160 mg per day	Since 2007
Extraction solvent 96% ethanol (V/V) DER 9-11:1	1 x 320 mg per day	Since 2006
Belgium		
Extraction with supercritical CO_2 DER 6.5-9:1	1 x 320 mg per day	Since 1996
Extraction solvent 90% ethanol (no DER given)	2 x 160 mg per day	Since 1996
Extraction solvent 94% ethanol (m/m) DER 9.0-12.0:1	1 x 320 mg per day	Since 2013
Bulgaria		
Extraction solvent hexane DER 7-11:1	2 x 160 mg per day	Not specified
Czech Republic		
Extraction solvent hexane DER 7-11:1	1 x 160 mg per day	Since 1996
Extraction solvent ethanol 90% (V/V) DER 8.0-9.52:1	1 x 320 mg per day	Since 1999
Extraction solvent ethanol 96% (V/V) DER 9-11:1	1 x 320 mg per day 2 x 160 mg	Since 2000 Since 1999
Extraction solvent ethanol 90% (V/V) DER 10-14.3:1	2 x 160 mg per day	Since 1999
Denmark		
Extraction solvent ethanol 96% corresponding to 2.88 to 3.84 mg *Serenoa repens* fruit	1 x 320 mg per day	Since 1997
Estonia		
Extraction solvent ethanol 96% DER 9-11:1	1x 320 mg per day	Since 2000
Finland		
Serenoae repentis fruct.extr.spir.oleos. DER 9-12:1	1 x 320 mg per day	Since 1999
Serenoae repentis fruct. extr. oleos. DER 6.5-9:1	2 x 160 mg per day	Since 2007
France		
Extract solvent : hexane DER 7-11 : 1 containing 97 % of fat acids (free or esterified) and 3 % of an unsaponifiable part	4 x 80 mg per day 2 x 160 mg per day	Since 1981 Since 1982
Extraction solvent CO_2 DER 6.5-9:1	2 x 160 mg per day	Since 2010
Germany		
Soft extract extraction solvent: ethanol 90% m/m DER 7.5-12.5:1 Soft extract extraction solvent: ethanol 90% m/m DER 10-14.3:1	1 x 320 mg per day 2 x 160 mg per day	Since 1976
Soft extract extraction solvent: ethanol 96% V/V DER 9-11:1	2 x 160 mg per day 1 x 320 mg per day	Since 1995
soft extract extraction solvent: ethanol 96% V/V DER 9-12:1	1 x 320 mg per day	Since 1998
soft extract extraction solvent: ethanol 90% V/V DER 8.0-9.52:1	2 x 160 mg per day 1 x 320 mg per day	Since 1998
soft extract extraction solvent: ethanol 90% V/V DER 8-13:1	1 x 320 mg per day	Since 1999

Hungary		
Extractum Serenoae repentis fructus DER: 8-9.52:1	1 x 320 mg per day	Since 2004
Sabalis serulatae extractum, extraction solvent: ethanol 96% m/m DER: 7.5-12.5:1	1 x 320 mg per day	Since 1997
Sabalis serulatae extractum, extraction solvent: ethanol 96% V/V DER: 9-11:1	1 x 320 mg per day	Since 1999 and 2002
extractum Serenoae repentis fructus extraction solvent: ethanol 96% m/m DER:10-14.3:1	2 x 160 mg per day	Since 2001
Italy		
extraction solvent: mixture of hexanes, cyclohexane and methylcyclopentane DER 7-11:1	1-2 x 320 mg per day	Since 1984
Extraction solvent ethanol 93% DER 9-12:1	2 x 160 mg per day 1-2 x 320 mg per day	Since 1999
Extraction solvent ethanol 96% DER 9-12:1	2 x 160 mg per day 1 x 320 mg per day	Since 1993 Since 1996
Extraction solvent CO_2 DER 6.5-9:1	2x 160 mg per day	Since 1993
Extraction solvent ethanol 90% DER 10-14:1	1-2 x 320 mg per day	Since 2000
Lithuania		
Serenoae repentis fructus extractum spissum extraction solvent: ethanol 96% DER 9 – 11 : 1	1 x 320 mg per day	Since 1999
Latvia		
Lipido-sterolic extract	2 x 160 mg per day	Since 1997
Extractum spissum extraction solvent ethanol 96 % DER 9.0-11.0:1	1 x 320 mg per day	Since 1999
Extr. fruct. *Serenoa repens* seu *Sabali serrulatae* spissum extraction sovent ethanol 90 % m/m DER 10-14.3:1	1 x 320 mg per day	Since 1999
Slovakia		
Serenoae extractum concentratum extraction solvent: ethanol 96% DER 9-11:1	1 x 320 mg per day	Since 2000
Slovenia		
extract (as soft extract) from *Serenoa repens* fruit (*Serenoa repens* (Bartram) Small fructus) extraction solvent: Ethanol 96% V/V DER 9-12:1	1 x 320 mg per day	Since 2008
Spain		
n-hexane lipidosterolic extract (DER not specified)	2 x160 mg per day	1985
Sweden		
Soft extract from *Serenoa repens* (Bartram) Small, fructus extraction solvent ethanol 96% DER 9-11:1	1 x 320 mg per day 2 x 160 mg per day	Since 2006 reclassified in 2010 as HMP
Soft extract from *Serenoa repens* (Bartram) Small, fructus extraction solvent ethanol 96% DER 9-12:1	1 x 320 mg per day	Since 2004 reclassified in 2011 as HMP

From the overview of the extracts used a compilation was made in order to select the extracts to be considered for the monograph. All preparations are for oral use.

Table 2: Compilation of extracts according to solvent, DER, posology and introduction on the European market.

Extraction solvent hexane standardised to 85-95% fatty acids (free and esterified)	2 x 160 mg per day 1 x 160 mg per day	Since 1994 Since 1996
Extraction solvent 90% ethanol (V/V) DER 8.0-9.52:1	1 x 320 mg per day 2 x 160 mg per day	Since 1999 Since 1996
Extraction solvent 96% ethanol (V/V) DER 9-12:1	1 x 320 mg per day 1 x 160 mg per day	Since 1999 Since 2007
Extraction with supercritical CO_2 DER 6.5-9:1	1 x 320 mg per day	Since 1996
Serenoae repentis fruct. extr. spir. oleos. DER 9-11:1	1 x 320 mg per day	Since 2004
Serenoae repentis fruct.extr.spir.spiss. DER 9-12:1	1 x 320 mg per day	Since 1999
Serenoae repentis fruct. extr. oleos. DER 6.5-9:1	2 x 160 mg per day	Since 2007
Extract (solvent: hexane) containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part (Standardised hexane extract) DER 7-11:1	4 x 80 mg per day 2 x 160 mg per day	Since 1981 Since 1982
Soft extract extraction solvent: ethanol 90% m/m DER 7.5-12.5:1 Soft extract extraction solvent: ethanol 90% m/m DER 10-14.3:1	1 x 320 mg per day 2 x 160 mg per day	Since 1976
Soft extract extraction solvent: ethanol 96% V/V DER 9-11:1	2 x 160 mg per day 1 x 320 mg per day	Since 1995
soft extract extraction solvent: ethanol 96% V/V DER 9-12:1	1 x 320 mg per day	Since 1998
soft extract extraction solvent: ethanol 90% V/V DER 8.0-9.52:1	2 x 160 mg per day 1 x 320 mg per day	Since 1998
soft extract extraction solvent: ethanol 90% V/V DER 8-13:1	1 x 320 mg per day	Since 1999
Extractum *Serenoae repentis* fructus DER: 8-9.52:1	1 x 320 mg per day	Since 2004
sabalis serulatae extractum extraction solvent: ethanol 96% m/m DER 7.5-12.5:1	1x 320 mg per day	Since 1997
extractum Serenoae repentis fructus extraction solvent: ethanol 96% m/m DER:10-14.3:1	2 x 160 mg per day	Since 2001
lipido-sterolic hexan extract	2 x 160 mg per day	Since 1997

Table 3: Compilation of similar **ethanolic** extracts according to solvent concentration and DER**.**

Soft extract (8-13:1), extraction solvent ethanol 90% to 96% (V/V)	1 x 320 mg per day 2 x 160 mg per day 1 x 160 mg per day	Since 1995 Since 1998 Since 1996
Soft extract (7.5-14.3:1), extraction solvent: ethanol 90% to 96% m/m	1 x 320 mg per day 2 x 160 mg per day	Since 1976 Since 1997

Table 4: Compilation of extracts other than ethanolic.

Extraction with supercritical CO_2 (6.5-9:1) **Belgium & France** Posology: 1 capsule per day in the morning with food. Therapeutic indication: symptomatic treatment of urinary retention due to benign prostate hyperplasia, after exclusion of serious complications.	1 x 320 mg per day	Since 1996

Extract (solvent: hexane) (DER 7-11:1) containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part **France** Posology: 2 capsules daily (no duration specified) Therapeutic indication: treatment in miction moderate disorders connected with BHP.	4 x 80 mg per day 2 x 160 mg per day	Since 1981 Since 1982

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

3.1.1.1. In vitro experiments

3.1.1.1.1. Inhibition of 5-alpha-reductase and other enzymes *in vitro*

Lipophilic extracts from *Serenoa repens* fruit inhibit the activity of 5a-reductase, an enzyme catalysing the conversion of testosterone into dihydrotestosterone (DHT). Various extracts (hexane, ethanol, supercritical CO_2) gave IC_{50} values between 25 µg/ml and 2200 µg/ml depending on the assay (Niederprüm *et al*., 1994; Sultan *et al*., 1984; El-Seikh *et al.,* 1988; Breu *et al*., 1992;; Weisser *et al*., 1996; Palin *et al*., 1998; Bayne *et al.,* 1999; ESCOP, 2003). These inhibitions occurred without influencing the secretion of PSA-(Bayne *et al*., 1999; Habib *et al*., 2005).

Dose-dependent and non-competitive inhibition of 5a-reductase was observed in both the prostatic epithelium and the stroma: the mean inhibitory effect of an ethanolic extract at a concentration of 500 µg/ml was about 29% in the epithelium and 45% in the stroma. The inhibition is mainly due to free fatty acids in the saponifiable fraction (see also Table 5). The nonsaponifiable fraction, containing phytosterols, triterpenes and fatty alcohols, and the hydrophilic components proved to be inactive. In a comparative study with finasteride, IC_{50} values of between 5.6 µg/ml and 40 µg/ml were obtained with the various lipophilic extracts (hexane, ethanol, supercritical CO_2), compared to an IC_{50} of 1 ng/ml for finasteride (Rhodes *et al*., 1993; ESCOP, 2003).

The hexane extract non-competitively inhibited both isoforms of 5a-reductase with IC_{50} values of 4 µg/ml for type 1 and 7 µg/ml for type 2, whereas finasteride was a competitive inhibitor of both isozymes, with a more selective inhibition of type 2 (IC_{50}: 400 nM for type 1; 10.7 nM for type 2) (Iehlé *et al*., 1995; ESCOP, 2003)

A hexane extract from *Serenoa repens* fruit inhibited the formation not only of dihydrotestosterone but also of the testosterone metabolites androstenedione and 5a-androstane-3,7-dione in primary cultures of human stromal and epithelial cells derived from benign prostatic hyperplasia tissues, suggesting that it inhibits the activity of both 5a-reductase and 17β-hydroxysteroid dehydrogenase. An ethanolic extract (IC_{50}: 132 µg/ml) and a hexane extract (IC_{50}: 91 µg/ml) inhibited the enzyme aromatase, which catalyses the conversion of androgens into oestrogens (Koch, 1995; ESCOP, 2003).

A hexane extract inhibited the conversion of testosterone into DHT in cultured human foreskin fibroblasts. In addition, it was shown to strongly inhibit the formation of 5α-androstane-3α, 17β-diol up to 90%, thus inhibiting the 5α-reductase and the 3-ketosteroid reductase (Sultan, 1984). In primary cultures of stroma and epithelial cells derived from BPH and prostate cancer tissues, HESr inhibited the

formation of all testosterone metabolites studied while 5α-reductase inhibitors (4-MA and finasteride) inhibited DHT formation (Délos, 1995).

Table 5: Inhibition of 5-alpha-reductase from rat prostate (Koch, 1995).

Extracts and substances	IC_{50} in µg/ml
***Serenoa repens* extracts**	
Ethanol (WS 1473)	71
Hexane	59
Saturated fatty acids	
Caprylic acid (C_8)	> 200
Caprinic (C_{10})	123
Laurinic acid (C_{12})	64
Myristinic acid (C_{14})	> 200
Palmitinic acid (C_{16})	> 200
Unsaturated fatty acids	
Oleic acid ($C_{18:1}$)	91
Gamma-linolenic acid ($C_{18:3}$)	24
Fatty acids ethyl esters	
C_8 to C_{16}	> 200
Oleic acid ethylester	> 200
Fatty alcohols	
C_{22}, C_{24}, C_{26} and C_{28} alcohols	> 200
Hydroxy fatty acids	
4-OH, 5-OH-C_{10} and 5-OH-C_{12}	> 200
Other substances	
Sitosterin and sitosterin glycosides	> 200
Gibberellin A_3 and gibberellinic acid	> 20
Olive oil	> 200
Progesteron	0.13
4-androstene-17-carboxylic acid	0.17
finasteride	0.004

Receptor binding studies by Abe et al. (2009)

Abe *et al*. (2009) investigated binding affinities of *Serenoa repens* fatty acids for (alpha(1)-adrenergic, muscarinic and 1,4-DHP) receptors. *Serenoa repens* fatty acids inhibited specific [^{3}H]prazosin binding in rat brain in a concentration-dependent manner with IC_{50} values of 23.8 to 136 µg/ml, and specific (+)-[^{3}H]PN 200-110 binding with IC_{50} values of 24.5 to 79.5 µg/ml. In addition, lauric acid, oleic acid, myristic acid and linoleic acid inhibited specific [^{3}H]N-methylscopolamine ([^{3}H]NMS) binding in rat brain with IC_{50} values of 56.4 to 169 µg/ml. Palmitic acid had no effect on specific [^{3}H]NMS binding.

Scatchard analysis revealed that oleic acid and lauric acid caused a significant decrease in the maximal number of binding sites (Bmax) for [^{3}H]prazosin, [^{3}H]NMS and (+)-[^{3}H]PN 200-110. According to the authors their results suggest that lauric acid and oleic acid bind noncompetitively to alpha(1)-adrenergic, muscarinic and 1,4-DHP calcium channel antagonist receptors.

A method has been developed for determining 5-alpha-reductase activity using LC/MS (using diHT). With this method, *Serenoa repens* extract inhibited 5alpha-reductase activity in rat liver with an IC_{50} of 101 µg/ml. Similarly, all the fatty acids except palmitic acid inhibited 5alpha-reductase activity, with IC_{50} values between 42.1 to 67.6 µg/ml.

In conclusion, lauric acid, oleic acid, myristic acid, and linoleic acid exerted binding activities of alpha(1)-adrenergic, muscarinic and 1,4-DHP receptors and inhibited 5alpha-reductase activity with IC_{50} values lower than those for *Serenoa repens* extract.

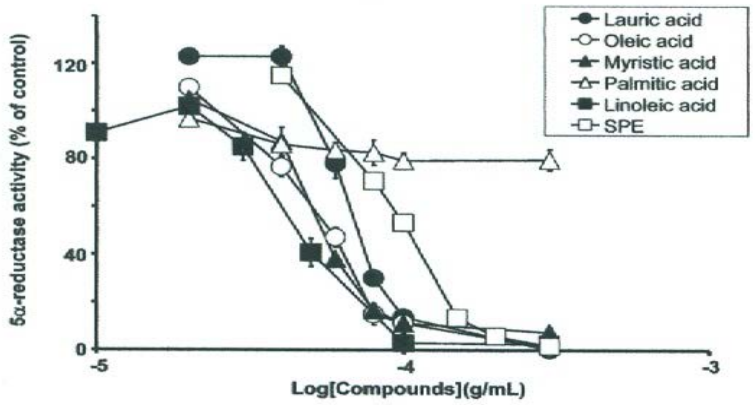

Figure 2: Inhibition of 5-alpha-reductase activity in the rat liver by *Serenoa repens* and free fatty acids. The activity of (-alpha-reductase was measured in the absence and presence of various concentrations (10-300 µg/ml) of *Serenoa repens* extract and free fatty acids. Each point represents the mean ± SE of 5 to 6 determinations (Abe *et al*., 2009).

Assessor's comments

Serenoa repens extracts, as well as isolated fatty acids have been shown to inhibit 5-alpha-reductase. This inhibition is concentration dependent and contributes to the plausibility of therapeutic use in cases of BPH.

3.1.1.1.2. Influence on androgenic receptors *in vitro*

A hexane extract from *Serenoa repens* fruit inhibited the receptor binding of androgens, but there is no concordance between different studies. In human prostatic cell lines LNCaP (lymph node carcinoma of the prostate) and PC3 (bone metastasis of prostatic carcinoma), which are respectively responsive and unresponsive to androgen stimulation, a hexane extract at 100 µg/ml induced a proliferative- effect in the LNCaP cell line, indicating a role of the androgen receptor in mediating the effects of the extract in these cells. In PC3 cells co-transfected with wild-type androgen receptors and CAT (chloramphenicol acetyl coenzyme A transferase) receptor genes under the control of an androgen responsive element, the extract inhibited androgen-induced CAT transcription by 70% at 25 µg/ml.

Ethanolic and CO_2 extracts had no, or only very weak, inhibitory activity on the receptor binding of androgens. Inhibition by 40.9% and 41.9% of dihydrotestosterone and testosterone in different tissue specimens by a hexane extract has been reported (Sultan *et al*., 1984; Rhodes *et al*., 1993; Breu *et al*., 1992; Koch, 1995; el-Sheikh *et al*., 1988; Carilla *et al*., 1984).

Assessor's comments

Experimental evidence points to a certain affinity of *Serenoa repens* preparations for androgenic receptors. No concentration relationship is reported.

3.1.1.1.3. Inhibition of alpha receptor binding

Six extracts from *Serenoa repens* fruit (two powdered extracts, four oils) inhibited [^{3}H]-tamsulosin binding to human prostatic alpha-adrenoceptors (IC_{50} = 50-100 µg/ml), [^{3}H]-prazosin binding to

cloned human alpha-adrenoceptors (IC_{50} = 10-20 µg/ml) and agonist-induced [^{3}H]-inositol phosphate formation by cloned alpha-adrenoceptors (63-69% inhibition by 400 ug/ml of powdered extracts; 33-46% inhibition by 800 µg/ml of extracted oils). The inhibition was non-competitive (Goepel *et al.*, 1999).

Assessor's comments

It is difficult to say whether the IC_{50} values are realistic, because information on the penetration of the fatty acids into the receptor sites is missing. The concentrations needed to partially inhibit inositol-phosphate appear high. Moreover the inhibition was not competitive raising doubts regards specificity.

3.1.1.1.4. Inhibition of eicosanoid synthesis

A hexane extract inhibited the calcium ionophore A23187-stimulated production of 5-lipoxygenase metabolites in human polymorphonuclear neutrophils at concentrations >5 µg/ml. The IC_{50} for inhibition of leukotriene B4 (LTB4) was approximately 13 µg/ml (Paubert-Braquet *et al.*, 1997).

A supercritical CO_2 extract was found to be a dual inhibitor of the cyclooxygenase (IC_{50}: 28.1 µg/ml) and 5-lipoxygenase pathways (IC_{50}: 18.0 µg/ml). A fraction containing acidic lipophilic compounds inhibited the biosynthesis of cyclooxygenase and 5-lipoxygenase metabolites with the same intensity as the native extract, while beta-sitosterol and fractions containing sterols and fatty alcohols as main components did not show inhibitory effects on either of the enzymes (Breu *et al.*, 1992a; Breu *et al.*, 1992b).

An ethanol extract inhibited formation of the cyclo-oxygenase generated thromboxane B2 (TXB2) (IC_{50}: 15.3 µg/ml) and synthesis of the 5-lipoxygenase product LTB4 (IC_{50}: 8.3 µg/ml). An alcoholic extract inhibited synthesis of the prostaglandins prostacyclin (PGI2) and prostaglandin E2 (PGE2). The concentrations are not specified (Hiermann 1989).

Assessor's comments

Outcomes of studies are given as IC_{50}-values on well characterised enzymes. This is positive as a concentration-response relationship is confirmed. Hexane, supercritical CO_2 as well as ethanolic extracts were tested on different enzymes involved in inflammation. Whether the concentrations required are relevant in a clinical context depends on the kinetics of the individual constituents.

3.1.1.1.5. Spasmolytic effects

A total lipidic extract and a saponifiable fraction from *Serenoa repens* fruit relaxed tonic contractions induced in various smooth muscle preparations by vanadate (EC_{50}: extract 43.9 µg/ml; saponifiable fraction 11.4 µg/ml), noradrenaline (EC_{50}: extract 530 µg/ml; saponifiable fraction 560 µg/ml), KCl (EC_{50}: extract 350 µg/ml: saponifiable fraction 430 ug/ml) and acetylcholine (EC_{50} of acetylcholine causing contractions of the urinary bladder: control: 4.41 µM; with extract at 1 mg/ml: 23.66 µM with saponifiable fraction at 1 mg/ml: 35.42 µM) or by coaxial electrical stimulation. The extract and the saponifiable fraction inhibited calmodulin-dependent cAMP phosphodiesterase activity (IC_{50}: extract 25.1 µg/ml; fraction 28.6 µg/ml) (Gutiérrez *et al.*, 1996a; Gutiérrez *et al.*, 1996b).

Assessor's comments

The IC_{50} values obtained are high, especially when contractions are induced by noradrenaline and KCl. Moreover *in vitro* experiments do not take into account the pharmacokinetic aspects, especially the penetration into the smooth muscle of the urinary tract.

3.1.1.1.6. Anti-inflammatory effect

De la Taille states that inflammation has a key role in the pathogenesis and progression of BPH and as a consequence inflammation serves as a target for BPH therapy (de la Taille, 2013).

In 1997, Paubert-Braquet *et al*. demonstrated that a lipidosterolic extract of *Serenoa repens* inhibited the A23187-stimulated production of leukotriene B4 (LTB4) production from human polymorphonuclear neutrophils starting at concentrations of 5 µg/ml. These effects were maximal at concentrations of 10 µg/ml (see above in the eicosanoid section: Paubert-Braquet *et al*.; 1997).

Sirab *et al*. (2013) explored the effects of a phytotherapeutic agent, lipidosterolic extract of *Serenoa repens* on the mRNA gene expression profiles of two representative models of BPH, BPH1 cell line and primary stromal cells derived from BPH. Treatment of these cells with the extract significantly altered gene expression patterns as assessed by comparative gene expression profiling on gene chip arrays. The expression changes were manifested three hours following *in vitro* administration of the extract, suggesting a rapid action for this compound. Among the genes most consistently affected by the treatment, the authors found numerous genes that were categorised as part of proliferative, apoptotic, and inflammatory pathways.

The authors evaluated the cell viability of the available BPH1 human prostate epithelial cells, as well as in primary stromal fibroblasts. The cells were exposed to 10 to 200 µg/ml and viability was assessed using the dimethylthiazol-diphenyltetrazolium test (MTT). Exposure to the extract lead to 100% decrease of cell viability, with a 50% lethal concentration of 60 µg/ml for BPH1 cells and 50 µg/ml for the fibroblasts.

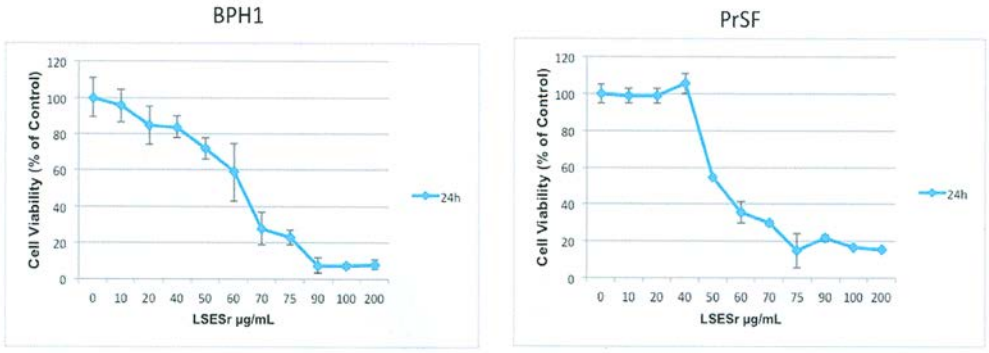

Figure 3: Results of the dimethylthiazol-diphenyltetrazolium test (MTT) to measure viability of human prostatic epithelial cells (BPH1) and primary stromal fibroblasts (PrSF) after exposure to different concentrations of a lipidosterolic extract of *Serenoa repens* (LSESr) (figure from Sirab *et al*., 2013).

Validation studies using quantitative real-time PCR confirmed the deregulation (up- or down regulation) of genes known to exhibit key roles in these biological processes including IL1B (interleukin 1-beta), IL1A (interleukin 1-alpha), CXCL6 (chemokine C-X-C motif ligand 6), IL1R1 (interleukin 1 receptor), PTGS2 (prostaglandin-endoperoxide-synthase 2), ALOX5 (arachidonate-5-lipoxygenase), GAS1 (growth arrest-specific 1), PHLDA1 (pleckstrin homology-like domain family A, member 1), IL6 (interleukin 6), IL8 (interleukin 8), NFkBIZ (nuclear factor of kappa light polypeptide gene enhancer in beta cells inhibitor zeta), NFKB1 (nuclear factor of kappa light polypeptide gene enhancer in beta-1 cells), TFRC (transferrin receptor [p90, CD71]), JUN (jun oncogene), CDKN1B (cyclin-dependent linase inhibitor 1B [p27, Kip1]), and ERBB3 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 [avian]). The incubations were done with concentrations of the lipidosterolic extract of *Serenoa repens* equal to 50% of the lethal concentration of the cell lines.

Subsequent analyses also indicated that treatment with the lipidosterolic extract of *Serenoa repens* can impede the stimulatory effects of certain pro-inflammatory cytokines such as IL6, IL17, and IL15 in these cells (Sirab *et al*., 2013).

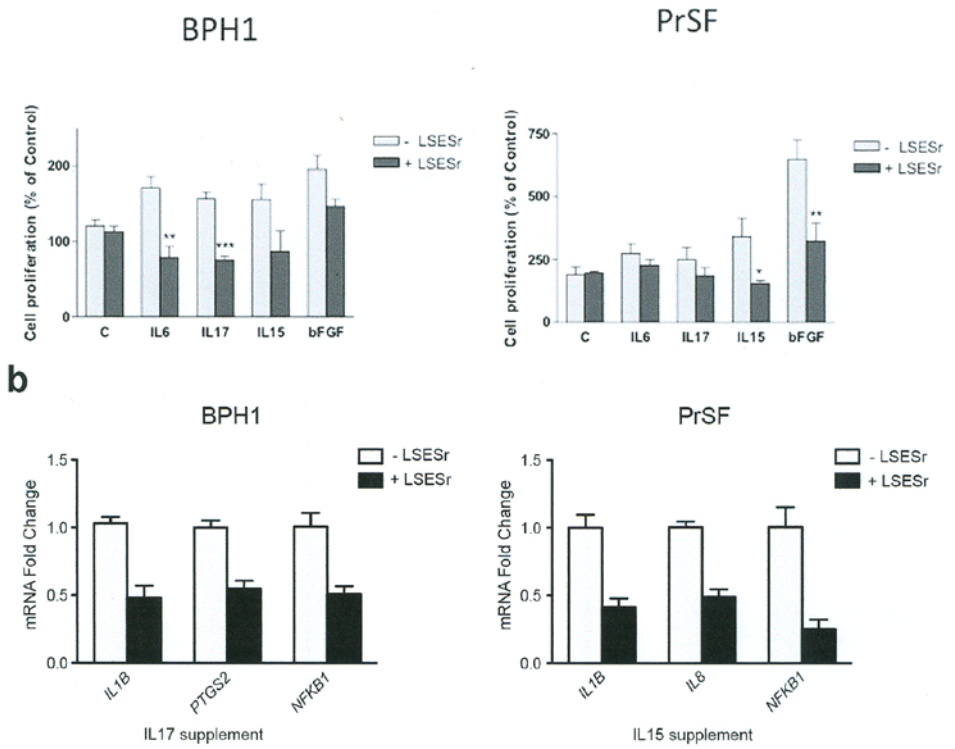

Figure 4: Effects of the lipidosterolic extract of *Serenoa repens* (LSESr) in BPH epithelial and stromal cells stimulated by inflammatory factors (upper panel). Cell proliferation index was determined using the Bromdeoxy-Uridine incorporation assay. Cells were treated with 10 ng/ml of recombinant human IL6, IL17, IL15 or Fibroblast Growth Factor (bFGF) for 24 hours in presence or absence of the extract (lower panel); Polymerase Chain Reaction (PCR) analysis for mRNA expression of some inflammatory markers in epithelial cells (BPH1) stimulated with IL17 (left) or in primary stromal fibroblasts (PrSF) stimulated with IL15 (right). Data are expressed as mean values (Standard Deviation) of duplicated experiments in presence or absence of the extract (Sirab *et al*., 2013).

The authors suggest that the inflammatory response and proliferation processes might to some extent be linked in BPH cells, and that the extract can disturb this link. The therapeutic results can be that inflammation and proliferation processes may be suppressed in both cell types.

Assessor's comments

The extract studied may be useful to treat BPH that manifests with inflammation characteristics. This study also supports a role for inflammation in BPH presumably by mediating the balance between apoptosis and proliferation. However, relatively high concentrations were used and it will depend on the penetration of extract constituents to the prostatic tissue to achieve relevant concentrations. Furthermore the effects on normal tissues should be investigated.

Inhibition of the expression of key inflammatory mediators by two different extracts (Latil et al., 2012)

The authors provide new insights into the anti-inflammatory properties of a commercially available hexane extract of *Serenoa repens* (standardised hexane extract). They studied the preventive action of the extract on leukocyte infiltration in benign prostatic hyperplasia by studying its impact on monocyte

chemo-attractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL2) and vascular cell adhesion molecule 1 (VCAM-1) expression *in vitro*. After pretreatment with the hexane extract, human prostate (epithelial and myofibroblastic) cells and vascular endothelial cells were stimulated with proinflammatory cytokines. MCP-1/CCL2 and VCAM-1 mRNA expression was quantified by real-time PCR. ELISA kits were used to determine MCP-1/CCL2 levels in culture supernatants and VCAM-1 expression in living cells.

The hexane extract reduced MCP-1/CCL2 mRNA levels in both epithelial (BPH-1) and myofibroblastic (WPMY-1) prostate cell lines. The hexane extract downregulated MCP1/CCL2 secretion by WPMY-1 cells in a concentration-dependent manner, more efficiently than *Serenoa repens* extracts obtained by supercritical carbon dioxide extraction. The hexane extract inhibited tumour-necrosis-factor-α-induced MCP-1/CCL2 secretion by the human vascular endothelial cell line EAhy.926, as well as surface VCAM-1 protein expression, in a concentration-dependent manner.

The authors concluded that the hexane extract impedes key steps of monocyte and T cell attraction and adherence by inhibiting MCP-1/CCL2 and VCAM-1 expression by human prostate and vascular cells in an inflammatory environment. They further conclude that these findings provide new insights into the anti-inflammatory effects of the hexane lipidosterolic extract of *Serenoa repens*, standardised hexane extract, in benign prostatic hyperplasia. Hexane LSESr inhibits early steps of leukocyte infiltration *in vitro* by down regulating MCP-1/CCL2 and VCAM-1 expression.

Assessor's comments

This publication indicates a possible interaction with nuclear receptors by the extracts studied.

Influence on prostatic cell proliferation and inflammation (Iglesias-Gato et al., 2012)

A commercially available *Serenoa repens* ethanolic extract inhibited epidermal growth factor (EGF) and lipopolysaccharide (LPS) induced proliferation of the prostatic epithelial, androgen independent cell line PC-3. At effective concentrations of 50 µg/ml, the extract partly displaced EGF from EGF receptor (EGFR) but fully blocked EGF-induced cell proliferation of PC-3 cells. Similarly, the extract inhibited LPS-induced proliferation of PC-3 cells without affecting LPS activation of the NFκB pathway via toll-like receptor-4 (TLR-4). Additionally, the extract reduced the constitutive secretion of monocyte chemotactic protein-1 (MCP-1), the LPS-induced secretion of IL-12 and inhibited MCP-1 and granulocyte-macrophage colony-stimulating factor (GM-CSF) production in the presence of LPS on PC-3 cells.

Assessor's comments

The results suggest that *Serenoa repens* extracts, in addition to other reported effects on BPH development and prostatitis, inhibit EGF-dependent growth and pro-inflammatory responses of the prostate epithelial cells. However, further information should have been presented on what is meant by effective concentrations.

3.1.1.1.7. Antiproliferative effect

In vitro studies conducted on different models showed an anti-proliferative effect of *Serenoa repens* extracts with or without apoptotic effects.

Serenoa repens extracts:

- Inhibited the prolactin-induced growth by acting on several steps of prolactin receptor signal transduction in transfected Chinese hamster ovary cells (Vacher *et al*., 1995).

- Affected the proliferative response of prostate cells (from biopsies of human prostate) to ß- FGF more than their basal proliferation (Paubert-Braquet, 1998) and the response to IGF in prostate epithelial cell line P69 (Wadsworth *et al*., 2004).
- Induced apoptosis in some models in addition to an anti-proliferative effect. (Petrangeli *et al*., 2009) showed induction of apoptosis and inhibition of the proliferation by *Serenoa repens extract* in an androgen-independent PC3 cell line. Complex changes in cell membrane organisation and fluidity of prostate cancer cells that have progressed to hormone-independent status were observed after treatment with *Serenoa repens* extracts (Petrangeli *et al*. 2009). However, other results failed to evidence the induction of apoptosis by these extracts in prostatic cancer cell lines but confirmed its effects on cell growth (Hill *et al*., 2004).

These anti-proliferative effects of *Serenoa repens* extracts were confirmed in, *in vivo* models of rat prostate hyperplasia induced by hyperprolactinemia in comparison with finasteride (inhibitor of 5-alpha reductase) (Van Coppenholle *et al*., 2000).

Assessor's comments

The results of these experiments must be regarded cautiously as it is difficult to extrapolate the findings to a human condition *in vivo*. Special attention must be paid to the concentrations needed for an effect.

3.1.1.1.8. Comparative analysis of extracts

Not all brands are created equal: a comparison of selected components of different brands of Serenoa repens extract (Habib & Wyllie, 2004)

In this publication Habib and Wyllie analysed different extracts for their content of free fatty acids. As shown in Figure 5, free fatty acids were selectively extracted before gas chromatographic analysis. By applying this extraction, free fatty acids could be separated from the esters and glycerides.

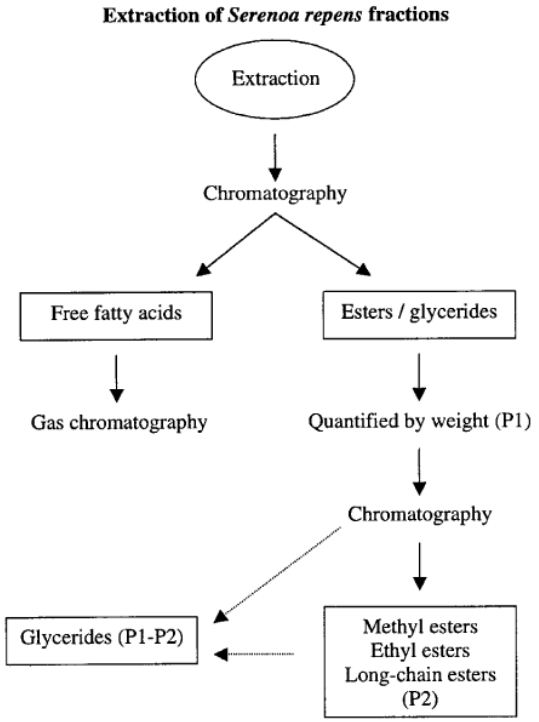

Figure 5: Preparatory chromatography separated the free fatty acids from the esters and glycerides. The free fatty acids were quantified by gas chromatography, the esters and glycerides by weight (P1). The methyl and ethyl esters and the long-chain esters were quantified by weight (P2). P1-P2 resulted in the noneluted quantification of the glycerides. Methyl- and ethylesters and long-chain fractions were subsequently quantified by gas chromatography. The unsaponifiable matter was quantified by weight (Habib & Wyllie, 2004).

As can be seen from Figure 6, there is considerable difference between different extracts. The graph was partially extracted from the original publication, hiding the commercial names of the extracts. Although these differences are variable they might result in different biological activity (see below in this section).

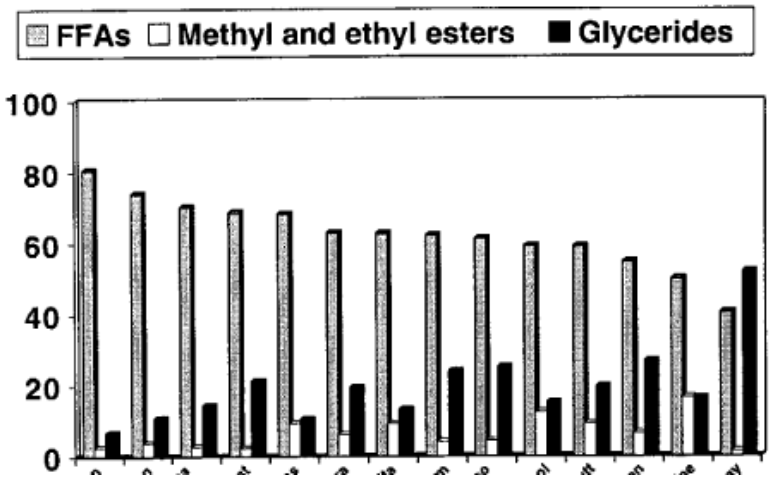

Figure 6: Differences in the content of free fatty acids (FFA), methyl and ethyl esters and glycerides in different commercially available extracts/products. The bars most to the left are representating a commercial hexane extract(Habib & Wyllie, 2004).

Assessor's comments

The authors could demonstrate a considerable difference between extracts when free fatty acids were initially separated from esters and glycerides. This difference is an important factor in considering the difference or similarity between extracts.

A phytochemical comparison of saw palmetto products using gas chromatography and ^{1}H nuclear magnetic resonance spectroscopy metabolomics profiling (Booker et al., 2014)
Fifty-seven samples were obtained from retail outlets or pharmacies from Canada, Finland, Germany, the Netherlands, the United Kingdom, South Korea, Spain, Switzerland and the United States. Of these products that were soft gel or hard gel capsules, tablets or tinctures, 29 were monopreparations containing only saw palmetto, and 28 were combined with other constituents such as vitamins, herbal extracts or minerals (labelled 'combi-preparations').

Thirty-four products were tested with ^{1}H NMR spectroscopy, 46 with gas chromatography and 26 preparations in both analyses.

It was striking that the daily dose of fatty acids per day differed considerably (up to 500x) from one preparation to another (Figure 7). The differences between the content of fatty acids declared on the package and the amount measured varied from 9.9 to 460.4%.

Metabolomics were done, based on ^{1}H NMR. Unfortunately the interpretation of the results was hampered by the fact that the extracts were not identifiable on the plots.

Quantitative analysis of fatty acids resulted in an overview of the composition of different preparations. The origin of some of the extracts was identified by the interested parties. A commercialised hexane extract (ES SP 12) was compared to a commercialised ethanolic extract (CH SP 27) (Figure 7 and 8). It can be seen from Figure 8 that the composition of both extracts is quite similar. However, according to the method of analysis described, the fatty acids were directly esterified for gaschromatographic analysis, without separation of the naturally occurring free fatty acids from the esters, as was done by Habib and Wyllie (2004).

Assessor's comments

No clear conclusion can be drawn from the findings, because direct comparison of the extracts analysed with products on the European market is not possible.

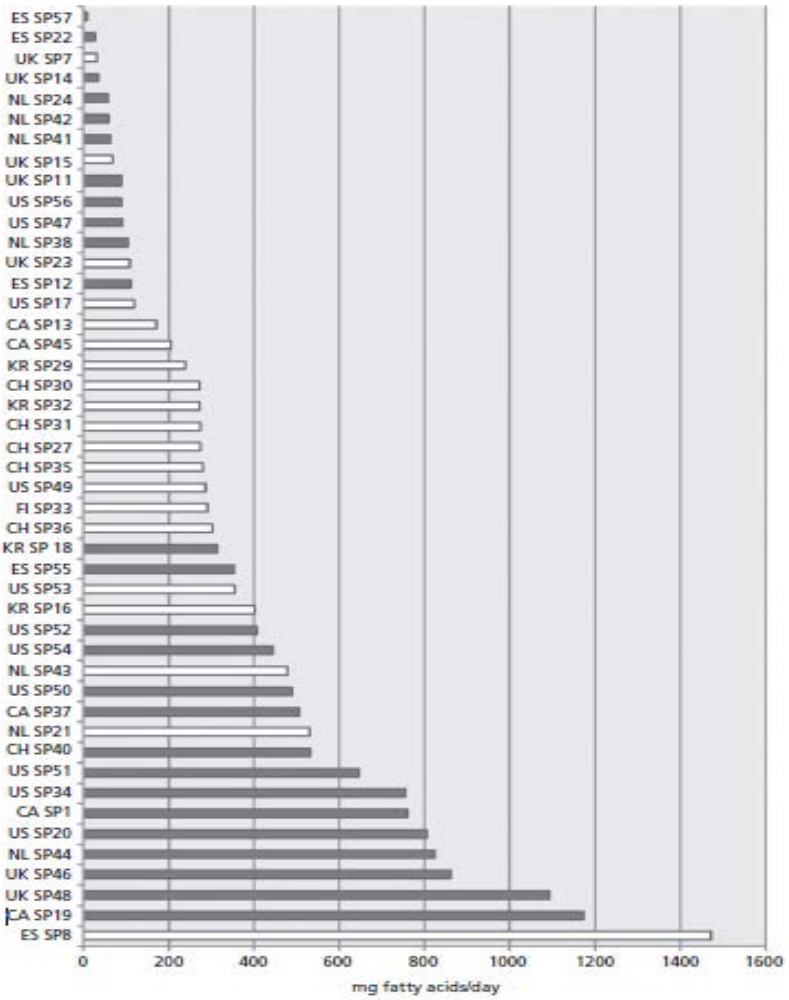

Figure 7: On the ordinate the codes of the preparations analysed and the country code of origin. On the abscissa the daily dose of fatty acids based on the lowest daily dosage for the specific products.
White bars: monopreparations containing only *Serenoa repens* extracts.
Dark bars: combination products that contained also vitamins or other herbal extracts.
(Booker *et al.*, 2014).

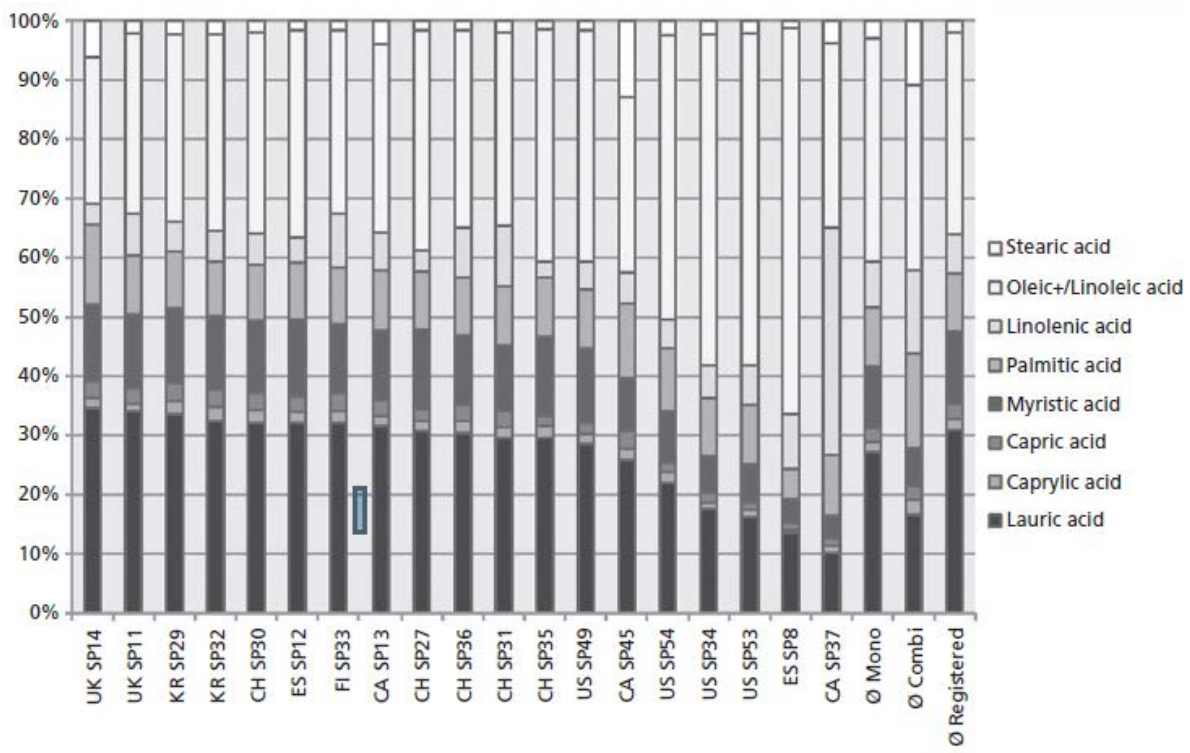

Figure 8: Comparison of the composition of *Serenoa repens* extracts. ES SP12 represents an hexane extract, CH SP27 represents an ethanolic extract (Booker *et al.*, 2014).

Metabolomics study of Saw palmetto extracts based on ^{1}H NMR spectroscopy (De Combarieu et al., 2015)

This study included critical CO_2-, ethanolic as well as hexane extracts. But the hexane extracts were prepared on laboratory scale, and consequently did not correspond to commercial extracts. There seemed to be differences between the type of extracts, ethanolic extracts being more different from CO_2- and hexane extracts, the latter showing more overlapping (Figure 9).

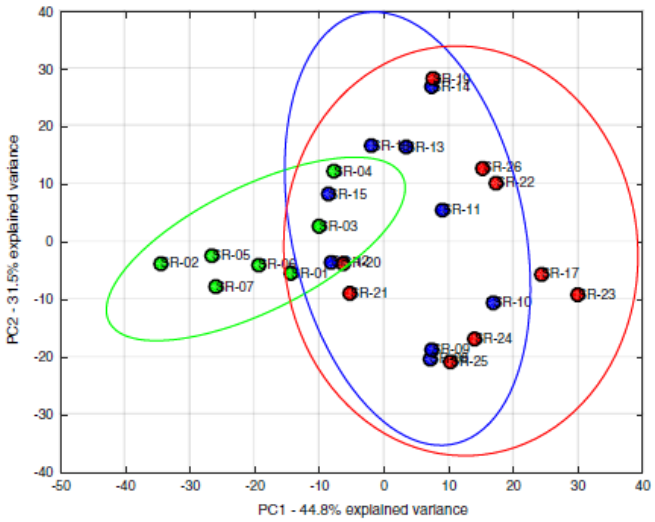

Figure 9: Plots of CO_2 supercritical extract batches (blue), hexane extract batches (red) and ethanolic extract batches (green). Ellipses are representing the 95% confidence intervals for the variability of

each cluster. PC1: 44.8% explained variance. PC2 31.5% explained variance (De Combarieux *et al*., 2015).

The data matrix was processed making use of a Principal Component Analysis (PCA). It should be noticed that less than 50% of the variance is explained.

Assessor's comments

The metabolomics based upon ^{1}NMR represents an attempt of clustering extracts. From the results direct comparison between specific extracts is not possible.

Alpha reductase inhibitory activity of different extracts in prostatic co-cultured epithelial and fibroblast cells (Scaglione et al., 2008)

The aim of this study was to compare the activity of different extracts of *Serenoa repens* marketed in Italy. Extracts were tested on 10 day co-cultured epithelial and fibroblast cells by a 5-alpha-reductase activity assay. In order to assess the variability in *Serenoa repens* products, 2 different batches for each brand were evaluated.

All extracts tested are able to inhibit both isoforms of 5-alpha-reductase. However, the potency of the extracts appears to be very different, as well as the potencies of 2 different batches of the same extract. This is probably due to qualitative and quantitative differences in the active ingredients. These results show that different extracts do not necessarily have the same clinical efficacy and bioactivity (Scaglione *et al*., 2008).

In Figure 10 it can be seen that differences exist in biological activity between extracts. The comparative study included the hexane extract which is commercially available in many countries of the EU. This extract revealed to be the most potent one on 5-alpha-reductase type I and II. The graph gives only the bullet symbols, without specifying standard errors or measures of spread; a weakness of the study outcome (Scaglione *et al*., 2008).

Scaglione *et al*. (2012) repeated the same experiments 4 years later. In total 10 different extracts were assayed for 5-alpha-reductase activity on 10 day fibroblasts and epithelial cells co-cultures. Human fibroblast growth factor (hFGF)-induced-proliferation inhibition was also assayed. Differences were observed between the tested extracts, but all were able to inhibit 5-a-reductase types I and II isoenzymes (5-alphaR-I and 5-alphaR-II) as well as fibroblast proliferation (Scaglione *et al*., 2012).

In both publications the hexane extract of a specific manufaturer is included. This hexane extract gave the most consistent results and the highest activity. Figure 10 shows a difference in potency of the extracts. When the concentrations were compared that inhibited both types of alpha-reductase by 50% (EC_{50}) differences with a factor 23 to more than 200 were seen between the hexane extract and the extract with the lowest biological activity.

It should be noted that only one concentration response curve was made for each extract.

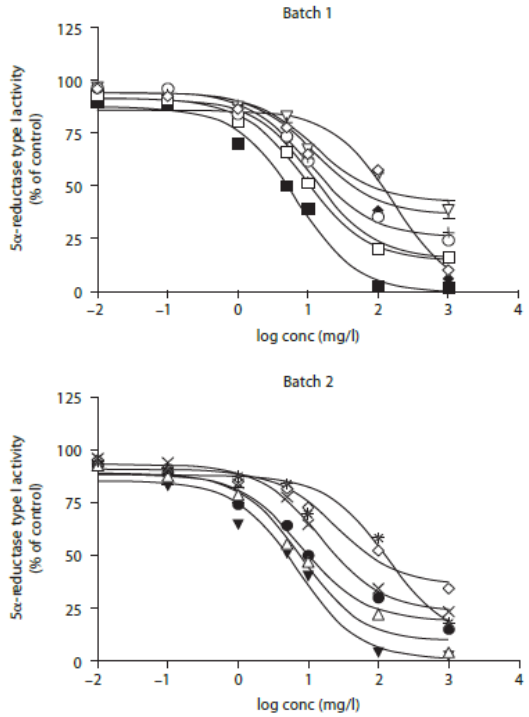

Figure 10: Inhibiting activity on 5-alpha-reductase by different commercialy available extracts. The number of experiments per concentration is not given. In both batches, the hexane extract (filled triangles and squares) had the strongest inhibiting activity (Scaglione *et al*., 2008).

Assessors's comments

The authors came to the conclusion that extract potency differs between products and so does proliferation inhibition potency. According to the authors quantitative and qualitative variations in the active ingredient are likely to account for these differences. These findings may be important when considering different extracts in clinical trials. They are however based on single concentration-response curves.

3.1.1.2. In vivo experiments

Antiandrogenic effects

In castrated or prepubescent mice and rats treated with testosterone or gonadotrophin, oral administration of a hexane extract from *Serenoa repens* fruit (300 mg per animal per day for 4-12 days) resulted in a loss of weight of the accessory sex glands. The extract did not show oestrogenic or progestogenic properties and had no adverse effect on the neuroendocrine feedback mechanism (Paubert-Braquet *et al.*, 1996).

In castrated rats treated with testosterone, oestradiol and the hexane extract (50 mg per kg per day orally for 30, 60 or 90 days), the weight of the dorsal prostate lobe was significantly lower at days 30, 60 and 90 and the weight of the lateral prostate lobe was significantly reduced at day 60, whereas the effect on the ventral lobe was very weak (Paubert-Braquet *et al*., 1996).

In another study, the hexane extract (180 or 1800 mg/day orally over 7 days) did not show any effect on prostate growth in either testosterone- or di hydrotestosterone-stimulated castrated rats.

An ethanolic extract administered orally (0.15 ml per 25 g body weight once weekly for 2 months), caused inhibition of prostatic growth in athymic nude mice, into which human benign hyperplastic

prostatic tissue had been transplanted and which was stimulated with dihydrotestosterone and oestradiol. In castrated rats treated with testosterone, the same ethanolic extract (100, 300 or 1000 mg/kg orally for 6 days) reduced the weight of the ventral prostate and the seminal vesicles including the coagulation glands (Koch, 1995).

A fraction from a methanolic extract of *Serenoa repens* fruit (2.5 and 5 mg/animal, administered subcutaneously for 3 days) and beta-sitosterol isolated from it (2-50 pg/animal subcutaneously) showed oestrogenic activity (increase in uterine weight) in immature female mice (Elghamry and Hänsel 1969).

Anti-inflammatory, anti-oedematous effects

Capillary permeability was reduced by oral administration of a hexane extract from *Serenoa repens* fruit (5-10 ml extract/kg body weight) in various models of inflammation in rats, mice and guinea pigs (Tarayre *et al*., 1983).

An ethanolic extract (10 mg/kg orally) inhibited carrageenan-induced rat paw oedema (Hiermann, 1989).

In the croton oil-induced mouse ear oedema test, local application of an ethanolic extract (500 µg) inhibited the oedema by 42%. An acidic polysaccharide (0.1-1 mg/kg., administered intravenously) isolated from an aqueous extract of *Serenoa repens* fruit showed anti-inflammatory activity against carrageenan induced rat paw oedema and in the pellet test in rats (Wagner et al., 1981a; Wagner *et al*., 1981b).

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Rats were administered 10 mg of hexane extract from Serenoa repens fruit, supplemented with 14C-labeled oleic acid. There was a greater uptake of total radioactivity in the prostate than in other genital organs (n=7) (i.e. seminal vesicles: mean 2.5x; bladder: mean 10x or other organs e.g. the liver (no quantitative data given (Chevalier *et al*., 1997).

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

The oral LD_{50} of a hexane extract from *Serenoa repens* was determined as 54 ml/kg in male rats. No mortality occurred after oral administration of 50 ml/kg to male mice (Tarayre *et al*., 1983).

No data concerning genotoxicity or carcinogenicity have been located. While data on reproductive toxicity are not needed, data on fertility are lacking.

There are several studies on cytotoxic effects of *Serenoa repens* in a number of human tumour cell lines (Baron *et al*., 2009; Bayne *et al*., 2000; Che *et al*., 2009; Hostanska *et al*., 2007; Petrangeli *et al*., 2009; Ravenna *et al*., 1996; Wadsworh, 2004).

Assessor's comments

The cytotoxicity studies have been made with different extracts (hexane, ethanol or not specified). In most cases only one concentration has been tested therefore information on any concentration-effect relationship cannot be evaluated. Several underlying mechanisms have been suggested on the basis of these studies: activation of mitochondrial apoptotic pathway (Baron *et al*., 2009), effects on cell membrane organisation (Petrangeli *et al*., 2009), antiandrogenic action (Ravenna *et al*., 1996) and effects on growth- and stress-related signalling pathways (Wadsworth, 2004). However, such *in vitro*

studies are considered to be of limited relevance in the assessment of toxicity risks of *Serenoa repens* extracts and it is not clear whether the studies are of relevance to the clinical safety of *Serenoa repens* extracts.

3.4. Overall conclusions on non-clinical data

Several experimental findings support the plausibility of the use of *Serenoa repens* in BPH. From *in vitro* experiments the following properties were reported: (1) inhibition of 5-alpha-reductase; (2) influence on androgen-receptor binding; (3) inhibition of alpha-receptor binding; (4) inhibition of eicosanoid synthesis; (5) spasmolytic effects and (6) anti-inflammatory effects. The level of activity can differ from one extract to another, probably dependent on the content of fatty acids. Some anti-androgenic and anti-inflammatory effects were confirmed in *in vivo* experiments.

Concentrations for *in vitro* experiments were mostly expressed as µg extract or oil per ml. It is difficult to relate these concentrations to what can be reached in human therapy. Depending upon the model used IC_{50} values differ (sometimes with a factor of more than 50). The concentrations of extract (expressed as weight per volume) needed for a detectable activity were much higher (up to 1000x) than seen for pure chemical entities (e.g. inhibition of 5-alpha-reductase by finasteride). Molar concentrations could not be compared due to the complex composition of the extracts. Also for *in vivo* experiments no direct relation can be made between the dose of the Serenoa preparation administered and human therapeutic doses. It can be concluded that preclinical pharmacological experiments mainly result in qualitative and semi-qualitative data adding to the plausibility of the mechanisms of action of *Serenoa repens* preparations.

Discussion is on-going about the phytochemical and phytopharmacological equivalence of the extracts made with different solvents. More particularly an equivalence is claimed for ethanolic and hexane extracts. Several analytical and pharmacological studies were evaluated in the assessment report. Most of the phytochemical studies do not separate the free fatty acids from esters and glycerides before (mostly gas chromatographic) analysis. It can be reasoned that esters might be converted into free fatty acids when absorbed. However, studies of the phytopharmacological activity suggest that there are considerable differences in pharmacological activity between extracts. Moreover it cannot be excluded that free fatty acids may be absorbed differently from esterified fatty acids and glycerides in the intestine.

Experimental pharmacokinetic data show that there is a preferential uptake of fatty acids in prostate tissue. Testing of the acute toxicity of the hexane extract in rats and mice is limited to LD_{50} determination, which is of little relevance for clinical use.

No data concerning fertility, genotoxicity or carcinogenicity are available.

4. Clinical Data

4.1. Clinical Pharmacology

EMA Guideline urinary incontinence 2013

The CHMP Guideline on the clinical investigation of urinary incontinence 2013 has been used as a basis for evaluation of the published clinical trials (EMA, 2013).

However, it should be noted that the scope of the Guideline does not include incontinence associated with benign prostatic hyperplasia (BPH), and, in particular, post voiding dribbling in males associated with BPH is not covered by this guideline.

Other published guidelines have also been consulted as described below:

American Urological Association: **Guideline on the Management of Benign Prostatic Hyperplasia (BPH) (2010)**

According to American Urological Association guidelines on management of BPH extracts of *Serenoa repens* fruit are reported to be by far the most commonly studied medicinal plant among the complementary and alternative therapies for BPH. The authors state that systematic reviews of the earlier evidence suggests that *Serenoa repens* extracts may have modest efficacy in the treatment of lower urinary tract symptoms (based on review articles of 1998 and 2000). The guidelines also state that more recent studies with more rigorous methods have generally failed to confirm a clinically important role for *Serenoa repens* in the management of BPH and that more definitive evidence regarding the use of *Serenoa repens* in BPH is needed.

However it should be noted that the more recent studies cited are those carried out by Bent *et al*. (2006) and Shi *et al*. (2008), respectively (see studies discussed below). Shi *et al*. (2008) in fact gave a positive conclusion for their study on *Serenoa repens*.

Canadian Prostate Health Council and the Canadian Urology Association: **Guidelines for the management of benign prostatic hyperplasia (2009)**

The Canadian Prostate Health Council and the Canadian Urology Association have published Guidelines for the management of benign prostatic hyperplasia. The authors state that, if patients are interested in complementary approaches (phytotherapeutic or other supplements) for lowering urinary tract LUTS secondary to BPH, they may be counseled that some plant extracts such as *Serenoa repens* (*Serenoa repens* fructus extract) has shown some efficacy in several small clinical trials.

Serenoa repens has been studied most rigorously including one published randomised controlled double-blind trial which failed to show any significant difference over placebo in symptom score, maximum flow rate, prostate size, residual urine volume, PSA levels or quality of life over a one-year period. The authors refer to Bent *et al*. (2006) and a review article which must be considered as an indirect approach.

European Association of Urology**: Guidelines on benign prostatic hyperplasia 2009 (de la Rosette *et al*., 2009)**

According to the guidelines of the European Association of Urology, the use of phytotherapy in treating lower urinary tract symptoms and benign prostatic hyperplasia has been popular in Europe for many years and has recently spread in the USA. The authors mention that it is always difficult to identify which plant component has the major biological activity. A few short term randomised trials and some meta-analyses show clinical efficacy without major side effects for herbal ingredients such as *Pygeum africanum* and *Serenoa repens.* They base their position only on review articles. They also noted that in some studies the efficacy of *Serenoa repens* was found to be equivalent to finasteride and α-blockers. The studies mentioned are included in this assessment report. Nevertheless the authors have raised many questions concerning the composition, the extraction and the mechanism of action of the herbal preparations used in the trials and have raised the need for additional randomised and placebo controlled trials.

World Health Organisation Consensus Committee 1991 leading to IPSS (Cockett *et al.*, 1991)

In 1991 an Expert WHO Committee was convened to establish a consensus concerning BPH. The purpose of their recommendations was to reach simple, uniform criteria, thus creating a 'universal language' in order to facilitate comparison of patients and therapeutic results, both in everyday practice and in the course of clinical trials.

The Expert Committee agreed criteria, including important aspects related to patients and outcomes, which were later developed into the International Prostate Symptom Score (IPSS). The WHO-Prostate Symptom Score translated into the **IPSS (International Prostate Symptom Score)**.

The IPSS is based on a scoring on six questions to the patient using a Likert scale ranging from 'not at all' to 'nearly always' (= scores of 0 to 5 per item).

The questions cover aspects of: Incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. Similar parameters and scoring are used in the American Urology Association Symptom Index.

Assessor's comments

The WHO-PSS is incorporated into the IPSS. The principal symptoms of BPH are included in this scale. Furthermore the WHO Guideline contains warnings with regard to criteria for possible exclusion of specific patients.

Definition of 'at risk patients'

Acute urinary retention is a serious complication of BPH. When starting treatment of BPH-patients with *Serenoa repens* it is useful to consider possible risk factors in order to take the right therapeutic decisions and to make conclusions from studies as correct as possible.

Several factors should be taken into consideration. They are extracted from the papers by Roehrborn (2006) and by Emberton (2006).

Hawthorne effect: a population intensively scrutinised and followed in a clinical trial might behave different in the knowledge of this.

There exists a natural converging effect or 'regression to the mean' artefact. Roehrborn (2006) cites a study with finasteride versus placebo, where the placebo arm showed an improvement in the IPSS which was particularly marked during the first year and tended to decrease within the 3 following years.

There is the definition of clinically relevant improvements. The most recent studies use assessment instruments like the IPSS. It has been shown that patients were able to perceive on average a 3-point absolute improvement as an overall subjective positive change in their status. Symptom progression is then defined as a deterioration in the IPSS of $\geq$ 4 points, to ensure that patients were really getting worse.

In relation to the former point, it must be said that patients with marked symptoms require a smaller change in score to feel improvement, than patients with moderate symptoms. This hampers straightforward evaluation of the % of patients with a clinically relevant alleviating of symptoms.

Furthermore there is the 'ceiling effect', i.e. improvement by at least 4 points on the IPSS will be more difficult to obtain in patients with more severe symptoms.

Some studies proved the risk for acute urinary retention as being related to the age: the relative risk for men aged 70-79 years versus men aged 40-49 years being 8 times higher (95% CI 3.7-16.4).

Men with moderate to severe lower urinary tract symptoms have a 3 times increased risk for acute urinary retention of versus men with mild symptoms (95% CI 1.9-5.4).

The risk for acute urinary retention is 4 times higher in men with a peak flow rate of $\leq$12 ml/sec versus men with >12 ml/sec (95% CI 2.3-6.6).

A prostate size of >30 ml enhances the risk for acute urinary retention with a factor 3 as compared to a prostate size of $\leq$30 ml (95% CI 1.0-9.0).

A postvoid residual volume of >50 ml enhances 3 times the risk of suffering from acute urinary retention.

PSA has also been seen as a predictive factor for acute urinary retention: a 4 year incidence in 6.5% of men with PSA <1 ng/ml as compared to 14% in men with a PSA >7 ng/ml. The presence of inflammatory infiltrate in the prostate is estimated at being present in 30 to 60% of men with BPH and will contribute to enhanced PSA levels.

Events related to quantitative variables may also vary from one study to another. Baseline symptom score and peak flow rate may behave paradoxically (Emberton 2006). However the above mentioned factors are useful to be taken into consideration when comparing clinical data and when defining risks during therapy.

Assessor's comments

The following factors need special attention when initiating therapy with *Serenoa repens*: an age of >70 years, the presence of moderate to severe lower urinary tract symptoms, a peak urinary flow of $\leq$12 ml/sec, a prostate volume of 30 ml, a postvoid volume of >50 ml and a serum PSA level of 1.4 ng/ml.

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Influence on receptor density

It has been found that a lipidosterolic extract of *Serenoa repens* competes with dihydrotestosterone at the level of androgenic receptors.
Patients with BPH for 1 to 3 years (n=35; 61-73 years) were included in a double-blind, placebo-controlled study. For 3 months patients took 2 x daily 160 mg of an extract of *Serenoa repens* fruit (n=18) or placebo (n=17) daily, up to the day before transvesical adenectomy.
When possible, estrogen and androgen receptor presence was evaluated using single-saturation dose assay (^{3}H-oestradiol and diethylstilbestrol) and the Scatchard analysis. As a confirmation enzyme immunoassay was used using anti-estrogen and anti-progesterone monoclonal antibodies.

Scatchard analysis	ERn		ERc	
	untreated	treated	untreated	treated
Positivity, n (%)	6/7 (86)	1/8 (12.5)	5/7 (71)	6/8 (75)
High-affinity site fmol/mg DNA	6.183 ±3.761	0.8	0.640 ±0.592	0.493 ±0.321
Low-affinity site fmol/mg DNA	105.937 ±86.488	6.4	7.917 ±6.426	4.632 ±2.958

	ARc fmol/mg protein	ARn fmol/mg DNA	ERc fmol/mg protein	ERn fmol/mg DNA
Positivity Untreated	9/10 23.878 ±10.384	6/10 153.183 ±76.909	7/10 17.371 ±10.102	8/10 261.90 ±135.42
Positivity Treated	6/10 24.467 ±12.697	1/10 108	6/10 17.533 ±11.815	0/10 ND

Table 6: Compilated tables for the evaluation of the presence of nuclear and cytosolic estrogen (ER) and androgen receptors (AR) using Scatchard analysis (from Di Silverio *et al*., 1992). Upper part of the table: ERn and ERc evaluated in BPH tissue samples evaluated by Scatchard analysis in patients untreated and treated with *Serenoa repens* extract. Lower part of the table: AR and ER measured in cytosolic and nuclear fraction evaluated by a single point assay in 10 untreated and 10 treated patients.

Two classes of binding sites were identified: one with high-affinity low-capacity binding and the other with low-affinity high-capacity binding. At the end of the treatment, both nuclear oestrogen and androgen receptors in prostatic tissue were significantly lower in the *Serenoa repens* group than in the placebo group (P <0.001). Cytosolic oestrogen and progesterone receptors remained almost unchanged. These results were confirmed by enzyme immunoassay (Di Silverio *et al*., 1992).

Assessor's comments

This study is of interest in so far that the group treated with *Serenoa repens* extract was nuclear estrogen receptor negative, not only when evaluated by a single-point assay, but also by Scatchard analysis, with confirmation by enzyme immunoassay.
However, there are limitations to the study. For reasons not explained, the number of samples examined does not correspond to the number of patients. The nature of the extract is not reported in the original publication, although secondary sources suggest that it could be a hexane extract.

Enzymatic and anti-inflammatory activity

Patients with different types of BPH (n=18; aged between 60 and 80 years, mean age 68) were included in a double-blind, placebo-controlled study. The patients suffered from mainly glandular, mainly stromal or a mixed type hyperplasia of the prostate. The patients took 2 capsules 3 x daily containing a *Serenoa repens* extract IDS 89 (no further specifications) or containing placebo, for 3 months.

The activity of 5-alpha-reductase, 3-alpha and 3-beta-hydroxysteroid oxidoreductases, and creatinine kinase was determined in mechanically separated epithelium and stroma, obtained by suprapubic prostatectomy.

The extract slightly decreased the substrate affinity of 5-alpha-reductase in the epithelium. In the stroma the V_{max} value of creatinine kinase increased to a greater extent than that of the 3-alpha and 3-beta-hydroxysteroid oxidoreductases. A reduction in periglandular stroma oedema, mucoid degeneration, intraglandular congestion and congestive prostatitis was observed in patients treated with the extract (ESCOP 2003; Weisser *et al*. 1997; Helpap *et al*. Urol. Pathol 1995; 3: 175-182).

BPH patients (n=35; age) entered an open parallel pilot study. They were randomised to receive either standardised hexane extract (2 x 160 mg per day) for 3 months or no treatment (n=16 and 19 respectively; age 66 and 67 respectively) for 3 weeks before surgery (Trans Urethral Resection of the Prostate of TURP). Inclusion and exclusion criteria were strictly applied in order to avoid any interference by anti-inflammatory drugs.

Histological examination revealed a higher concentrations of lymphocytes B in the group without treatment as compared to the treated patients, although the difference was not significant (P=0.097). TNF-alpha (P=0.012) and IL-1beta (P=0.004) were significantly lower in the Serenoa group. IPSS was significantly reduced by Serenoa after 3 months of treatment (P=0.006) (Vela Navarrete *et al*., 2003).

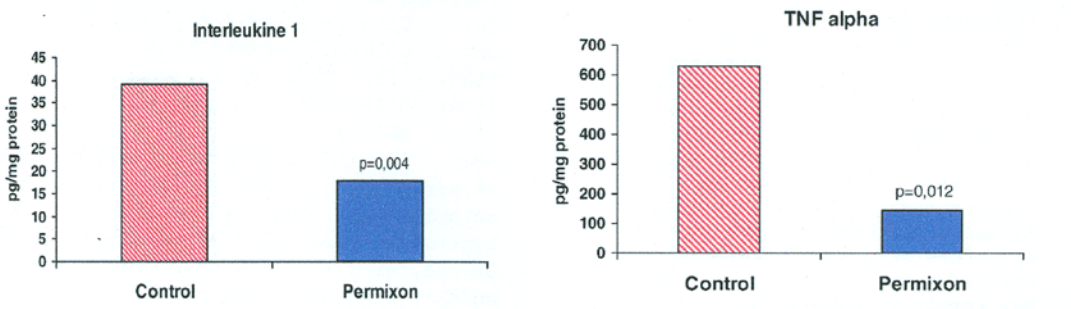

Figure 11: Levels of interleukin 1 and and TNF alpha in prostate tissue taken from patients on *Serenoa repens* and control patients after 3 months treatment (Vela Navarrete *et al*., 2003).

A significant 5.1 point reduction in the IPSS score was observed in the Serenoa treated group as compared to the control patients. The individual analysis of symptoms showed a significant reduction for obstructive (P=0.04) and irritative (P=0.05) symptoms. There was no significant modification in the uroflowmetric parameters, in prostate volume or in PSA levels after 3 months' treatment.

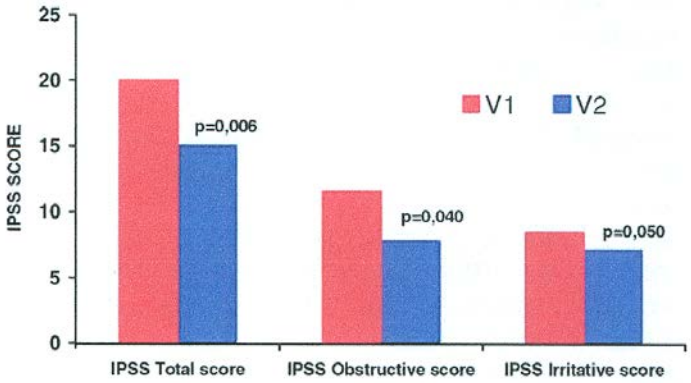

Figure 12: Difference in symptoms between start (V1) and after 3 months (V2) in the *Serenoa repens* group (Vela Navarrete *et al*., 2003).

Assessor's comments

Although it was described as an open study, the title mentioned '*double blind pilot'* assay. Finally 29 patients underwent a surgical intervention: 17 controls and 12 patients receiving *Serenoa repens*.

Hormone levels

Healthy volunteers (n=32) were enrolled in a one-week, randomised, parallel, open study. The patients daily took 5 mg finasteride, 320 mg of an hexane extract of *Serenoa repens* or placebo. 5-alpha-reductase activity was assessed by determination of serum levels of di-H-testosterone (DHT).

There was no influence of serum DHT levels in the placebo and the *Serenoa repens* groups. Finasteride significantly reduced serum DHT levels (P < 0.01 versus baseline). After the first dose of finasteride the DHT-levels were reduced by 65%. After multiple doses reduction was 52-60%. No significant reduction was detected between groups with respect to serum testosterone (Strauch *et al*., 1994).

BPH patients (n=25) were randomly assigned to treatment with a hexane hexane extract from *Serenoa repens* fruit (320 mg per day during 3 months; n=10) or no treatment (n=15). After suprapubic prostatectomy, concentrations of testosterone (T), dihydrotestosterone (DHT) and epidermal growth factor (EGF) were determined in prostatic tissue.

Treatment with *Serenoa repens* resulted in lower DHT levels (P <0.001) and EGF (P <0.01); the T levels were increased (P <0.001) (Di Silverio *et al*., 1998).

Twenty patients with BPH were enrolled in an open study. They received 320 mg of a liposterolic extract daily for 30 days. No changes were detected in plasma levels of testosterone, follicle stimulating hormone or luteinizing hormone (Casarosa *et al*., 1988).

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Twelve healthy young male volunteers in a fasting state, took 320 mg of a lipophilic extract of *Serenoa repens*. An unspecified component with a retention time of 26.4 minutes was measured by HPLC. After 1.5 hours a mean peak plasma concentration of 2.6 µg/ml was achieved. The AUC was 8.4 mg/h/ml. The component had an elimination half-life of 1.73 hours. This study is of limited value as the purpose of the study was not to identify the component (De Bernardi di Valserra *et al*., 1994).

4.2. Clinical Efficacy

Table 7: Symptoms according to Vahlensieck (ESCOP, 2003; Loew *et al*. 1999; Vahlensieck et al. 1993)

Grades	Symptoms	Therapy
Grade I Pre-phase	No micturition disturbance Maximal Urinary flow >15ml/sec No residual urinary volume No bladder abnormalities	Spasmolytics Bowel regulation Abstinence of alcohol Avoiding low temperatures Pharmacotherapy or phytotherapy
Grade II Phase of growth	Intermittent micturition disturbance Maximal urinary flow 10-15 ml/sec Bladder wall starts to be thickened	Spasmolytics Bowel regulation Alcohol abstinence Avoiding low temperatures

		Pharmacotherapy or phytotherapy
Grade III Residual volume phase	Permanent micturition disturbance Maximal urinary flow <10 ml/sec Residual urinary volume >50 ml Bladder wall thickened	Pharmacotherapy or phytotherapy Surgery: TURP or prostatectomie
Grade IV Phase of decompensation	Permanent micturition disturbance Maximal urinary flow <10 ml/sec Residual urinary volume >100 ml Bladder dilated Renal complications	Catheterisation followed by surgical intervention

4.2.1. Dose response studies

Reference	Patients	Intervention	Outcome
Stepanov *et al*., 1999	N = 100	R / SC / DB SR (= standardised hexane extract): 160 mg, 1 x /day 160 mg, 2 x / day Duration: 3 months	IPSS compared to baseline At 1 month: P <0.05 At 3 months: P <0.001 For both groups Other parameters at 3 months Urinary flow maximal Urinary flow mean Residual volume P <0.001 Between groups No significant differences

DB = double blind
IPSS = international prostate symptom score
N = number of patients
R = randomised
SC = single centre
SR = *Serenoa repens*

No further details about the age of the patients and patient withdrawal were given. Initial IPSS scores of the patients included are not communicated. The hexane extract can be considered as an example of a commercially available preparation. Clinical adverse events occurred at similar incidence in both groups (BID 24%; OD 22%). The relation to *Serenoa repens* seemed unlikely (Stepanov *et al.,* 1999).

Reference	Patients	Intervention	Outcome
Giannakopoulos *et al*., 2002	N = 100 Mean age = 63-64 years Mean IPSS = 20	DB / R SR (extraction solvent not specified) 160 mg 2 x / day 160 mg 3 x /day Duration: 6 months	IPSS compared to baseline 2 x = - 7.6 3 x = - 8.48 From baseline P <0.001 NS between groups Other parameters Quality of life index: P <0.05 Maximum flow rate: P <0.05 Mean flow rate: P <0.05 Residual volume: P <0.001 NS between groups

DB = double blind
IPSS = internationally accepted BPH-symtom score
NS = not significant
R = randomised
SR = *Serenoa repens*

The conclusion of the authors is that the *Serenoa repens* preparation was a well-tolerated agent that may significantly improve lower urinary tract symptoms and flow measurements in men with BPH. All parameters evaluated improved more in the higher dosage group. Limitations of the study are the lack of power calculation and the unknown extraction solvent (Giannakopoulos *et al*. 2002).

4.2.2. Clinical studies (case studies and clinical trials)

4.2.2.1. Systematic reviews with different extracts of Serenoa repens

Reference	Patients	Intervention	Outcome
Ulbricht *et al*., 2006 Critical review of a previous review, a meta-analysis and clinical trials	Data from 33 publications with SR preparations N = 2939 systematic review N= 2859 meta-analysis N= 1659 randomised placebo controlled N = 60 non randomised N = 1360 comparative N = 679 combinations N = 224 dose finding	Different SR extracts in variable doses Duration: majority of the clinicals trials 1 to 6 months	When positive results towards PL: NNT varies between 2 and 5 and ARR between 23 and 59%.

ARR = Absolute Risk Reduction
N = number of patients
NNT = Number Needed to Treat
PL = placebo
SR = *Serenoa repens*

Comments by the review authors

Serenoa repens has been reported to be superior to placebo and possibly equivalent to finasteride (with fewer adverse effects) in the alleviation of lower urinary tract symptoms due to BPH. One trial has reported superiority of alfusozin over *Serenoa repens*. The majority of the studies has been brief, included small sample sizes, and have not employed standardised outcomes measurements such as the IPSS. More recent, well-designed trials have failed to find any significant benefit of *Serenoa repens* for the treatment of BPH.

Nonetheless, the weight of available evidence favours the efficacy of *Serenoa repens* for this indication; despite the heterogeneity of study designs and results reporting, two pooled analyses have suggested modest benefits of *Serenoa repens*.

Assessor's comments

The authors made a critical analysis of 33 publications with various SR preparations and different interventions. Although they highlight several flaws in the studies, their conclusion was a positive opinion on the therapeutic value of SR for symptoms due to BPH. However, this conclusion is weakened by including different extracts.

Reference	Patients	Intervention	Outcome
Görne, 2014 Systematic review of clinical trials made with ethanolic extracts	Sytematic review of 4 randomised controlled studies N = 469 in placebo controlled studies N = 265 in reference controlled study	Different ethanolic SR extracts in variable doses. Duration of the studies: from 13 to 72 weeks.	Better outcomes achieved with SR extracts Indivual symptoms: - residual volume - nocturia and dysuria - peak flow IPSS and AUASI

SR = *Serenoa repens*

In the review performed by Goerne *et al*. (2014) the results of controlled clinical trials with alcoholic extracts in the therapeutic indication lower urinary tract symptoms (LUTS) with and without BPH were analysed. A literature search retrieves 4 double-blind controlled and 3 open trials, which were carried out between 1980 and 2014.

The number of patients per group varied from 20 to 170. The treatment duration in the studies was up to 6 months.

Only one of the 4 studies included leads to statistically different outcomes in favour of *Serenoa repens*. This study (Mattei *et al*., 1990) is also separately included in the assessment report.

Assessor's comment

Four clinical studies were reviewed. They are all reviewed separately in this AR. The results of this meta- analysis are not convincing for ethanolic extracts of *Serenoa repens*. The number of patients per group is variable; the intervention was done during at least 13 weeks. Outcomes were scored on separate parameters or scored on IPSS and AUASI.

4.2.2.2. Controlled clinical trials comparing different extracts of Serenoa repens to placebo

Reference	Patients	Intervention	Outcome
Barry *et al*., 2011	N = 369 Mean age = 61.0 AUASI score 14.42 to 14.69 Drop out = 12	R / MC / DB SR (ethanolic extract) 320 mg / day for 24 w Followed by: SR 640 / day for 24 w SR 960 / day for 24 w Follow-up 72 weeks	Primary AUASI score: SR=PL (P=0.91) Secondary: SR= PL * BPH index (P=0.95) * AUASI QOL (P=87) * AUA nocturia (P=0.19) * Peak flow rate (P=0.84) * Postvoid residual (P=0.31) * PSA level (P=0.97) * IIEF scale (P=0.76) * MSHQ-EjD (P=0.25) * ICS score (P=0.94) * Jenkins Sleep Dysfunction Scale score (P=0.98)

AUA = American Urology Association
AUASI = American Urological Association Symptom Index
DB = double blind
ICS = international incontinence scale
IIEF = international index of erectile function
MC = multicenter
MSHQ-EjD = male sexual health questionnaire ejaculatory dysfunction
N = number of patients
PSA = prostate specific antigen
QOL = quality of life
R = randomised
SR = *Serenoa repens*

AUA = American Urology Association
AUASI = American Urological Association Symptom Index
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N = number of patients
PSA = prostate specific antigen
QOL = quality of life
R = randomized
SR = *Serenoa repens*

Patients

The baseline characteristics of the patients are provided in detail. The AUASI score can vary between 8 and 35. With mean values between 14 and 15 the patients are moderately affected, but there is a spread between 8 and 24. The age of the patients is representative of daily practice. However, there are many exclusion criteria and some are difficult to avoid when using medication in case of BPH e.g. (1) any prior invasive intervention for BPH; (2) phytotherapy for BPH or a 5-alpha reductase inhibitor within 3 months and an alpha blocker within one month; (3) transaminase values such as ALT (SGPT), AST (SGOT) or GGT greater than 3 times the upper limit of normal in the clinical center lab at SV1.0; confirmed on a second measurement, as obtaining this information is not always feasible; (4) prothrombin time greater than 3 seconds above the upper limit of normal, or more than 3 seconds above the control value in the clinical center at SV1.0; confirmed on a second measurement (see former remark); (5) ECG reading suggesting active ischemia or recent myocardial infarction until appropriate consultation confirms the absence of an acute coronary syndrome; (6) PSA level greater than 10 ng/ml at the first screening visit, as cases of prostatitis are mostly characterised by an enhanced PSA; (7) a documented bacterial prostatitis within the past year or two documented independent urinary tract infections of any type in the past year.

Other exclusion criteria are acceptable and should be checked before prescribing or delivering medication for BPH: (1) a reported allergic reaction to *Serenoa repens*; (2) taken phenylephrine, pseudoephedrine, tricyclic antidepressants, and anticholinergic or cholinergic medication within 4 weeks of the first screening visit, with the following exception: topical anticholinergic eye drops used for glaucoma; (3) taken an estrogen, androgen, or any drug producing androgen suppression, or anabolic steroids within 6 months; (4) known clinically significant renal impairment (i.e., creatinine greater than 2 mg/dl); (5) requiring the daily use of a pad or device for incontinence, or ICSmaleIS score >14 at screening; (6) unstable medical condition within the past 3 months; (7) history or current evidence of carcinoma of the prostate or bladder, pelvic radiation or surgery, urethral stricture, or prior surgery for bladder neck obstruction; (8) active urinary tract disease or has undergone cystoscopy or biopsy of the prostate within one month prior to the first screening visit or has an imminent need for urologic surgery; (9) known primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function; (10) known severe bleeding disorder or need for ongoing therapeutic anticoagulation with coumarins or heparin; (11) cancer, which is not considered cured (except basal cell or squamous cell carcinoma of the skin): a potential participant is considered cured if there has been no evidence of cancer within five years of randomisation, however a history of bladder cancer or prostate cancer is exclusionary whether the participant is considered cured or not; (12) any serious medical condition likely to impede successful completion of the study.

Intervention

The sample size was calculated to provide 90% power. The number of patients who completed 72 weeks of treatment was slightly below the 157 patients per group to reach this power. All patients were excluded that were unable to follow protocol directions due to organic brain or psychiatric disease as well as patients with a history of alcoholism or any other substance abuse. In the opinion of the investigator such conditions would affect compliance with the protocol. The authors reported an adherence of 98.2%.

The intervention was done with a commercialised ethanolic extract. The second part of the intervention was done with supra-therapeutic doses, which hampers extrapolation to practice. Blinding was assessed by asking patients about the difference between placebo and verum: no differences were seen between both groups. The duration of the intervention is considered acceptable.

Outcomes

The authors reported no significant differences in primary or secondary outcomes between *Serenoa repens* and placebo. The AUASI is considered to be a validated scale and is interesting to obtain also the outcomes on the separate parameters. The authors did subgroup analysis with regard to the following patient characteristics: race; age; AUASI score (cut-off value = 16); BPH impact index; peak urinary flow; postvoid residual volume; baseline PSA; education. AUASI score changes were not different between placebo and *Serenoa repens*.

The number of adverse events did not differ between both groups. At least 5% of the patients experienced side effects. There was also no difference in the number of participants experiencing adverse events, exception made for more physical injuries or traumas in the *Serenoa repens* group as compared to placebo (24/136 of which one serious; vs 10/137 patients; $P < 0.01$).

No data about co-medication were presented.

Assessor's comments

The authors conclude that they found that *Serenoa repens* ethanolic extract used at up 3 times of the standard daily dose had no greater effect than placebo. The study design can be considered as valid,

as well as the outcome measures. Restrictive exclusion criteria for the patients, type of extract and doses were applied.

Reference	Patients	Intervention	Outcome
Bent *et al*., 2006	N = 225 Peak urinary flow <15 ml/s BPH (AUASI) ≥8 with mean = 15.4 Mean age = 63.0 Lost for follow-up = 9	R / MC / DB SR (CO_2 extract: containing 92.1% of fatty acids): 2 x 160 mg / day Duration: 12 months	Primary: AUASI score Δ SR/PL = 0.04 (NS) Peak urinary flow Δ SR/PL = 0.43 (NS) Secondary: Δ Prostate volume = -1.22 ml Δ Residual volume = - 4.51 ml Δ BPH impact score = -0.24 Δ SF36 score mental = -1.18 Δ SF36 score physical = 0.61 Δ sexual function = -0.13

AUASI = American Urological Association Symptom Index
DB = double blind
ICS = international incontincence scale
IIEF = international index of erectile function
MC = multicenter
MSHQ-EjD = male sexual health questionnaire ejaculatory dysfunction
N = number of patients
PSA = prostate specific antigen
QOL = quality of life
R = randomised
SR = *Serenoa repens*

Patients

Patients had a AUASI of at least 8; the mean values for both groups were 15.7 ± 5.7 and 15.0 ± 5.3 for *Serenoa repens* and placebo respectively. The patients cannot be considered as moderately affected, because there was a spread between 8 and 35. Among the included patients there might have been those who needed surgery instead of a treatment with *Serenoa repens*. However patients with a peak urine flow <4 ml/s or a residual volume >250 ml after voiding were excluded. Other exclusion criteria were: (1) history of prostate cancer; (2) previous surgery for BPH; (3) urethral stricture; (4) neurogenic bladder; (5) medications known to affect urination; (6) severe concomitant disease (7) creatinine > 2 mg/dl; (8) PSA >4ng/dl. Of these criteria (7) is usually not observed in routine practice and (8) may be too severe in pathological conditions.

Intervention

Patients were randomised according to the initial AUASI values, with a cut-off of 20: patients with a score between 8 to 19 (moderate) were equally randomised with patients having a score between 20 and 35 (severe). A power calculation was made and the number of patients included allowed a power of 90% for a difference in AUASI score of 3.0 with a standard deviation of 6.0.

A CO_2 extract was selected for the study. The content of fatty acids was assessed at the midpoint of the study: it contained 90.7% fatty acids and 0.33% of total sterols. However this extract cannot be directly compared to the marketed CO_2 extract in Europe. Blinding was assessed and comparable in both groups. No data about adherence were communicated.

Outcomes

There were no differences in primary or secondary outcomes between the groups. Eight adverse effects were reported in 6 patients taking *Serenoa repens* and 18 side effects in 11 patients taking

placebo. As the number of side effects is relatively low, it is difficult to draw any conclusions from these figures. No data about co-medication were presented.

Assessor's comments

The authors conclude that therapeutic doses (2 x 160 mg) of the CO_2 extract of *Serenoa repens* used does not improve lower urinary tract symptoms caused by BPH. However the grade of prostatic symptoms may have been a source of variation which hampers extrapolation of the findings to daily practice. Indeed some of the patients may have needed surgery. Furthermore, there was no information on compliance and co-medication. The extract used appears to be safe.
The type of extract used is not the same as the commercialised CO_2 extract available in Europe.

Reference	Patients	Intervention	Outcome
Willets *et al*., 2003	N = 100 Mean age = 63.9 At least 3 symptoms of prostatism Drop out = 7	R / SC / DB SR (critical CO_2 extract) 160 mg 2 x / day for 12 w	Primary IPSS: vs. baseline within groups (P <0.001) IPSS: SR= PL (P=0.131) Secondary QoL: SR=PL (P=0.292) Peak flow lowered in both groups: SR=PL (P=0.098) IIEF: SR=PL with no change from initial values

DB = double blind
IIEF = International Index of Erectile Function
IPSS = International Prostate Symptom Score
N = number of patients
PL = placebo
QoL = Quality of Life
R = randomised
SC = single center
SR = *Serenoa repens* critical CO_2-extract

Patients

Patients had at least 3 symptoms of prostatism e.g. increased frequency of urination, nocturia, hesitancy, dribbling or poor stream. The patients were required to have a maximum urinary flow rate of 5-15 ml/s, a PSA level of <4 ng/ml. The initial IPSS scores were not communicated, but were significantly different between both groups. No spread measures were given.

An age of more than 80 was an exclusion criterion. Further exclusion criteria were: a serious medical condition, the use of androgens, alpha-blockers, 5-alpha-reductase inhibitors or herbal preparations for urinary problems during the 4 weeks before inclusion; a history of serious urogenital abnormalities.

Intervention

Randomisation was described (balanced-blocks procedure). The required number of patients was calculated with aim of detecting a change of $\geq$2.5 units in the IPSS between the treatment and the placebo group. A number of 100 patients were necessary to obtain a power of 80% and an alpha of 95%. The number of patients who finally participated was slightly lower than 100.

An Australian CO_2 extract was used for the study. The content of fatty acids is not reported. This extract cannot be directly compared to the marketed CO_2 extract available in Europe. Blinding was assessed and comparable in both groups. No data about compliance were communicated.

The duration of the study is considered as limited and not sufficient to detect differences between *Serenoa repens* and placebo.

Outcomes

There were significant differences in the IPSS for both groups between baseline values and scores obtained at the end of the study. The same results were obtained for the other parameters, exception made for the IIEF, which did not change but was significantly influenced by age as shown by regression analysis (P = 0.008).

However the evaluation of the primary outcome is seriously hampered by the significant baseline difference in IPSS.

Assessor's comments

The authors conclude that therapeutic doses (2 x 160 mg) of the Australian CO_2 extract of *Serenoa repens* as well as placebo improved the IPSS over time and that there was no detectable significant difference between both groups. In their conclusion the authors refer not always to monopreparations. This study cannot be taken into consideration for the monograph for a number of reasons including: (1) the initial IPSS of the patients is insufficiently characterised; (2) there exists a significant baseline difference between groups, and this fact is not explained sufficiently; (3) the extract used is not commercialised in Europe and may be different to extracts available in Europe.

Reference	Patients	Intervention	Outcome
Gerber. *et al*., 2001	N = 85 IPSS > 8 Mean initial IPSS = 15.8 (PL) to 16.7 (SR) 1 month running-in: exclusion of responders to PL Mean age = 65y Lost for follow-up = 7%	R / DB – MC or SC (?) SR (extract containing 85 to 95% fatty acids and sterols; extraction solvent not mentioned) 160 mg, 2 x / day Duration: 6 months	Primary IPSS: SR > PL (P = 0.038) QoL: SR = PL Secondary Sexual function SR = PL Peak flow rate SR = PL

DB = double blind
IPSS = International Prostate Symptom Score
MC = multicenter
N = number of patients
PL = placebo
QoL = Quality of Life
R = randomised
SC = single center
SR = *Serenoa repens* extract

Patients

Patients were eligible for the study if they had an IPSS of more than 8, however there were no individual limits given. According to the mean values most of the patients may belong to moderately affected by BPH.

The following exclusion criteria were valid: (1) former prostate surgery; (2) history of prostate cancer or urethral stricture; (3) treatment with finasteride, *Serenoa repens* or other alternative therapy during the past 6 months; (4) treatment with an alpha-blocker during one month previous to inclusion.

Intervention

Before inclusion, patients were tested during a one month run-in period. If their IPSS was lower than 8 after this period, they were excluded. The subsequent randomisation method is described. Information on the extract is given in the study table, but no further information was provided about the extraction solvent. As the study is done with a preparation on the American market, there may be no equivalent in Europe. The standardisation limits are considered large, which could lead to batch to batch

variations. No power calculation is reported, as a consequence the number of patients may be too low leading to a type-I error in the statistical analysis.

The duration of the study is borderline sufficient for practice.

Outcomes

There is a significant difference in the IPSS between both groups, with a greater lowering of the IPSS in the *Serenoa repens* group. Although the QoL improved to a greater degree in the *Serenoa repens* group, there was no statistical difference between both groups. No improvement occurred in the sexual function questionnaire results. The peak urinary flow rate improved slightly in both groups, although there was no improvement between the groups.

There was only one patient complaining of mild dyspepsia.

Assessor's comments

The authors conclude that therapeutic doses (2 x160 mg) of a non-specified extract of *Serenoa repens* improved the IPSS significantly over placebo after 6 months treatment in patients with what would appear to be moderate BPH.
The number of participants may be too limited to avoid a type-I statistical error, however the authors eliminated placebo responders which restricted the population to real responders. Due to the lack of information no extrapolation can be made to extracts marketed in Europe and considerable batch to batch variations are likely in view of the extract used.
As a consequence, this study has not been considered further in the development of the monograph.

Reference	Patients	Intervention	Outcome
Löbelenz, 1992 (German)	N = 60 BPH grade I and II Urinary flow of < 20 ml/s Age = 48 to 82 y No drop outs	R / MC / DB SR extract 100 mg 3x/d Duration: 6 weeks	Urinary flow rate improved: SR: in 67% vs. PL: in 53% NS

BPH = Benign Prostate Hyperplasia
DB = double blind
MC = multicenter
N = number of patients
PL = placebo
QoL = Quality of Life
R = randomised
SR = *Serenoa repens* extract

Patients

Eligible patients presented with BPH stadia I and II. However there is no discussion of the use of a validated scale, which hampers the description of the real status of the patients. Defining the cut-off value for the urinary flow at 20 ml/s may include patients with only minor symptoms for whom achieving a therapeutic goal is nearly impossible.

Intervention

The randomisation procedure was not described. The type of extract is not described. The posology is somewhat unusual in terms of the dose and frequency of intake. No reference can be made to any posology or extract included in Table 1 (Overview of extracts, posology and marketing data within the EU). No power calculation is reported and as a consequence the number of patients may be too low, leading to a type-I error in the statistical analysis. The duration of the study is too short to be relevant for practice.

Outcomes

The authors did not find significant differences in the therapeutic outcome. A positive trend is reported for the group treated with *Serenoa repens.* A majority of these patients improved.

The improvement of the urinary flow was limited: from 12.3 ml/s to 13.5 ml/s; similar findings were reported for placebo: from 13.0 ml/s to 13.6 ml/s.

Assessor's comments

Despite the efforts made by the authors to explain the possible advantages of *Serenoa repens*, this study cannot be taken into consideration for the monograph, for several reasons: (1) the baseline characteristics of some individual patients may have been quite close to normal; (2) the number of patients is too low; (3) the study period is not adequate; (4) the extract cannot be compared to commercialised preparations in EU-member states; (5) only one urinary parameter is evaluated.

Reference	Patients	Intervention	Outcome
Mattei *et al*., 1990 (German)	N = 40 Age = 45 to 72y Patients with 'manageable' BPH Lost for follow-up = 5%	R / SC / DB SR (ethanolic extract; no strength given): 160 mg 2 x / day Duration: 13 weeks Evaluation after 30, 60 and 90 days	Dysuria (4-point scale) Compared with baseline SR: day 30 and 90 (P <0.05) SR: day 60 (P <0.01) PL: NS Residual volume (4-point scale) SR: day 30 (P <0.05) SR: day 60 and 90 (P <0.01) PL: NS Pain and feeling of pressure (4-point scale) SR: day 30 (P <0.05) SR: day 60 and 90 (P <0.01) PL: NS
NS = Non Significant DB = double blind SC = Single Centre N = number of patients		PL = placebo R = randomised SR = *Serenoa repens* extract	

Patients

As mentioned in summary table, patients suffered from a mild to moderate grade of BPH. No validated scale was used for determining baseline characteristics: enlarged prostate volume and abnormal micturition, but no surgical intervention necessary.

Exclusion criteria were: serious urogenital disease and prostate cancer.

Intervention

The randomisation methodology was not described. Patients were allocated to placebo or to a *Serenoa repens* extract marketed at that time (ethanolic). The treatment period may have been too short to obtain robust results. No power calculation is mentioned, as a consequence the number of patients may have been too low, leading to a type-I error in the statistical analysis.

Outcomes

The reported outcomes were evaluated on day 30, 60 and 90. Dysuria, void volume and pain or feeling of pressure gradually improved over time in the treated patients versus the placebo group. After 30 days there was a significant difference for the 3 symptoms. Improvement over time is a positive outcome. The authors do not use validated scales, but the symptoms are related to BPH.

Only one patient in both groups complained about stomach pain.

Assessor's comments

The authors concluded a positive outcome for 3 urinary parameters with 2 x 160 mg of a *Serenoa repens* extract. The urinary symptoms gradually improved over time, which can be regarded as a positive outcome of the study.
However, the number of participants may be too limited to avoid a type-I statistical error. Also the treatment period should have been longer in order to examine long term effects. An ethanolic extract is used.

Reference	Patients	Intervention	Outcome
Shi *et al.*, 2008 Study carried out in China and published in English	N = 94 Age = 62 to 68y (95% CI) IPSS mean values: 16.85 (SR) and 14.46 (PL) Drop outs = 2	R / MC / DB SR [1](; no further details about strength; composition and extraction solvent): 2x / day (no strength given!) Duration: 3 months Compliance rate 95%	Flow rate SR: 14.07 ± 2.56 ml/sec PL: 11.74 ± 1.23 ml/sec P<0.001 Relative urinary resistance SR < PL : P = 0.002 IPSS improvement (- > 3) SR in 39.1% PL in 2.2% P<0.001

CI = confidence interval
DB = double blind
MC = multicenter
N = number of patients
PL = placebo
R = randomised
SR = *Serenoa repens*

Patients

With IPSS values between 13 and 19 (95% CI) patients can be considered as moderately affected. SR patients had a significantly higher IPSS as compared to PL patients (P=0.043). The following other baseline characteristics of patients were investigated: PSA, creatinine, urinary flow rate (< 15 ml/s) and prostate size. The age of the patients is representative for daily practice. These parameters were comparable between both groups. Only Chinese patients were included.

An extensive list of exclusion criteria is mentioned: (1) history of prostate cancer; (2) the use of any drugs, herbs or other nonprescription preparations for lower urinary tract symptoms (LUTS) associated with BPH within 4 weeks of screening, including finasteride, α-or ß-blockers, diuretics, calcium channel blockers and anticholinergic drugs; (3) abnormal laboratory parameters, including PSA >4 ng/ml, serum creatinine more than 160 µMol/l, urine bacterial count greater than 100,000/ml, urinary nitrogen BUN > 8 mg/dl, urinary flow rate >15 ml/s and voiding volume <150 ml; (4) patient inability to understand or follow the study protocol; (5) current or previous participation in another clinical trial;

[1] Commercial name of the preparation: Prostaplex.

(6) BPH judged by a urologist to require surgical treatment; (7) previous bladder or prostate surgery; (8) micturition problems associated with an identified bladder pathology (neurogenic bladder, bladder neck stenosis, lithiasis or bladder cancer), urethral stricture; (9) recurrent urinary tract infections; (10) serious condition like known renal, hepatic or cardiac insufficiency, diabetes mellitus, recent MI; (11) known alcohol abuse; (12) known sensitivity to the ingredients in the product, significant depression or other psychiatric disease noted during the initial screening; (13) any other cancer in the last 5 years except skin cancer; (14) being on anticoagulation therapy.

These exclusion criteria make the population rather selected as compared to routinely involved patients, because not all of these conditions are checked in daily practice.

Intervention

The randomisation procedure is mentioned, but no methodological details are described. No sample size was calculated, and consequently the study was not powered. The number of patients may have been too low to avoid type-I error. A 3 months duration can be considered as too short to confirm robust results. Compliance evaluation is based upon pill count and did not differ between both groups. The intervention was done with a commercialised *Serenoa repens* extract. No further details are given on the preparation, and even the amount of extract per capsule is not reported.

Outcomes

The post-intervention mean IPSS values did not differ between both groups. This is not surprising, as the *Serenoa repens* group had a significantly higher initial value than the placebo group. Whereas the latter lowered, the former hardly changed. When a change of $\geq$3.0 was taken as therapeutically relevant, significantly more patients in the intervention group improved. Taken this criterion into consideration, about 4 in 10 patients had some benefit from the *Serenoa repens* preparation. This measure is a realistic one, as it can be easily transferred to daily practice. Urinary resistance and flow rate also improved. Both parameters are relevant for the patients.

No data about side-effects were reported. The drop-outs were due to lost for follow-up.

Assessor's comments

The authors conclude that the *Serenoa repens* preparation used resulted in significant short-term improvement of BPH symptoms. The calculation of the % of patients improved is a positive fact, as it gives information on the individual patient level.
Weaknesses of the study are (1) the low number of patients; (2) the significant difference in IPSS baseline between both groups; (3) the short duration; (4) the lack of qualitative and quantitative description of the preparation used.
The results of the study cannot be taken into account for the monograph.

Reference	Patients	Intervention	Outcome
Helfand *et al.*, 2012	N = 339 Age = ≥45 y Drop outs = not known	R / DB / PL SR (N = 167) no further details about strength; composition and extraction solvent): no posology specified PL (N = 172) Duration: 18 months	Jenkins Scale (sleep disturbance): SR = PL Association between AUASI and Jenkins Scale Significant correlation between both (P <0.001)

AUASI = American Urology Association Symptom Inventory
DB = double blind
N = number of patients
PL = placebo
R = randomised
SR = *Serenoa repens*

Assessor's comments

This study refers to the CAMUS trial (Barry *et al.,* 2011), where the effect of *Serenoa repens* on lower urinary tract symptoms in BPH patients is studied in a dose-dependent design (see earlier in this report). The study only indirectly contributes to the evaluation of the therapeutic value of *Serenoa repens*.

No new issues are emerging, as it is quite obvious that sleep disturbances due to BPH can occur. There seems to exist a close correlation between the Jenkins and the AUASI scales. The CAMUS trial was carried out with a commercialised ethanolic extract.

4.2.2.3. Clinical trials with a well-defined hexane extract

Meta-analysis

Reference	Patients	Intervention	Outcome
Boyle *et al.*, 2004 Meta-analysis of published and non-published studies with a commercialised hexane extract	Data from 17 studies available N = 1956 open label N = 899 PL controlled N = 42 with prazosin N = 1097 with finasteride N = 63 with alfuzosin N = 703 with tamsulosin N = 60 with Pa/PL	*Serenoa repens* hexane extract SR 320 mg per day Design - 4 open studies - 9 PL controlled - 1 SR vs prazosin 4 mg/d - 1 SR vs finasteride 5 mg/d - 1 SR vs alfuzosin 7.5 mg/d - 1 SR vs tamsulozin 0.4 mg/d - 1 SR / Pa / PL Duration 30 to 720 days	SR from baseline Δ IPSS = - 4.78 SEM = 0.41 PL from baseline Δ IPSS = - 4.54 SEM = 0.64 Additional by SR Peak urinary flow Δ = + 1.02 ml/sec SEM = 0.50 ml/sec (P = 0.042) Nocturnal voids Δ = - 0.38 SEM = 0.07 (P <0.001)

Δ = difference SR vs PL
IPSS = International Prostate Symptom Score
N = number of patients
Pa = *Pygeum africanum*
PL = placebo
SEM = Standard Error of the Mean
SR = *Serenoa repens extract*
vs = versus

Assessor's comments

Strengths

Although most of the studies considered by Boyle et al. (2004) have been discussed individually in this assessment report, the meta-analysis is interesting because, apart from the published studies, three non-published studies were included (data on file from a pharmaceutical company). By this fact the meta-analysis adds to the knowledge of possible clinical efficacy of Serenoa repens.

The fact that all studies were performed with the same hexane extract makes this meta-analysis more valuable when compared to the more recent Cochrane review, which deals with different kinds of extracts. Grouping studies with the same preparation is important from a regulatory point of view.

Among the studies included, seven used IPSS as the outcome measure.

Additional effects by Serenoa repens on peak urinary flow and nocturnal voids were evaluated. There was slight but a significant improvement of these parameters as compared to placebo. The standard deviation on these outcomes was limited.

Weaknesses

Four studies were open label. Evaluation could only be done by comparing the baseline values.

Although significant, the differences obtained with Serenoa repens were modest. Comparison of IPSS is indirect and calculation of significance is not appropriate.

Study 25 cited by Boyle et al. (2004) fulfills several criteria of an ideal protocol. The number of patients is sufficiently high in both groups and the study lasted for 360 days. It did not show a significant difference between Serenoa repens and placebo when IPSS was taken into consideration. This study was not published, which points to a publication bias. When considering the negative result, it should be taken into account that there exists a natural converging effect or 'regression to the mean' artefact. Roehrborn (2006) cites a study with finasteride versus placebo, where the placebo arm showed an improvement in the IPSS which was particularly marked during the first year and tended to decrease after 3 years. Expectancies of patients are covering a duration of more than 1 year. But when a study will be set up with a duration of several years, the risk of losing patients over this longer period will be a possible drawback.

Conclusion

Boyle et al. (2004) carried out a meta-analysis of studies performed with the same commercially available hexane extract. Several of the studies included in the meta-analysis were unpublished. As only seven studies used the IPSS as outcome (cf. date of publication) this parameter could only be evaluated for these trials. Nearly all studies reported on peak urinary flow and nocturia. Serenoa repens modestly but significantly improved both.

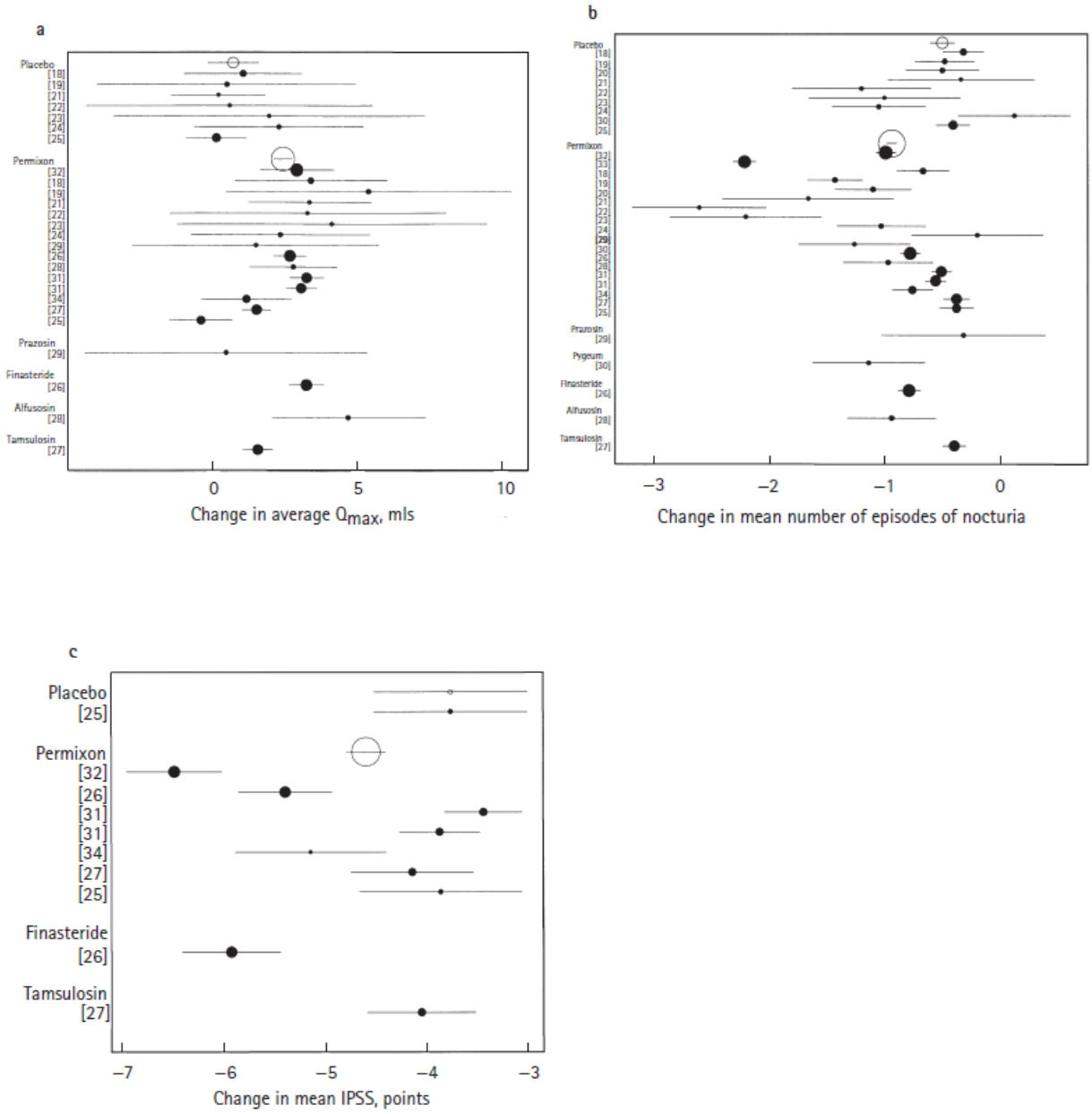

Figure 13: Visualised changes of the urinary outcomes according to Boyle *et al*. (2004). Changes in panel a: mean Qmax; in panel b: mean number of voids per night; in panel C: mean IPSS, by study and treatment group. The size of the points is proportional to the square root of the number of subjects. The summaries for the *Serenoa repens* hexane extract and placebo arms of the studies are plotted with open circles. The horizontal lines indicate the 95% CI.

Individual trials

Reference	Patients	Intervention	Outcome
Descotes *et al.*, 1995	N = 215 BPH stage I or II Mean age = 66.3 y Drop out = 39	R / MC / DB SR (= hexane extract) 160 mg, 2 x / day SB run-in period of 4 weeks to PL Duration of subsequent trial: 4 weeks	<u>Compared to PL:</u> Dysuria: Δ = 15.2% (P=0.019) Urinary frequency (day): - 11.3% (P=0.012) Urinary frequency (night): Δ = 14.8% (P=0.028) Urinary flow rate: + 20.0% (P = 0.038) <u>Clinical rating by patients</u> SR satisfactory in 71.3% PL satisfactory in 67.5% <u>Clinical rating by physicians</u> SR satisfactory in 56.6% PL satisfactory in 47.2% Both NS

Δ = difference SR vs PL
DB = double blind
MC = multicenter
N = number of patients
NS = not significant
PL = placebo
R = randomised
SB = single blind
SR = *Serenoa repens* extract

Patients

Patients were recruited in general practice and hospital setting (hospital out-patients). They had to demonstrate a mild to moderate BPH (= stage I or II). The following parameters were taken into consideration for inclusion: (1) dysuria; (2) daytime as well as nocturnal urinary frequency; (3) the maximum urinary flow rate had to be >5 ml/s.

Exclusion criteria were: (1) excessively mild or severe symptoms of BPH including incontinence, bladder distension, urine flow<5 ml/s; (2) cancer; (3) prior treatment for BPH; (4) urogenital infection; (5) hematuria; (6) diabetes; (7) any prior surgery that could induce dysuria.

The above mentioned criteria can be considered as in accordance with daily practice. IPSS was not yet used for describing the baseline conditions as the study was initiated before the validation of IPSS. Patients with complications or at a stage requiring surgery were excluded.

Intervention

Before inclusion, patients received placebo in a single blind design. Only patients who remained below an improvement level of 30% from baseline in peak urinary flow rate entered the second phase of the study. The randomisation procedure was not described in detail.

The intervention took place with a well-defined commercially available hexane extract. No power calculation was made. The number of patients might be sufficient, but this is a hypothesis.

The short duration of the study is partially compensated by a placebo-run-in period. However, this short duration does not allow for long-term effect evaluation.

Outcomes

Three urinary parameters improved significantly with *Serenoa repens* as compared to placebo. A significantly higher % of patients experienced an improvement in dysuria (31.3% vs. 16.1%). Significant improvement in urinary parameters contrasts with the clinical ratings by patients and physicians, although there is a trend in favor of *Serenoa repens*. This may point to the importance of combining global impressions with individual symptoms. The study lacked a validated scale for measuring quality of life.

Reasons for exclusion from the analysis were: inclusion error, protocol violation, treatment withdrawal and lost for follow-up. Only one drop-out occurred in the *Serenoa repens* group, due to complaints of fatigue, depression and stomach upset. The preparation and placebo were well tolerated by more than 95% of the patients.

Assessor's comments

The study dates from before the validated IPSS was available for evaluation. The inclusion and exclusion criteria for patients can be considered as close to general practice. The short duration of the study is partially compensated for by a placebo run-in period. The extract used is well known, and the therapeutic dose corresponds to the actual market situation.
The discrepancy between the results obtained for the urinary parameters and the global impressions by patients and physicians may indicate the need for longer term clinical studies (at least 6 months).

Reference	Patients	Intervention	Outcome
Cukier *et al.*, 1985 (French)	N = 168 Mean age = 69 years Drop out = 13%	R / MC / DB SR (= hexane extract) 160 mg, 2 x / day Duration: 10 weeks	Compared to PL Urinary frequency (night): - 18.6% (P <0.001) Urinary frequency (day): - 18.2% (P <0.001) Residual volume SR: - 14.7% PL: + 53.2% (P <0.05)

DB = double blind
MC = multicenter
N = number of patients
PL = placebo
R = randomised
SR = *Serenoa repens* extract

Patients

Patients were described as suffering from a *prostatic adenoma* (cf. French terminology). No further details were given as basal urinary parameters are concerned. The patients were enrolled as outpatients. All preceding therapies were interrupted at least 2 weeks before enrollment. Hormonal treatment had to be stopped 2 months before inclusion.

Patients were excluded if the symptoms did not occur for at least 6 months. Note that in the Cochrane analysis (Taklind *et al*., 2012) it is incorrectly reported that patients suffering for more than 6 months was considered as an exclusion criterion. All medication interfering with the urinary parameters was not allowed.

Intervention

The intervention took place with a well-defined commercially available hexane extract, although the strength of a single tablet was 80 mg. As the number of patients is concerned, the authors refer to the study of Champault *et al*. (1984). In this study significant differences were obtained with about 100 patients. Based upon these numbers the authors included a higher number of patients.

In the original study the design is described as '*double-insu*', which is a synonym for 'double blind'. The authors describe also a 'decodage', which can be considered as un-blinding, when analysing the results. However, in the English translation, the design is mentioned as *single blind*. In the Cochrane analysis (Tacklind *et al*., 2012) the study is described as patient and provider blinded. The reason for this confusion is unclear. No randomisation procedure is given.

The short duration of the study does not allow for long-term effect conclusions.

Outcomes

Urinary parameters improved significantly with *Serenoa repens* as compared to placebo. Doctor's opinion is in favor of *Serenoa repens* (66.7% good results vs. 26.7% for placebo after 30 days) a result that remains until the end of the study (69.7% good results).

Both *Serenoa repens* and placebo were well tolerated (94.4% and 91.3% respectively).

Reasons for exclusion from the analysis were mostly lost for follow-up or serious health complications which made the patients no longer compliant with inclusion criteria.

Assessor's comments

The study dates from before the validated IPSS was available for evaluation.
Strengths: The inclusion and exclusion criteria for patients can be considered as close to general practice. The extract used is well known, and the therapeutic dose corresponds to the actual market situation.
Weaknesses: There exists some confusion about the blinding. The study has a relatively short duration, although there is a placebo run-in period. The therapeutic urinary outcomes are partial and the impression by the clinicians may be influenced by subjectivity.

Reference	Patients	Intervention	Outcome
Champault *et al.*, 1984	N = 110 Mean age = not reported Drop out = 15%	R / MC / DB SR (= hexane extract) 160 mg, 2 x / day Duration: 4 weeks	Compared to PL Urinary frequency (night): - 40.8% (P <0.001) Urinary flow rate: + 45.5% (P <0.001) Residual volume SR: - 41.9% PL: + 9.3% (P <0.001) Global efficacy (patients & clinicians): SR > PL (P <0.001)

DB = double blind
MC = multicenter
N = number of patients
PL = placebo
R = randomised
SR = *Serenoa repens* extract

Patients

Patients were described as suffering from dysuria, nocturia and poor urinary flow. Baseline values for nocturia, flow rate and post-micturition are presented in the publication.

Exclusion criteria: (1) patients with an acute or unstable episode; (2) adenomas requiring early surgery; (3) prostate cancer; (4) genito-urological complications.

Intervention

The intervention took place with a well-defined commercially available hexane extract, although the strength of a single tablet was 80 mg. The Cochrane analysis wrongly mentions 2 x 80 mg per day i.o. 2 x (2 x 80 mg) per day. No power calculation was made.

The short duration of the study does not allow for long-term effect evaluation.

Outcomes

The urinary parameters improved significantly with *Serenoa repens* as compared to placebo. Doctor's opinion was in accordance with the measurements. Intragroup as well as intergroup differences were reported and remained in favor of *Serenoa repens*.

Both *Serenoa repens* and placebo were well tolerated and no drop-outs occurred due to side effects. All side effects are described as minor. Reasons for exclusion of the analysis were mostly lost for follow-up or treatment with antibiotics.

Assessor's comments

The study dates from before the validated IPSS was available for evaluation. The inclusion criteria match with daily practice, but no stage of BPH has been determined. The very short duration only allows for initial effects, not therapeutically relevant. The extract used is well known, and the therapeutic dose corresponds to the actual market situation. There is a concordance between the therapeutic urinary outcomes and the impression by the clinicians.

Reference	Patients	Intervention	Outcome
Emili *et al*., 1983 (Italian)	N = 30 Age = 44 to 78y No drop outs	R / SC / DB SR (= hexane extract) 160 mg, 2 x / day Duration: 4 weeks	<u>Compared to PL</u> Dysuria improved in SR: 92.3% in PL: 33.3%

DB = double blind
N = number of patients
PL = placebo
R = randomised
SC = single center
SR = *Serenoa repens* extract

Patients

No details about the stage of BPH were provided. The patients were affected by simple prostatic hypertrophy for which surgical or endoscopic treatment was not yet necessary.
Exclusion criteria: prior treatment for BPH.

Intervention

The intervention took place with a well-defined commercially available hexane extract. No power calculation was made. Due to the low number of patients in each group, a type-I error may have been possible.

The short duration of the study does not allow for long-term conclusions.

Outcomes

The number of micturitions during day and during night are presented as individual results in the publication. Symptoms of obstruction, volume of the prostate, urinary flow and post micturition residue were tabled as well on individual level. No statistical evaluation of the differences between intervention and placebo was made.

Both *Serenoa repens* and placebo were well tolerated and no drop-outs occurred due to side effects.

Assessor's comments

The study dates from before the validated IPSS was available for evaluation. The inclusion criteria are not described in detail, but for all outcomes individual results are given.
The very short duration only allows for initial effects not therapeutically relevant. The groups of patients are relatively restricted. The extract used is well known, and the therapeutic dose corresponds to the actual market situation. However no statistical analysis was made, which hampers the translation into the monograph.

Reference	Patients	Intervention	Outcome
Reece-Smith *et al*., 1986	N = 80 Age = 55 to 80y Patients with Symptomatic BPH Lost for follow-up = 12.5%	R / SC / DB SR (= hexane extract): 160 mg 2 x / day Duration: 12 weeks	Difference from baseline SR : P <0.01 to 0.001 PL : P <0.01 to 0.001 Difficulty in micturition Urinary urgency Hesitancy Terminal dribbling Nocturia Between groups: NS

DB = double blind
N = number of patients
NS = not significant
PL = placebo
R = randomised
SC = single center
SR = *Serenoa repens* extract

Patients

Patients were included after scoring by the clinician and by a self-administered questionnaire. They had to fulfill an extensive list of genito-urinary conditions for inclusion. No validated scale was used.

Exclusion: patients with a malignant disease.

Intervention

The randomisation procedure was not described in detail. The intervention took place with a well-defined commercially available hexane extract. No power calculation was made. The number of patients might be sufficient, but this is a hypothesis.

Outcomes

Evolution of the urinary parameters is compared with baseline values. There were no statistically significant differences between *Serenoa repens* and placebo.

A few patients on *Serenoa repens* (N=3) experienced gastro-intestinal discomfort.

Assessor's comments

The study dates from before the validated IPSS was avaialble for evaluation. The inclusion and exclusion criteria for patients can be considered as close to general practice. The relatively short duration of the study allows only for short term evaluation. The extract used is well known, and the therapeutic dose corresponds to the actual market situation.

Reference	Patients	Intervention	Outcome
Tasca *et al*., 1985 (Italian)	N = 30 Mean age = 61.5 years Drop out = 10%	R / SC / DB SR (= hexane extract) 160 mg, 2 x / day Duration: 8 weeks	Compared to PL Urinary frequency (night and day) decreased more (P <0.05) Peak urinary flow rate increased more (P <0.05)

DB = double blind
N = number of patients
PL = placebo
R = randomised
SC = single center
SR = *Serenoa repens* extract

No data on exclusion given.

Patients

Patients underwent a 2 month wash-out period to eliminate the influence of any other specific therapies. The suffered from stage 1 or 2 prostatic adenoma. Patients were subjected to an intravenous urography at the time of selection. The volume of the prostate, the residual volume after micturition, urinary flow and bacterial contamination were tested before inclusion.

Exclusion criteria: not being affected by any noteworthy hepatic, renal or cardiac disorder.

Intervention

The randomisation procedure was not described in detail. The intervention took place with a well-defined commercially available hexane extract. No power calculation was made. The number of patients is limited which enhances a type-I statistical error.

Outcomes

Two urinary parameters showed a statistically different improvement. There was no statistical difference in residual volume and micturition time.

The extract was well tolerated. Only one patient left due to 'collateral effects'.

Assessor's comments

The study dates from before the validated IPSS was available for evaluation. The inclusion and exclusion criteria for patients can be considered as close to general practice. The number of patients is too limited to avoid type-I statistical error. The relatively short duration of the study allows only for short term evaluation. The extract used is well known, and the therapeutic dose corresponds to the actual market situation.

Reference	Patients	Intervention	Outcome
Boccafoschi & Annoscia, 1983	N = 22 Mean age = 68 years (55-80 y) No drop outs	R / MC / DB SR (= hexane extract) 160 mg, 2 x / day Duration: 8.5 weeks	Compared to PL Increased: * voiding volume (P <0.005) * peak and mean urinary flow rates (P <0.02) Reduced: * nycturia (P <0.05) * dysuria (P <0.01) Overall comparison: SR better than PL (P <0.05)

DB = double blind
N = number of patients
MC = multicenter
NS = not significant
PL = placebo
R = randomised
SR = *Serenoa repens* extract

Patients

No stage of BPH was mentioned for the included patients. Patients suffered from BPH for at least one year. Most of them underwent other treatments before. At the time of inclusion the following urinary parameters were checked: dysuria, feeling of heaviness at the pelvic level, nocturia and daytime pollakisuria, micturition volume, urinary flow and micturition time.

Exclusion criteria: cancer; currently on other medication; urinary tract infection.

Intervention

Patients were allocated using a 'randomised list'. The intervention took place with a well-defined commercially available hexane extract. No power calculation was made. The number of patients is limited which enhances a type-I statistical error.

Outcomes

Most urinary symptoms improved significantly with *Serenoa repens* as compared to placebo, although absolute differences were mostly small.

Practically no side effects were observed with either *Serenoa repens* or placebo. Only one case of itching was reported with placebo.

Assessor's comments

The study dates from before the validated IPSS was avaialble for evaluation. The inclusion and exclusion criteria for patients can be considered as close to general practice. The number of patients is too low to avoid a type-I error. The relatively short duration of the study allows only for short term evaluation. The extract used is well known, and the therapeutic dose corresponds to the actual market situation.

4.2.2.4. Clinical trials with well-defined supercritical CO2 extract

Reference	Patients	Intervention	Outcome
Braeckman *et al.*, 1997a	N = 238 Mean age = 65 years Moderate BPH Drop out = 5%	R / MC / DB SR (= supercritical CO_2 extract) 160 mg, 2 x / day Duration: 12 weeks	<u>Compared to PL:</u> Pollakisuria: -19% Nocturia: - 20% P <0.05 for both Urgency: - 36% Dysuria: - 25% P <0.01 for both Prostatic volume decrease: P <0.001 <u>Improvement vs. PL</u> Urinary volume (P <0.05) Total symptom score: * day 60 (P <0.05) * day 90 (P <0.01) <u>No significant difference</u> * Mean and maximal urinary flow * Residual urinary volume <u>Quality of life rated by patients</u> * at 1 month (P <0.015) * at 2 - 3 months (P <0.001) <u>Quality of life rated by doctors</u> * at 1 month (P <0.002) * at 3 months (P <0.001)

DB = double blind
N = number of patients
MC = multicenter
NS = not significant
PL = placebo
R = randomised
SR = *Serenoa repens* extract

Patients

Patients were examined for the following parameters at the time of inclusion: (1) prostatic volume; (2) maximum and mean urinary flow rate; (3) micturition volume; (4) residual volume; (5) total symptom score.

Exclusion criteria: (1) age >80 years; (2) prostate/other cancers; (3) urinary flow <5 ml/s or >15 ml/s; (4) residual volume >60 ml; (5) currently on medications for BPH; (6) urinary tract infection.

Patients may be considered as concordant with patients seen in daily practice.

Intervention

The randomisation procedure was described. The sample size was calculated to obtain a power of 90% to detect a difference on the total symptom score of 1.5, assuming that the common standard deviation would be 3.0 using a two group t-test with a 0.050 two-sided significance level. For the final number of patients to include, a drop-out of 30% was hypothesised.

A commercialised CO_2 extract was selected for the study in a standard posology. Blinding was assessed and comparable in both groups. No data about adherence were communicated.

The relatively short duration of 12 weeks allows only for short term evaluation.

Outcomes

The quantitative results are listed in the summary table. As there existed a significant baseline difference for urgency, the percentage of patients achieving zero scores for this parameter was evaluated: 53.5% for *Serenoa repens* and 34.4% for placebo (P <0.05). There was a highly significant interaction with time for the total symptom score (P <0.001), with a more positive evolution in the *Serenoa repens* group. Urinary flow and residual volume did not differ significantly between the groups, however there was a tendency towards better results with *Serenoa repens*. There were no significant differences between treatment centers (n=8).

Side effects probably correlated to the medication were reported by 4 patients in the placebo group and by 3 patients in the *Serenoa repens* group. There were no serious side effects, and there was no statistical difference in frequency between the groups.

Assessor's comments

The authors conclude that the extract used in therapeutic doses is an efficacious and well-tolerated therapy in early symptomatic BPH. The study is well conducted with a sufficient number of patients, representative for daily practice. The extract used is commercialised in some member states of the EU. The IPSS was not yet available but a total score of symptoms, as well as separate symptoms were evaluated.

4.2.2.5. Clinical trials comparing Serenoa repens to other medicines

Comparative trials are included, because of the importance to compare outcomes obtained with *Serenoa repens* extracts to other medication considered as valid for WEU. The standardised hexane extract refers to a product on the European market.The individual studies are evaluated on patient, intervention and outcome level, and a conclusion is made.

Comparison to finasteride

Reference	Patients	Intervention	Outcome
Carraro *et al*., 1996	N = 1098 with IPSS >6 Mean age = 64.5 years Dropout due to side effects = 4% (SR = 28; finasteride = 14) Lost for follow up = 13.4	R / MC / DB Finasteride: 5 mg per day SR (=hexane extract): 2 x 160 mg per day Duration: 26 weeks	<u>Primary: IPSS (since start)</u> Finasteride: - 39% SR: - 37% NS between groups <u>Secondary criteria:</u> * QoL score * Mean urinary flow NS between groups <u>Secondary criteria:</u> * Peak urinary flow: Finasteride > SR : P = 0.035 * Sexual function score: Finasteride > SR : P <0.001 * Prostate volume reduction: Finasteride > SR : P <0.001 * Serum PSA lowering: Finasteride > SR : P <0.001

DB = double blind
N = number of patients
MC = multicenter
IPSS = international prostate symptom score
PSA = prostate specific antigen
R = randomised
QoL = quality of life
SR = *Serenoa repens* extract

Patients

The study was conducted in 87 urology centers in 9 European countries. Some patients with only minor symptoms may have been included as the cut-off value started from IPSS >6. Mean values of both groups were at least comparable (IPSS = 15.7). All other urinary parameters completely matched between both groups.

Exclusion criteria: (1) prostate cancer; (2) bladder disease; (3) abnormal liver function; (4) diuretics or drugs with antiandrogenic or alpha-receptor properties in the preceding 3 months; (5) urogenital infections; (6) disease potentially affecting micturition.

Intervention

The study was well conducted. A power calculation was not made. In the concept of the study non-inferiority parameters were not considered. The extract of *Serenoa repens* is commercially available in EU member states. The doses of both medications are convenient. The duration of the study is sufficient.

Outcomes

Most parameters significantly improved in both groups as compared to baseline values. Although the peak urinary flow was higher for finasteride, there was only 0.7 ml/sec difference. The number of withdrawals due to side effects was higher for *Serenoa repens*: 28 versus 14. No further details are given.

Assessor's comments

The authors conclude that in the treatment of men with mild or moderate symptoms of BPH, both treatments are clinically equivalent in this study. Because both compounds are equally effective, the authors highlight the need to reevaluate the clinical androgen-dependency of BPH.
The study is well conducted in a large number of patients, for a sufficient time. No placebo group was included.

Reference	Patients	Intervention	Outcome
Kaplan *et al*., 2004	N = 64 with chronic non-bacterial prostatitis pelvic pain syndrome Mean age = 43-44 years	SB / R Finasteride (N=30): 5 mg per day SR (N=34) nature of the preparation not specified): 325 mg per day Duration: 1 year	<u>Primary outcomes</u> <u>NIH-CPSI from baseline</u> F : significant improvement after 3, 6 and 12 months. SR : significant improvement after 3 months P-values not communicated <u>NIH-CPSI between groups</u> % patients with significant improvement after 1 year: F (65%) > SR (24%) P = 0.02 <u>Secondary outcomes</u> AUA Sx: F = SR Peak flow: F = SR PSA: F = SR

SB = single blind
NIH-CPSI = National Institute of Health Chronic Prostatis Symptom Index
AUA Sx = American Urological Association Symptom Score
PSA = prostate specific antigen
F = finasteride
SR = *Serenoa repens* extract

Assessor's comments

Despite the extended duration, this study is of limited value because of the complicated pathology of the chronic non-bacterial prostatitis pelvic pain syndrome. This explains the relatively young age of the participants.
The study lacks a power calculation and the *Serenoa repens* preparation used is not described. A number of the patients had previously been treated with antibiotics and/or alpha-blockers. Furthermore, no placebo group was included.

Comparison to tamsulosin and alfuzosin

Reference	Patients	Intervention	Outcome
Argirović & Argirović, (2013)	N = 297 recruted Age = 57 – 66 years IPSS 16 – 18 Drop-out: 32 T = 11 SR = 10 T + SR = 11	Prospective pilot study. T = 0.4 mg/d SR (ethanolic extr.) = 320 mg/d T + SR = 0.4 mg + 320 mg Duration: 6 months	IPSS No significant difference between the groups. Significant improvement from baseline.

IPSS = International Prostate Symptom Score
SR = *Serenoa repens*
T = tamsulosin

Patients

Patients are representative for BPH patients. They were recruited on the basis of no need for surgery. Were excluded: patients with bladder cancer, bladder stones, previous pelvic radiotherapy, neurogenic bladder dysfunction, repeated infections of the urinary tract.

Intervention

An ethanolic extract was used, without further specification of the percentage of ethanol.

An intervention of 6 months was planned, but patients who did not respond sufficiently after 3 months were excluded for further participation. Responders were considered as having improved by > 25% on the IPSS.

Outcomes

All groups significantly improved from baseline which may be a real effect after 6 months. However participants were selected after 3 months by exclusion of non-responders. No side effects occurred in the *Serenoa repens* group. All therapeutic regimens were relatively well tolerated.

Assessor's comments

The authors conclude that no additional benefit was seen when *Serenoa repens* ethanolic extract was added to tamsulosin in patients with moderate BPH.
The results of this study may be influenced by the fact that the selection of patients occurred during the study, based on responders. No side effects occurred in the *Serenoa repens* group. Both therapeutic regimens were well tolerated.

Reference	Patients	Intervention	Outcome
Glemain *et al.*, 2002 (French)	N = 329 Mean age = 65 years (>50 y) IPSS ≥ 13 Drop out due to side effects: Tamsulosin= 5 Tamsulosin + SR = 7 Lost for follow up = 64	R / MC / DB T LA, 0.4 mg / day T 0.4 mg + SR (standardised hexane extract) 160 mg, 2 x / day Duration: 52 weeks	Primary: IPSS (since start) T = - 5.2 ± 6.4 T + SR = - 6.0 ± 6.4 P = 0.286 Secondary: Evacuation: P = 0.239 Irritation: P = 0.475 Responders (IPSS): P = 0.361 Peak flow: P = 0.564 QoL (Urolife): P = 0.442 QoL, (IPSS): P = 0.091

DB = double blind
IPSS = Internation Prostate Symptom Score
N = number of patients
MC = multicenter
NS = not significant
QoL = Quality of Life
R = randomised
SR = *Serenoa repens* extract
T = Tamsulosine

Patients

Inclusion criteria were related to urinary tract complaints: night- and daytime pollakisuria; intermittent micturition; poor flow (≤15 ml/s and ≥7 ml/s)); imperiosity.

Exclusion criteria: (1) previous surgery on the prostate, vesicle collar or pelvic area; (2) residual post urine volume of >300 ml; (3) prostate cancer; (4) urinary infection; (5) use of alpha- or beta-blockers, alpha-agonists, cholinergics or anticholinergics; (6) hepatic insufficiency; (7) cardiovascular or cerebrovascular event; (8) allergy to intervention drugs.

Treatments for BPH (such as alpha-blockers) stopped at least 15 days before randomisation; other treatments, such as plant extracts and finasteride, were stopped 1 month before randomisation.

Intervention

The study was well conducted. A power calculation was made: a superiority test was taken as the base for calculation of the number of patients: alpha was fixed on 5% and the power (1-β) on 80%. The theoretical number of patients to be included was 284. More patients were included.

Outcomes

The analysis of the results was done using the ITT (intent-to-treat) concept with 326 evaluable patients. In both groups (T and T + SR) the IPSS went down, with a relatively high spread on this primary outcome. Nevertheless about 2/3 of the patients were considered as good responders: 63.7% for tamsulosin and 68.6% for tamsulosin + *Serenoa repens*. Good responders had at least a decrease of 25% on the IPSS.

The medications were well tolerated. Lightheadness and hypotension were considered as the most serious side effects.

Assessor's comments

The authors conclude that no additional benefit was seen when *Serenoa repens* was added to tamsulosin in patients with moderate BPH. They do not recommend treating patients with such a combination.
Both therapeutic regimens were well tolerated.

Reference	Patients	Intervention	Outcome
Debruyne *et al.*, 2002	N = 704 BPH : IPSS > 10 Mean age = 65 years (between 50-85 years) Withdrawal: Tamsulosine = 54 SR = 56	R / MC / DB Tamsulosine LA (T), 0.4 mg / day SR (Standardised hexane extract) 320 mg, 1 x / day Duration: 12 months	Primary: IPSS (since start) T = SR = - 4.4 Secondary: Peak flow: increase T=SR Irritative symptoms: decrease T = SR Obstructive symptoms: Decrease T=SR

BPH = Benign Prostate Hyperplasia
DB = double blind
IPSS = Internation Prostate Symptom Score
N = number of patients
MC = multicenter
NS = not significant
R = randomised
SR = *Serenoa repens* extract

Patients

The study was conducted in 98 urology centers in Europe. The cut-off value of >10 ensures that all patients will have had symptoms. Mean values of both groups were at least comparable (IPSS = 15.2 and 15.5 for tamsulosin and *Serenoa repens* respectively). All other urinary parameters completely matched between both groups.

Exclusion criteria: (1) other bladder diseases affecting micturition; (2) urethral stenosis; (3) prostate cancer; (4) pelvic radiotherapy; (5) a history of repeated urinary tract infections or chronic prostatitis. Some other exclusion criteria were used that may not always be taken into consideration in daily practice: (7) significant cardiovascular diseases; (8) haematuria; (9) insulin-dependent diabetes mellitus; (10) liver diseases or abnormal liver tests; (11) other medication interfering with study medication.

In general the population may be considered as representative, at least with regard to the inclusion criteria.

Intervention

The study was well conducted. A power calculation was made taking into consideration an alpha = 2.5% (one-sided test), beta = 10% and a standard deviation of 5 for the IPSS. Criteria for non-inferiority were set: not to exceed the upper limit of the two-sided 95% confidence interval. The extract of *Serenoa repens* is commercially available in EU member states. The doses of both medications are convenient. The duration of the study is sufficient.

Outcomes

Analysis of the primary efficacy variable was carried out on the per protocol (PP) dataset, which included all patients with an available IPSS at endpoint (12 months). Secondary efficacy variables were analysed on both PP and intent-to-treat (ITT) efficacy datasets.

Most parameters significantly improved in both groups as compared to baseline values (see also figure 14).

The number and type of adverse events was comparable between both groups. There were significantly more retrograde ejaculation in the tamsulosin group (P <0.001).

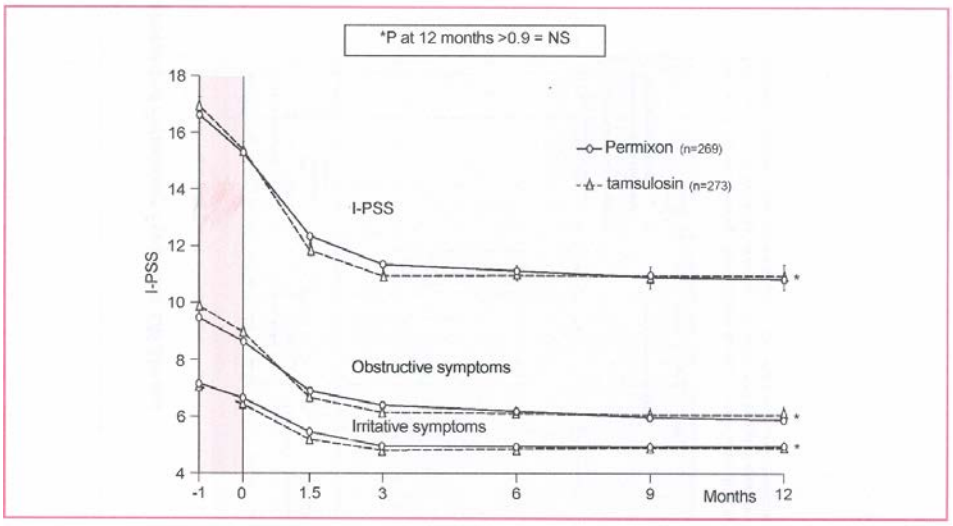

Fig. 2. Evolution of mean profiles of I-PSS over time (PP dataset).

Figure 14: Evolution of symptoms during the study (Debruyne *et al.*, 2002).

Assessor's comments

The authors conclude that their study demonstrated the clinical equivalence of *Serenoa repens* with tamsulosin in the treatment of lower urinary tract symptoms due to BPH. Both treatments provide similar improvements in symptoms and urinary flow rate, with a similar tolerability profile, except for a higher incidence of retrograde ejaculation reported in the tamsulosin group.
The study is well conducted in a large number of patients, for a sufficient duration.

Reference	Patients	Intervention	Outcome
Debruyne *et al.*, 2004	N = 124 (subset) BPH : IPSS > 19 Mean age = 65 years	R / MC / DB Tamsulosine LA (T), 0.4 mg / day SR (= hexane extract) 320 mg, 1 x / day Duration: 12 months	Primary: IPSS (since start) Decrease SR = 7.8 Decrease T = 5.8 Between groups: P = 0.051 Secondary: Irritative symptoms decrease: SR > T : P = 0.049 (after 3 months) SR > T : P = 0.03 (during 12 months)

BPH = Benign Prostate Hyperplasia
DB = double blind
IPSS = Internation Prostate Symptom Score
N = number of patients
MC = multicenter
NS = not significant
R = randomised
SR = *Serenoa repens* extract
T = tamsulosine

Assessor's comments

This study is a subset analysis of the PERMAL study by Debruyne *et al*. (2002). In this analysis *Serenoa repens* (hexane extract marketed in Europe) was shown to be slightly superior to tamsulosin in reducing the irritative symptoms of patients with a high initial IPSS. It should be noted care must be taken when extrapolating these results as the study was not designed for this kind of subset investigation.

Reference	Patients	Intervention	Outcome
Hizli & Uygur, 2007	N = 60; equally divided over 3 study groups BPH: IPSS ≥10 Mean age = 43 - 73 years No withdrawals	Open label * Tamsulosin LA (T), 0.4 mg / day (N = 20) * SR (extract not specified) 320 mg, 1 x / day (N=20) * T + SR (N=20) Duration: 6 months	Primary: IPSS (between) T = - 4.6 (SD 3.3) SR = - 6.1 (SD 2.7) T + SR = - 4.9 (2.3) P = 0.16 Secondary (between): Peak flow P = 0.38 Prostate volume P = 0.61 Residual volume P = 0.42 Quality of life P = 0.14

BPH = Benign Prostate Hyperplasia
DB = double blind
IPSS = Internation Prostate Symptom Score
N = number of patients
MC = multicenter
NS = not significant
R = randomised
SR = *Serenoa repens* extract
T = tamsulosin

Exclusion: serious urologic conditions.

Assessor's comments

This study was also conducted with a limited number of patients, without power calculation to justify the number of patients to be included. On the other hand, IPSS scores were well defined at the time of inclusion. An extensive list of usual exclusion criteria was used (among others serious health conditions and abnormal liver function tests).
The authors used a three-arm open label design, with one group on combined tamsulosin and Serenoa repens. The doses of both medications were those used in daily practice, however the Serenoa repens extract was not specified. The duration of the study is relevant for practice.
The authors found that treatment of BPH with both Serenoa repens and tamsulosin alone is equally effective, and combined therapy does not provide extra benefits (see also Glémain et al. 2002). Serenoa repens was shown to be a well-tolerated agent, with no adverse effects reported in this study.
The authors considered their investigation as a pilot study that should be followed by a larger clinical trial with a longer duration. The merit of the study is the comparison in the three groups. However no placebo group was included and no details were provided on the Serenoa repens extract used.

Reference	Patients	Intervention	Outcome
Grasso *et al*., 1995	N = 63 BPH Mean age = 62 years No withdrawals	DB – Comparative A = 2.5 mg 3 x /d (N = 32) SR (extract not specified) 160 mg, 2 x / day (N = 31) Duration: 3 weeks	Boyarsky's rating scale: A > SR for total and obstructive score (P=0.01) A = SR for irritative score Quality of micturition: A = SR (P=0.132) Urinary flow rates: A = SR (P=0.345)

A = alfuzosin
BPH = Benign Prostate Hyperplasia
DB = double blind
IPSS = International Prostate Symptom Score
N = number of patients
PL = placebo
R = randomised
SR = *Serenoa repens* extract

Assessor's comments

This was conducted with a limited number of patients. There was no power calculation to justify the number of patients included. No randomisation procedure was given. The dose of alfuzosine was lower than the standard dose of 10 mg per day and also the posology was different. The dose of *Serenoa repens* seems the usual dose, but no details are given about the composition of the extract. The study period (3 weeks) is too short to make therapeutic extrapolations.
The Boyarski rating scale is used. This scale scores 7 symptoms. Alfuzosin gave significantly better results than *Serenoa repens* on the totality of the scale. Urinary parameters improved more with alfuzosin than with *Serenoa repens* as compared to baseline, but there was no significant difference between the groups.

4.2.2.6. Open and uncontrolled studies with Serenoa repens preparation in monotherapy

4.2.2.6.1. Open and post marketing surveillance studies with supercritical CO_2 extracts before 2000

The ESCOP monograph reports on studies done before 2000 (ESCOP 2003). The original individual studies are not assessed in this AR. The ESCOP conclusions can be approximately summarised as follows:

Patients

Most of the patients were included on separate urological parameters. Only one study used IPSS. More than 4300 patients were included.

Interventions

The dose of extract was 320 mg per day. The duration varied from 12 weeks to 6 months.

Outcomes

Improvement of subjective parameters was reported, more particularly: (1) nocturnal and daytime urinary frequency and (2) dysuria.

Objective parameters were improved as well: (1) urinary flow rate; (2) residual urinary volume.

No serious adverse effects were reported.

Separate study by Braeckman et al. (1997b)

In one study patients (N = 132) followed two dosage regimens: 320 mg once daily and 160 mg twice daily. The duration of the trial was one year. Both regimens improved the efficacy parameters: IPSS (in 60% of patients), quality of life (85% of patients were satisfied), prostatic volume (- 12% at the end of the study), peak urinary flow rate (16%). No differences were seen between the dosage regimens.

4.2.2.6.2. Open studies with hexane extracts before 2000

The ESCOP monograph (ESCOP 2003) includes 11 studies conducted in patients with BPH (total number of patients and duration not mentioned). None of these studies are published in English (French, German and Italian). These studies showed improvements in symptoms such as nocturnal and daytime urinary frequency and dysuria as well as in objective measurements such as urinary flow rate and residual urine volume. Original individual studies are not assessed within this AR.

A 24-week German study evaluated different dosages: 24 patients were treated with 320 mg and 25 patients with 960 mg daily. Both dosages demonstrated the same efficacy with respect to urinary frequency, dysuria, peak urinary flow rate and voiding volume. Two patients in the lower and 5 patients in the higher dosage group complained about adverse effects, mostly gastro-intestinal (Dathe & Schmid, 1991).

4.2.2.6.3. Open studies conducted with hexane extracts after 2000

Reference	Patients & intervention	Results as compared to baseline
Giulianelli *et al*., 2012	591 patients (35-65 years) 320 mg 1x daily hexane extract Duration: 6 months	Q_{max}: 10.7 (T0) to 13.7 (T1) (P <0.0001) IPSS: T0 > T1 (P <0.0001) NIH-CPSI: T0 > T1 (P >0.0001) IIEF-5: T0 < T1 (P <0.0055)
Pytel *et al*., 2002 **Pytel *et al*., 2004**	155 patients (mean age 65) of whom 130 evaluated IPSS > 6 160 mg 2x daily hexane extract Duration: 2 years	IPSS reduction (no level of significance) QOL improved (no level of significance given- Q_{max} increased 'noticeable' Sexual function improved markedly during the 2nd year (P = 0.001)
Aliaev *et al*., 2002	26 patients followed from 1995 to 2002 320 twice a day	IPSS reduction (no level of significance) Q_{max} increased Quality of life not worse.

IIEF-5 = International Index of Erectile Function - 5
IPSS = Internation Prostate Symptom Score
NIH-CPSI = Chronic Prostatitis Symptom Index
QOL = Quality of Living
Q_{max} = uroflow ml/sec

In the study by Giulianelli et al. (2012) patients with chronic BPH with associated inflammation were included. All urologic parameters significantly improved after 6 months. The authors used an extract registered in several countries of the EU. PSA was also significantly lowered (P < 0.0001), although the initial values were already low (1.9 lowered to 1.4). The study was done in an open design, but all three evaluation questionnaires gave positive results. There was no reporting on side effects (Gulianelli 2012).

Pytel et al. (2002 and 2004) enrolled patients with documented BPH and lower urinary tracts symptoms (LUTS). IPSS, quality of life (QOL), index of sexual function (MSF-4), size of the prostate, urodynamic and biological parameters were estimated after 6 (V6), 12 (V12), 18 (V18) and 24 months (V24). Apart from the parameters tabled, plasma hormones (testosterone, DHT, estradiol, LH, androstendion) did not change. Nine patients developed 10 side effects but they were unrelated to the treatment

4.2.2.6.4. Open studies with ethanolic extracts

A study is reported by Breza *et al*. (2005) with 634 patients (40 to 92 y) suffering from symptomatic BPH with final evaluation in 596 patients after one year. Over this periode the IPSS improved, as well as the quality of life and the urinary flow, without influencing the PSA.

4.2.3. Clinical studies in special populations (e.g. elderly and children)

None reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

A relatively large number of clinical studies have been conducted on *Serenoa repens* preparations. However, there is considerable variation as far as patients (e.g. IPSS from 6 tot 32 at inclusion), intervention (e.g. different preparations in different doses) and outcomes (e.g. IPSS or separate symptoms) are concerned and it is not appropriate to draw general conclusions on the therapeutic efficacy of *Serenoa repens* preparations as is done in the most recent Cochrane Collaboration Study (Tacklind *et al*., 2012). The merits of the Cochrane review are that the studies have been collected and analysed. However, the conclusions are considered as too general stating that: "*… Serenoa repens, at double and triple doses, did not improve urinary flow measures on prostate size in men with lower urinary tract symptoms consistent with BPH."*

Taking account of these issues the Cochrane meta-analysis cannot be used as the basis for the HMPC monograph. The overall conclusions on clinical pharmacology and efficacy have to be based on analysis of the individual studies, taking into consideration the preparation tested, patients, intervention and outcomes.

Patients

As far as the patients are concerned, in most studies they can be considered as representative of daily practice. However, it should be noted that in many cases extensive exclusion criteria are applied, making the patient population somewhat less representative of the one typical patient population. It should also be noted that in some cases a large variation in grade of BPH symptoms may be allowed e.g. by including patients with an IPSS starting from a level of >6. In controlled (placebo) or comparative studies the number of patients varies, and studies in small patient groups were generally not justified by a power calculation.

Intervention

Double-blind, randomised, placebo controlled trials are considered as the gold standard for evidence based practice evaluation. In this assessment report several types of studies are evaluated. Older studies are usually not double-blind, randomised, placebo controlled trials with extracts marketed in EU member states and do not use IPSS or AUASI as the starting point and primary outcome: e.g. studies with the standardised hexane extract and the standardised supercritical CO_2 extract. An evolution in the published studies can be seen: the more recent well-conducted studies with the marketed products are comparative studies, wherein the *Serenoa repens* preparations are compared to other medication, in particular 5-α-reductase inhibitors (e.g. finasteride) and α-blocking agents (e.g. alfozosin and tamsulosin).

IPSS and AUASI should not be considered as the only scoring systems to evaluate the effectiveness of the preparations used. Before the validation of IPSS, separate symptoms were used as valid outcomes, close to daily practice.

Outcomes

Descotes *et al*. (1995) conducted a 4 week study with the standardised hexane extract with positive outcomes. The short duration may have been compensated by the fact that they only included patients who were not responding to placebo. The positive outcomes of the study by Cukier *et al*. (1985) and Champault *et al*. (1984), can be questioned whether therapeutically relevant because the studies results were evaluated after very short periods. Studies by Emili (1983) and Reece-Smith (1986) were conducted with a limited number of patients and also for short periods, with no significant differences between the hexane extract and placebo. Boyle *et al*. (2004) made a meta-analysis of studies performed with the same commercially available hexane extract. Some of the studies were not

published, which adds to the strength of the meta-analysis. As only seven studies used the IPSS as outcome (cf. date of publication), this parameter could only be evaluated for these trials. Nearly all studies reported on peak urinary flow and nocturia. *Serenoa repens* modestly, but significantly improved both. However, because we excluded the Cochrane meta-analysis, the meta-analysis by Boyle *et al*. (2004) is not used to prove well established use.

In some cases a second selection of patients occurred during the study, excluding patients who did not respond sufficiently after 3 months. This selection can hamper the conclusions related to therapeutic outcomes.

More recent comparative studies however were done with a sufficient number of patients, and over longer periods. Carraro *et al*. (1996) found an equivalent outcome on the IPSS for the hexane extract and finasteride after 26 weeks. Glémain *et al*. (2002) compared the hexane extract with therapeutic doses of tamsulosin. Equivalent therapeutic outcomes were obtained after 52 weeks. Debruyne *et al*. (2002) found similar outcomes for the hexane extract and tamsulosin after 52 weeks. This last study can be taken as the best example available of a study done with sufficient patients over a period long enough to conclude on well established use.

Taking account of the available studies, the information is considered sufficient to support the use of the hexane extract as a well-established medicinal product with recognised efficacy and acceptable safety.

Only one well conducted controlled clinical trial with the supercritical CO_2 extract has been published (Braeckman *et al*. 1997a). The IPSS was not available at the time of the study, however, a total score of symptoms, as well as individual symptoms were evaluated. There were no comparative studies available.

Taking account of the limited studies, the information is not considered sufficient to support the use of the supercritical CO_2 extract as a well-established medicinal product with recognised efficacy and acceptable safety.

The available data do not support the ethanolic extracts as well-established medicinal products.

Other double blind, randomised, placebo controlled studies have been carried out with extracts that were not sufficiently documented and registered in EU member states. Despite the fact that the studies were generally well conducted, the results cannot be used to elaborate the monograph.

Open studies with large numbers of patients add to the experience with hexane and supercritical CO_2 extracts. In all these studies *Serenoa repens* was shown to have some degree of therapeutic activity. If needed causal relationship can be evaluated, using the same techniques as for pharmacovigilance, but in opposite direction, i.e. in relation with positive outcomes. As these studies were conducted over longer periods, they add to the clinical safety evaluation.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

A single-centre double-blind study has been performed with 225 men with moderate-to-severe symptoms of BPH. Patients were randomised to a dose of 160 mg (2 x daily) *Serenoa repens* fructus extract containing 92.1% total fatty acids (extraction solvent not specified) and to placebo, during one year. Participants underwent two eligibility screening visits, a 1-month single-blind run-in period, and were seen for follow-up visits at 1, 3, 6, 9 and 12 months after randomisation.

There were no significant differences observed between the *Serenoa repens* and placebo allocated patients in the risk of suffering at least one serious adverse event (5.4% vs. 9.7% respectively; P = 0.31). There was also no statistical difference with regard to non-serious symptomatic adverse events (34.8% vs. 30.1% respectively; P = 0.48). Overall, the data from this trial provide reassurance about the lack of serious clinical adverse effects with *Serenoa repens* extract when used over a period of one year (Avins *et al*., 2008).

Bressler (2005) confirms the fact that no serious adverse effects have been reported with *Serenoa repens*, apart from one case of cholestatic hepatitis (see Section 5.3.1.). The herbal medicine can cause headaches and diarrhoea, if taken in large amounts. No changes in blood chemistry have been noted.

5.2. Patient exposure

The *Serenoa repens* extract used in the CAMUS (Complementary and Alternative Medicine for Urological Symptoms) trial showed no evidence of toxicity at doses up to 3 times the usual clinical dose over an 18-month period (Avins *et al*., 2013).

A total of 369 patients were randomised in the CAMUS trial; 357 were included in a modified intent to treat analysis. Participants were randomised to 320, 640 and 960 mg daily of an ethanolic *Serenoa repens* extract or to an identical-appearing placebo in an escalating manner at 6-month intervals for a total of 18 months of follow-up. Adverse event assessments, vital signs, and blood and urine laboratory tests were obtained at regular intervals.

There were no statistically significant differences between the groups in the rates of serious or non-serious adverse events, changes in vital signs, digital prostate examination findings or study withdrawal rates. Overall, there were no significant intergroup differences in laboratory test abnormalities, while differences in individual laboratory tests were rare and small in magnitude. No evidence of significant dose-response phenomena was identified (Avins *et al*., 2013).

5.3. Adverse events and serious adverse events and deaths

5.3.1. Hepatic function and gastro-intestinal system

Case of a 58y old patient with liver damage

A case of acute liver damage was reported in a 58 year-old man. He was admitted in the hospital ward with severe pain in the right hypochondrium and asthenia. There was no abuse of alcohol. The patient took a commercially available preparation of *Serenoa repens* to ease the symptoms of BPH at the dose 3 capsules a day as suggested by the manufacturer. This dose was equivalent to 660 mg of fructus powder. No other medication or food supplements were taken. Blood tests showed hypertransalinasemia and high cholestasis indexes. An abdominal ultrasound scan revealed mild liver enlargement suggesting patchy steatosis. Ten days after discontinuation of *Serenoa repens* all symptoms disappeared; no rechallenge was made.

The case was methodologically well developed as possible causal relationship was concerned: (1) co-medication was excluded; (2) liver enzymes were quantified; (3) virus markers were detected: only CMV IgG was positive but no antigen could be identified in blood samples; (4) the follow-up of the patient included a check after 1 year; (5) the fatty acids in the capsules taken were quantified with and a chromatogram published; (6) heavy metals were excluded and (7) reference on other case reports was made (Lapi *et al*., 2010).

Case of a 65y old patient with pancreatitis

A 65-year old patient was admitted to hospital with epigastric pain for two days and with two episodes of vomiting. The patient had a history of diabetes, hypertension, hyperlipidemia, gout, Barrett oesophagitis and chronic gastritis. He occasionally drunk one can of beer, but his last one was taken one week before admission. He denied smoking. He was treated with acetylsalicylic acid, pantoprazole, ramipril, simvastatine-ezetimibe and glyburide-metformin.

One week prior to his admission he started a herbal medicine containing *Serenoa repens* capsules with 160 mg soft extract 2 x daily for symptoms of BPH. Circulating pancreatic lipase and amylase were 3 to 15 times elevated upon admission. Triglycerides and liver function tests were normal.

The patient was treated with tamsulosin for BPH during his hospital stay. After 3 days the circulating pancreatic enzymes normalised.

Cholelithiasis, duct obstruction, infection and trauma were excluded. However, alcohol levels were not taken, and alcohol cannot be completely ruled out as a possible cause of pancreatitis.

The authors associated the use of *Serenoa repens* with the symptoms of pancreatitis. However, the possible mechanism of action is unexplained. Triglycerides are not enhanced. The extract of *Serenoa repens* inhibits the cyclo-oxygenase and 5-lipoxygenase, behaving like an anti-inflammatory agent. This mechanism of action should lead to an amelioration of the symptoms.

Although no clear causal relationship could be established, the authors warn against using OTC herbal medications. No further follow-up was done (Wargo *et al*., 2010).

Case of a 61y old patient with pancreatitis

A 61-year-old Caucasian man with a history of benign prostatic hyperplasia and gastroesophageal reflux disease developed epigastric pain associated with nausea 36 hours prior to presentation.

He denied drinking alcohol prior to the development of his symptoms. His home medications included *Serenoa repens*, which he had been taking for the last three years, lansoprazole and multivitamins. The type of *Serenoa repens* preparation was not specified. Laboratory results revealed elevated lipase and amylase levels. An abdominal ultrasound demonstrated a non-dilated common bile duct, without choledocholithiasis. Computed tomography of his abdomen showed the pancreatic tail with peripancreatic inflammatory changes, consistent with acute pancreatitis. All medication the patient took before admission was stopped. The patient's condition improved with intravenous fluids and pain management. On the fourth day of hospitalisation his pancreatic enzymes were within normal limits: he was discharged home and advised to avoid taking *Serenoa repens*. All other medication was resumed. No follow-up was reported.

A causal relationship with *Serenoa repens* was proposed, although the patient was already using this medication (Bruminhent *et al*., 2011).

Case of a 55y old patient with acute hepatitis and pancreatitis

A 55-year-old white male with a remote history of alcoholism, sober for more than 15 years and no history of cholelithiasis, presented with severe nonradiating epigastric pain associated with nausea and vomiting. Patient's current medical problems dated back 14 months when he visited the emergency room with these symptoms but was only treated as an outpatient and told he had pancreatitis. Four months previously, he was admitted for similar complaints and was found to have acute hepatitis and pancreatitis, but detailed workup failed to reveal any etiology. Current symptoms started on the day of presentation with progressively worsening, nonradiating sharp epigastric pain accompanied by 3 episodes of profuse nonprojectile, nonbilious vomiting.

He denied weight loss, fever or chills, jaundice, melena, pruritus, change of urine or stool color and gave no history of recent endoscopic evaluation. The patient's other significant comorbidity is benign prostatic hypertrophy, and in the last 4 years has treated urinary obstruction with *Serenoa repens* or intermittent catheterisation. No information was given about the *Serenoa repens* preparation.

He was found to be acutely ill-looking, slightly icteric with normal vital signs. His abdomen was soft with right hypochondrial and epigastric tenderness without guarding or rebound. Liver was not palpable and Courvoisier, Cullen and Gray Turner signs were negative. Rectal examination did not reveal abnormal findings. No follow-up was organised.

A causal relationship was suggested, although the patient already took the medication for four years (Jibrin *et al*., 2006).

Assessor's comments

The individual case reports are of moderate quality. The patients are described, as well as their circumstances of living. However, the preparations used are not very well characterised and this makes it difficult to check possible phytochemical and therapeutic equivalence with products on the European market. At least in one case the temporality can be questioned as discussed by Shakir & Layton (2002): too much time elapsed between the initiation of therapy and the hepatic symptoms. According to the principles elaborated by the same authors, there is no experimental evidence for hepatotoxicity by *Serenoa repens* preparations.
Therefore hepatotoxicity has not been raised in the monograph.

5.3.2. Overview of the Vigilyze database

Results of the overview of side effects collected in the WHO Vigilyse database were reviewed. The data cannot be directly translated to the monograph, but can help to compare specific reporting with well-defined extracts in well-defined therapeutic conditions. Individual reports about impaired liver function are supported by the number of liver and biliary system disorders. However, according to Teschke *et al*. (2013) on a recent published article discussing the causality assessment of herbal hepatotoxicity, the causality confirmation was surprisingly rare for individual cases of suspected herbal hepatotoxicity, which often were published as narrative and anecdotal reports without valid and transparent data collection that require stringent efforts for causality attribution.

Because gastro-intestinal side effects and an increase of hepatic enzymes are the most frequently mentioned, these undesirable effects were included in the monograph (see also 5.3.3.)

5.3.3. Side effects mentioned with the authorised products in EU countries

Gastro-intestinal system

Pyrosis and gastric pain when taken on an empty stomach.

Rarely: nausea, eructation diarrhoea and pyrosis (some SmPC's of hexane extracts mention a frequency between 0.1 and 1% others between 0.01 and 0.1%). This frequency is included in the monograph

Hormonal side effects

Reversible gynecomastia cases have been observed rarely. For hexane extracts a frequency of (≥ 1/1000 to < 1/100) frequency uncommon, is included in the monograph.

Allergy

Allergic reactions have occurred: frequency not known.

Skin rash have been reported very rarely.

Hypersensitivity reactions very rare (‹0.01%).

Cardiovascular effects

Uncommon: rise in blood pressure.

Ocular effects

Some of the SmPCs of marketed products mention intra-operative floppy iris syndrome during cataract extraction. The frequency is unknown. However, because of lack of causal relationship, this undesirable effect is not included in the monograph (Chang *et al*., 2008; Flach *et al*., 2009; Yeu & Grostern, 2007).

Headache

Due to regular reporting of headache, the product information of hexanic extract of *Serenoa repens*, more particularly section 4.8 of the SmPC, was recently updated and approved (with Headache as undesirable effect) in all Member States where the medicinal product is authorised/registered. Therefore headache was included as undesirable effect for hexane extracts in the monograph: headache (≥ 1/100 to < 1/10) : Frequency common (Avins *et al*., 2013; Agbabiaka *et al*., 2009).

5.3.4. Cases of overdosing

A total of 11 spontaneous case reports of overdose with the hexane extract were received in male patients aged from 61 to 91 years old, of 2 or 3 times the recommended dosage with a maximum overdose at 960 mg per day. Three cases were serious, two patients with underlying cardiovascular diseases and one intentional overdose of multiple drugs (oxazepam, gabapentine, doxazosine) associated with coma, of which the patient fully recovered. In four other serious cases, unspecified gastrointestinal disorders were associated (Communicated by Interested party: see Overview of Comments).

Reports with other *Serenoa repens* extracts and ADRs after high doses of *Serenoa repens* intake were identified (Lapi *et al*., 2010; Villanueva and González, 2009; Weinrobe and Montgomery, 2001).

These cases concerned patients who took *Serenoa repens* as herbal supplements without supervision and at a dose higher than that recommended. Moreover, the hexane extract was not the same as the hexane extract described in the monograph. In one publication, it was associated with many other herbal extracts.

As a consequence these reports do not contribute to part 4.9. of the monograph and no instructions related to overdose can be given in the monograph.

5.4. Laboratory findings

See 5.3.

5.5. Safety in special populations and situations

5.5.1. Case study in paediatrics

Telogen effluvium is a form of alopecia characterised by abnormality of hair cycling, resulting in excessive loss of telogen hair. A case of a girl with telogen effluvium has been reported where she presented with hot flushes that appeared after treatment for 2 months. with a food supplement containing *Serenoa repens*. The patient, an 11 year old white girl of 37 kg was treated for 2 months with 1 tablet a day of a preparation containing 30% *Serenoa repens* (containing 95% phytosterols) 120 mg fatty acids (nature not revealed) 50 mg sulfonyl methane, green tea, zinc, biotin, copper and tocotrienols (quantities not given).

During the 2nd month of treatment the girl experienced hot flushes several times a day for many days. When the product was discontinued the hot flushes no longer occurred. The girl experienced menarche 45 days after stopping the treatment and her menstruation showed abnormal duration and volume of blood loss. Polymenorrhea was present for one year after the menarche.

A correlation between the onset of hot flushes and the use of *Serenoa repens* was investigated by using the Naranjo probability scale. A score of 6 was obtained, indicating the relationship of causality as probable (Miroddi *et al*., 2012)

5.5.2. Medicines interactions

Healthy volunteers (6 men and 6 women) were included in a kinetic study. The objective was to evaluate possible influence on CYP2D6 or CYP3A4. Probe substrates were dextromethorphan (CYP2D6) and alprazolam (CYP3A4), administered before and after ingestion of 320 mg *Serenoa repens* (commercial preparation containing 197.7 mg non-esterified fatty acids and 3.55 mg phytosterols per soft capsule; extraction solvent not specified) during 14 days.

There was no influence on the ratio between dextromethorphan and its metabolites before and after administration of *Serenoa repens*. There was also no significant difference for the AUC and the elimination half-life of alprazolam. These results indicate that extracts of *Serenoa repens* at generally recommended doses are unlikely to alter the disposition of co-administered medications primarily dependent on the CYP2D6 and CYP3A4 pathways for elimination.

This study must be considered as a preliminary investigation of possible interaction potential of *Serenoa repens* only in view of the lack of information on the product evaluated (Markowitz *et al*., 2003).

A *Serenoa repens* fructus extract, containing 85 to 95% fatty acids and sterols (lipidosterolic hexane extract), was found to inhibit the cytochrome P450 isoenzymes CYP2D6, CYP2C9 and CYP3A4 *in vitro*. (Williamson *et al*., 2013). However, clinical observations suggest that these *in vitro* effects may not be clinically relevant.

On the other hand, Mooiman *et al*. (2014) did not find an interaction of a lipidosterolic hexane extract with 7-benzyloxy-4-trifluoromethyl-coumarin, midazolam and docetaxel on CYP3A4 *in vitro*.

Anticoagulants

The INR of one patient taking warfarin modestly increased after he took a combination herbal medicinal product (*Serenoa repens*, pumpkin and vitamin E; nature of the *Serenoa repens* extract not stated). The age of the patient was 61 years. He had a stable INR of around 2.4. The INR increased to 3.4 within 6 days after initiating and normalised within a week after stopping the product (Yue & Jansson, 2001).

This product has also been associated with an increased INR in another 73-year old patient not taking anticoagulants. The patient had an increased INR of 2.1 (normal values between 0.9-1.2), which lowered after the patient was given vitamin K, but only normalised 1 week after product intake was stopped (Yue & Jansson, 2001).

Excessive bleeding during surgery of a 53-year old patient has been reported. The patient underwent surgery for removal of a brain tumour. The patient took *Serenoa repens* (nature of the extract not stated) for BPH. He lost an estimated 2 litres of blood and bleeding did not return to normal until 5 days after the intervention (Cheema *et al*., 2001).

Serenoa repens may inhibit CYP2C9 *in vitro*, but the clinical relevance of this inhibition is not known. The presence of vitamin E in the product may be responsible for an additional anticoagulant effect.

Some product information (Summary of Product Characteristics) warns of an enhanced risk of bleeding when taken together with other medicinal products (such as Phenprocoumon, Warfarin, Clopidogrel, Acetylsalicylic acid, NSAR).

According to other SmPCs a few cases of suspected interactions with warfarin have been reported and increased INR-values have been described; the mechanism for these possible interactions is not clear.

Benzodiazepines

No pharmacokinetic interaction appears to occur between *Serenoa repens* and alprazolam or midazolam in clinical conditions.

In a clinical study with 12 healthy volunteers 320 mg *Serenoa repens* lipidosterolic extract (standardised but not specified) for 16 days did not affect the pharmacokinetics of a single dose of 2 mg alprazolam given on day 14 (Markovitz *et al*., 2003).

In another study with 12 healthy subjects, 160 mg *Serenoa repens* lipidosterolic extract (85 to 95% fatty acids and sterols) twice daily for 28 days did not affect the metabolism of a single dose of 8 mg midazolam, a probe drug for CYP3A4 (Gurley *et al*., 2004).

Caffeine

Serenoa repens does not appear to affect pharmacokinetics of caffeine.

In a clinical study with 12 healthy subjects 160 mg *Serenoa repens* lipidosterolic (85 to 95% fatty acids and sterols) extract given twice daily for 28 days did not alter the pharmacokinetics of a single dose of 100 mg caffeine given at the end of treatment. Caffeine is metabolised by CYP1A2. An interaction between CYP1A2 metabolised medicines and *Serenoa repens* is unlikely (Gurley *et al*., 2004).

Chlorzoxazone

Serenoa repens does not appear to affect the pharmacokinetics of chlorzoxazone.

In a clinical study with 12 healthy subjects 160 mg *Serenoa repens* lipidosterolic extract (85 to 95% fatty acids and sterols) given twice daily for 28 days did not alter the pharmacokinetics of a single dose of 250 mg chlorzoxazone. Chlorzoxazone is metabolised by CYP2E1. An interaction between CYP2E1 metabolised medicines and *Serenoa repens* is unlikely (Gurley *et al*., 2004).

Dextromethorphan

Serenoa repens does not appear to affect the pharmacokinetics of dextromethorphan.

In a clinical study with 12 healthy subjects 320 mg *Serenoa repens* lipidosterolic extract (standardised, not specified) daily for 16 days did not alter the metabolism of a single 30 mg dose of

dextromethorphan. Dextromethorphan is a substrate for CYP2D6. An interaction between CYP2D6 metabolised medicines and *Serenoa repens* is unlikely (Markovitz *et al*., 2003).

Conclusion

There may be an increased response to anticoagulant treatment in patients who take *Serenoa repens* preparations. *Serenoa repens* does not appear to have a clinically relevant effect on the majority of cytochrome P450 isoenzymes and no other interactions with *Serenoa repens* have been found. Evidence seems to be limited to case reports. It is recommended that patients on anticoagulants discuss the use of any herbal product they wish to try with their healthcare practitioner; increased monitoring may be necessary.

Reported drug-drug interactions with *Serenoa repens* are mostly of poor quality, as the nature of the extract is not always stated in publications and the preparations used are mostly combined products. Furthermore, reporting is partially extracted from Periodic Safety Update Reporting (PSUR), which is not in the public domain.

5.6. Overall conclusions on clinical safety

In general *Serenoa repens* preparations are well tolerated. A possible causal relationship with liver damage and pancreatitis has been reported occasionally. The Serenoa preparations involved were not specified or are not included in the monograph. Clinical trials are generally not relevant as an indicator of hepatic safety because patients with liver diseases are often excluded.

Most minor side effects are related to the gastro-intestinal system, especially when taken on an empty stomach. There is plausibility for gynecomastia. Cases of allergy have been reported. Increases in blood pressure and ocular effects have been reported according in some SmPCs of marketed products. These minor effects are reported as side effects and kept in drug information databases. Mostly no scientific evidence is given.
Side effects are more methodologically reported in the SmPC of hexane extracts on the market as compared to ethanolic extracts. This is the reason why undesirable effects are slightly differently reported in the well-established and traditional side of the monograph (parts 4.8).

A few cases of suspected interactions wit warfarin have been reported. Increased INR values have been described. As a matter of precaution, a warning is included in the monograph.

There is no therapeutic use in children, adolescents and women.

6. Overall conclusions

Quality

There are no significant concerns with the identity and quality of *Serenoa repens* preparations. The fruit of the plant is the subject of a monograph in the Ph Eur: *Serenoae repentis fructus*. However hexane extracts are considered as phytochemically different from ethanolic extracts as composition in free and esterified fatty acids is concerned. To demonstrate this difference separation of free and esterified fatty acids is necessary before gas chromatographic analysis.

Safety

In general *Serenoa repens* preparations are well tolerated. Liver damage and pancreatitis have been reported occasionally with other preparations than those included in the monograph. There is no

evidence to indicate that *Serenoa repens* is harmful in the specified conditions of use. There is no therapeutic use in children, adolescents and women.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (LD_{50} values).

Efficacy

Several experimental findings support the use of *Serenoa repens* in BPH. From *in vitro* experiments the following properties were identified: (1) inhibition of 5-alpha-reductase; (2) influence on androgen-receptor binding; (3) inhibition of alpha-receptor binding; (4) inhibition of eicosanoid synthesis; (5) spasmolytic effects and (6) anti-inflammatory effects. The activity can differ from one extract to another, probably dependent upon the content of fatty acids. Anti-androgenic and anti-inflammatory effects were confirmed in *in vivo* experiments. These findings have a qualitative or semi-quantitative character, due to the sometimes high concentrations and high doses needed. Therefore the mechanisms of action are not further documented under part 5.1. of the monograph.

Toxicity of the hexane extract appears low. There are no data on genotoxicity, carcinogenicity or fertility.

Clinical studies are reported using a range of herbal preparations prepared with different extraction solvents.

Studies are reported with specified extracts including hexane, ethanolic and supercritical CO_2 extracts available commercially on markets in EU Member States. Other studies are reported with unspecified extracts or those not available within the EU.

Most placebo controlled randomised clinical trials with the commercialised hexane extract date back for more than 15 years. These studies suffer of one or more weaknesses as the number of patients, the duration of treatment and the outcomes are concerned. Trials comparing the efficacy of the commercialised hexane extract with finasteride or tamsulosin are more convincing. In the pivotal study by Debruyne *et al*. (2002), the hexane extract taken for 12 months had an efficacy comparable to tamsulosin, which is considered as being the standard therapeutic agent. The study was done with 320 mg once daily although a dose of 160 mg twice daily could also accepted based on authorised products.

Taking account of the available clinical evidence, the information is considered sufficient to support the use of the hexane extract as a well-established medicinal product with recognised efficacy and acceptable safety.

Only one well conducted controlled clinical trial with the supercritical CO_2 extract has been published. The IPSS was not available, but a total score of symptoms, as well as individual symptoms were evaluated. There were no comparative studies available. Taking account of the limited studies, the information is not considered sufficient to support the use of the supercritical CO_2 extract as a well-established medicinal product with recognised efficacy and acceptable safety.

Open studies with thousands of patients add to the experience with hexane and supercritical CO_2 extracts. As these studies were conducted over longer periods, and no serious adverse events occurred, they add to a positive clinical safety evaluation.

Double blind, randomised, placebo controlled studies were done with extracts that were not sufficiently documented and apparently not registered in EU member states. Despite the fact that the studies were generally well conducted, the results cannot be used to elaborate the monograph.

Although ethanolic extracts are widely used in EU member states, the clinical data available are limited. The available data do not support the ethanolic extracts as well-established medicinal products. However, the traditional uses of the ethanolic extracts are accepted within the Member States and they are well documented in literature including standard herbal reference books.The use of the ethanolic extracts is considered plausible on the basis of clinical studies with related extracts and the long-standing use and experience. The benefit-risk balance of commercialised ethanolic extracts is positive and a traditional use can be granted.

Benefit - risk

Herbal preparations of *Serenoa repens* are widely used for treatment of lower urinary tract symptoms related to BPH. One hexane extract and several ethanolic extracts have been marketed for at least 30 years in the EU. Although BPH symptoms may vary and there is tendency to see converging of these symptoms in verum as well as in placebo groups, positive therapeutic outcomes have been reported for hexane extracts of *Serenoa repens* in several clinical studies with placebo. Furthermore the therapeutic outcomes with hexane extracts of *Serenoa repens* were comparable with tamsulosin and finasteride. Both substances tamsulosin and finasteride are considered as having a proven benefit for patients with BPH. Positive outcomes on BPH symptoms could be seen after 4 weeks to 12 months.

Despite the frequent use throughout the EU, relatively few undesirable effects were reported. Liver damage and pancreatitis have been reported very rarely in relation to the use of *Serenoa repens*. Other undesirable effects are not specific.

A few cases of suspected interactions with warfarin have been reported and increased INR values have been described.

In general, the herbal preparations of *Serenoa repens* have a positive benefit – risk ratio.

Conclusive remarks on therapeutic use

Only the hexane extract of the fruit of *Serenoa repens* is considered to be supported by sufficient evidence to grant a well-established use as a medicinal product with recognised efficacy and acceptable safety.

Although there is one study with a supercritical CO_2 extract resulting in a positive outcome, the evidence is not considered sufficient for well established use, as the study only lasted 12 weeks. The requirement for 30 years of experience on the market is not fulfilled for the supercritical CO_2 extract. Therefore traditional use can only be accepted for the ethanolic extracts. The therapeutic indication for the ethanolic extracts taken to the monograph is the same as the one accepted for other traditional herbal medicinal products used in case of benign prostate hyperplasia.

Community list entry

The minimum required data on mutagenicity (Ames test) are not available for the herbal preparations covered by the traditional use section of the monograph, therefore inclusion in the European Union list of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products is not recommended.

Therapeutic area for browse search on EMA website: Urinary tract and genital disorders

ATC-code (well-established use): G04CX02

Annex

List of references