# Fructus Serenoae Repentis

## Definition

Fructus Serenoae Repentis consists of the dried ripe fruits of *Serenoa repens* (Bartr.) Small. (Arecaceae) (*1–3*).

## Synonyms

*Brahea serrulata* (Michx.) H. Wendl., *Chamaerops serrulata* Michx., *Corypha repens* Bartr., *Sabal serrulata* (Michx.) Nichols, *Sabal serrulata* (Michx.) Nuttall. ex Schult., *Serenoa serrulata* Hook., *Serenoa serrulata* Roem. et Schult., *Serenoa serrulatum* (Michx.) Benth et Hook, *Serenoa serrulatum* Schult. (*1, 3–5*).

## Selected vernacular names

American dwarf palm tree, dwarf palm tree, dwarf palmetto, fan palm, sabal, sabal fructus, Sägepalmenfrüchte, saw palmetto, saw palmetto berries, serenoa (*1, 2, 5, 6*).

## Geographical distribution

Indigenous to the south-east of the United States of America, from South Carolina to Florida (*2, 6*).

## Description

Low scrubby palm growing in sandy soil, with characteristic creeping rhizome, one end of which rises a short distance above ground, surrounded by a dense crown of leaves with saw-like margins. Petioles slender and spinose on edges; blade fan-shaped, with palmate divisions that are slightly cleft at the summit. Inflorescence densely tomentose and shorter than the leaves. Fruit a 1-seeded drupe (*6*).

## Plant material of interest: dried ripe fruits

### *General appearance*

Drupe superior, ellipsoidal, ovoid or somewhat globular, 1.5–3.0 cm long, 1.0–1.5 cm in diameter; dark brown to black with a smooth, dull surface, somewhat oily, with a few large, angular depressions and ridges due to contraction of the

inner layer on drying; summit marked by remains of style; base marked by stem-scars or has remains of stem. Epicarp and sarcocarp together form a thin coriaceous shell enclosing a hard but thin endocarp; endocarp externally reddish-brown and somewhat fibrous, as is inner layer of the sarcocarp; inner layer of endocarp smooth, enclosing an ellipsoidal or ovoid, hard somewhat flattened, anatropous, reddish-brown seed marked on the raphe side by an arillus-like appendage and marked on the opposite side near the end by the micropyle, which forms a slight projection; has a large endosperm of thick-walled parenchyma and a very small embryo at the micropyle (*2*, *3*, *6*).

### *Organoleptic properties*

Odour: pronounced, aromatic, fruity; taste: sweetish, aromatic, slightly acrid (*6*).

### *Microscopic characteristics*

Sarcocarp covered by a small-celled, thin-walled epidermis. Outermost layers of pulp wall contain yellowish-brown or brownish-red substances; inner layers have scattered single cells containing brown substances; occasional large, thick-walled, punctate stone cells with wide lumens. Innermost layer of sarcocarp wall consists almost completely of thick-walled, punctate, irregularly shaped stone cells. Outer layer of the seed coat consists of thick-walled large cells; cells in middle layer smaller and thin-walled; cells of innermost layer small and flattened; contents of all seed-coat cells non-punctate brown. Outer endosperm cells radially elongated, coarse-walled and inner cells larger, thick-walled and coarsely punctate. Vascular bundles accompanied by fibres with stigmata which have siliceous solids attached (*3*, *6*).

### *Powdered plant material*

Yellowish-brown. Fragments of sarcocarp, the cells of which contain yellowish-brown or brownish-red amorphous substances; whitish fragments of endosperm, the cell walls considerably thickened and with large pores; occasional stone cells, nearly colourless, more or less tabular or irregular in shape, up to 140 µm in length, with walls about 15 µm thick, showing numerous simple or branching pores (*2*, *6*).

## General identity tests

Macroscopic and microscopic examinations (*2*, *3*, *6*), and thin-layer chromatography (*7*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*8*).

### *Foreign organic matter*

Not more than 2% (*2*, *3*).

### *Total ash*

Not more than 5% (*3*).

### *Acid-insoluble ash*

Not more than 1% (*2*, *3*).

### *Water-soluble extractive*

Not less than 8% (*2*, *3*).

### *Loss on drying*

Not more than 12% (*3*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*9*). For other pesticides, see the *European pharmacopoeia* (*9*), and the WHO guidelines on quality control methods for medicinal plants (*8*) and pesticide residues (*10*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*8*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*8*) for the analysis of radioactive isotopes.

### *Other purity tests*

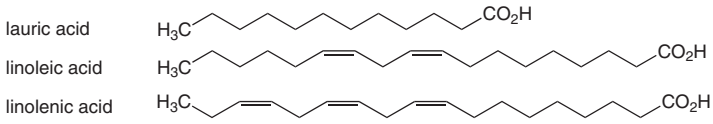
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays

Quantitation of fatty acids, both free and as their corresponding ethyl esters, by gas chromatography. The total fatty acid content is not less than 9.0%, and the amounts of individual fatty acids are not less than 3.0% oleic, 2.0% lauric, 1.2% myristic, 1.1% palmitic, 0.4% linoleic, 0.2% caphoic, 0.2% caprylic, 0.2% capric, 0.1% palmitoleic, 0.1% stearic and 0.1% linolenic acids (*3*).

## Major chemical constituents

The major constituents are free fatty acids and their corresponding ethyl esters; sterols and lipids. The primary fatty acid constituents include oleic, lauric, myristic, palmitic, linoleic, caphoic, caprylic, capric, palmitoleic, stearic and linolenic acids (*5*, *11*, *12*). The major sterols include β-sitosterol, stigmasterol and daucosterol (*13*). The lipids consist of triglycerides of fatty acids. The structures of some of the free fatty acids are presented below.




## Medicinal uses

### *Uses supported by clinical data*

Treatment of lower urinary tract symptoms (nocturia, polyuria, urinary retention) secondary to BPH stages I and II, as defined by Alken (*1*, *4*, *14*–*33*), in cases where diagnosis of prostate cancer is negative.

### *Uses described in pharmacopoeias and in traditional systems of medicine*

As a diuretic and to treat an enlarged prostate (*2*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

As an aphrodisiac, a sedative and a nutritional tonic, as well as for the treatment of bronchitis, cystitis, dysmenorrhoea, sore throat and the common cold (*5*).

## Pharmacology

### *Experimental pharmacology*

#### Antispasmodic activity

Both lipid and saponifiable fractions of Fructus Serenoae Repentis reduced norepinephrine-induced contractions in vitro of rat aorta ($IC_{50}$ 0.53 and 0.50 mg/ml, respectively), as well as potassium chloride-induced contractions of rat uterus ($EC_{50}$ 0.35 and 0.43 mg/ml, respectively) (*34*). A 90% ethanol extract of the fruit reduced vanadate-induced contractions of the rat uterus ($EC_{50}$ 11.41 µg/ml). Norepinephrine-induced contractions of rat deferential duct, and potassium chloride-induced contractions of guinea-pig ileum and bladder smooth muscle tissue were reduced by the addition of a 90% ethanol extract of the fruit (0.33 and 0.15 mg/ml, respectively) (*35*).

### Anti-inflammatory activity

Intragastric administration of an ethanol extract of the fruit to rats (5.0 g/kg body weight) inhibited carrageenan-induced footpad oedema (*36*). External application of a 90% ethanol extract of the fruit (500 µg) to mice inhibited croton oil-induced ear oedema by 42% (*37*).

Intragastric administration of an *n*-hexane extract of the fruit to rats (10 ml/kg body weight) decreased capillary permeability induced by histamine, compound 48/80 and dextran, and generalized oedema induced by dextran (*38*). A carbon dioxide (supercritical) extract of the fruit inhibited cyclooxygenase and 5-lipoxygenase in vitro ($IC_{50}$ 28.1 and 18.0 µg/ml, respectively) (*39*). A lipidosterolic extract of the fruit inhibited the in vitro production of leukotriene $B_4$ in human polymorphonuclear neutrophils stimulated with the calcium ionophore A23187 (*40*). An ethanol extract of the fruit also suppressed A23187-stimulated synthesis of leukotriene $B_4$ ($IC_{50}$ 8.3 µg/ml) and thromboxane $B_2$ ($IC_{50}$ 15.4 µg/ml) in rat peritoneal leukocytes in vitro (*37*).

### Immunostimulatory activity

Intraperitoneal administration of a polysaccharide fraction, isolated from an aqueous extract of the fruit, to mice (10 mg/kg body weight) had immunostimulant activity, as measured by the colloidal carbon clearance test (*41*). An increased rate of phagocytosis by human polymorphonuclear leukocytes was observed in cells treated with a polysaccharide fraction of the extract (10 µg/ml) (*41*).

### Anti-gonadotropic effects

*n*-Hexane extracts of the fruit had anti-androgenic and anti-estrogenic activity in vitro (*42–47*). Dihydrotestosterone and testosterone uptake by cytosolic androgen receptors of human foreskin and other tissues was inhibited by 40.9% and 41.9%, respectively, after treatment of the tissues with the extract (*42*). In another study, the binding of [$^3$H]dihydrotestosterone to both cytosolic and nuclear androgen receptors in cultured human foreskin fibroblasts was inhibited by 90% and 70%, respectively, after treatment of the cells with a sterol fraction of the *n*-hexane extract ($IC_{50}$ 7.1 units/ml) (*43*). An *n*-hexane fruit extract inhibited androgen binding to cytosolic androgen receptors of rat prostatic tissue in a specific and competitive manner ($IC_{50}$ 330.0–367.5 µg/ml) (*44, 45*). However, in contrast to these findings, the same extract did not inhibit the binding of [$^3$H]dihydrotestosterone to androgen receptors in cultured human foreskin fibroblasts (*46*). Oral administration of an *n*-hexane extract (160 mg/day) inhibited the binding of $^3$H-labelled 17β-estradiol to the nuclear estrogen receptors in samples of prostatic tissue from patients with BPH. Binding to the cytosolic and nuclear estrogen and androgen receptors was measured by saturation analysis and an enzyme-linked immunosorbent assay (*47*).

The effect of an *n*-hexane extract of the fruit was evaluated in two human prostatic cell lines, LNCaP and PC3, which are respectively responsive and unre-

sponsive to androgen stimulation. The extract (100 µg/ml) induced proliferation and differentiation in LNCaP cells, but not in PC3 cells, suggesting that the androgen receptor plays a role in mediating the effects of the fruit in LNCaP cells (*48*). In PC3 cells cotransfected with genes for wild-type androgen receptor and a chloramphenicol acetyltransferase reporter under the control of an androgen-responsive element, the extract (25 µg/ml) inhibited androgen-induced chloramphenicol acetyltransferase transcription by 70% (*48*).

*n*-Hexane, 90% ethanol and supercritical carbon dioxide extracts of the fruit inhibited 5α-reductase activity in vitro (*37*, *43*, *46*, *49–53*). A lipidosterolic extract of the fruit (100 µg/ml) inhibited 5α-reductase activity in the rat ventral prostate by 50%, and reduced conversion of testosterone into dihydrotestosterone in human foreskin fibroblasts by 90%. The conversion of dihydrotestosterone to 5α-androstane-3α-17β-diol by 3α-ketosteroid oxidoreductase was also partially inhibited in cultured human foreskin fibroblasts (*43*). An *n*-hexane extract of the fruit inhibited the activity of both 5α-reductase and 17β-hydroxysteroid dehydrogenase in cultures of epithelial cells ($IC_{50}$ 60 and 40 µg/ml, respectively) and fibroblast cells ($IC_{50}$ 30 and 200 µg/ml, respectively) obtained from the prostates of patients with BPH (*50*). One study reported no effect of several lipidosterolic extracts of the fruit on the activity of 5α-reductase from human prostate or on dihydrotestosterone binding to the rat prostatic androgen receptors at concentrations up to 100 µg/ml (*51*). The reasons for these conflicting results are unclear, and may be due to the different methodologies used. Recently, it has been demonstrated that human 5α-reductase has two isoforms, type 1 and type 2; finasteride, a testosterone 5α-reductase inhibitor has been shown to be a selective inhibitor of the type 2 isoform (inhibitory concentration [$K_i$] 7.3 nmol/l). Furthermore, an *n*-hexane extract of the fruit was a non-competitive inhibitor of the type 1 isoform ($IC_{50}$ 7.2 µg/ml) and an uncompetitive inhibitor of type 2 ($IC_{50}$ 4.9 µg/ml) (*52*). A 90% ethanol extract of the fruit showed a dose-dependent inhibition of 5α-reductase activity in the epithelium (29% inhibition) and stroma (45% inhibition) of prostate tissue from patients with BPH (*52*). When the extract was fractionated into saponifiable, non-saponifiable and hydrophilic subfractions, only the saponifiable subfraction (consisting mainly of lauric, oleic, myristic and palmitic acids) was active. Of these fatty acids, lauric acid was the most active: it inhibited epithelial and stromal 5α-reductase activity by 51% and 42%, respectively. The inhibition by lauric acid was noncompetitive and dose-dependent up to a concentration of 0.2 mmol/l. The nonsaponifiable fraction, consisting mainly of phytosterols, was weakly active, while the hydrophilic subfractions, containing carbohydrates, amino acids and polysaccharides, were inactive (*53*). A supercritical extract of the fruit inhibited 5α-reductase activity in homogenates of cultured human foreskin fibroblasts ($IC_{50}$ 0.025 mg/ml) (*46*).

One study compared testosterone metabolism in primary cultures of epithelial cells and fibroblasts obtained from the prostates of patients with BPH and prostate cancer. In all cultures, androst-4-ene-3,12-dione, formed by the oxidation of testosterone by 17β-hydroxysteroid dehydrogenase, accounted for 80%

of all metabolites recovered. An *n*-hexane extract of the fruit inhibited the formation of androst-4-ene-3,12-dione in both cell types, indicating that it inhibited the activity of 17β-hydroxysteroid dehydrogenase, unlike finasteride, which was inactive (*50*).

An increase in the activity of 3α-hydroxysteroid-oxidoreductase (the enzyme that metabolizes dihydrotestosterone into the inactive androstenediol form) in prostate tissue from patients with BPH was reported following treatment of patients with an *n*-hexane extract of the fruit (320 mg daily for 3 months). Analysis of enzyme kinetics showed that the $V_{max}$ of 3-hydroxysteroid-oxidoreductase was significantly enhanced in the prostate stroma of treated patients. Since 3-hydroxysteroid-oxidoreductase also has a strong substrate affinity for prostaglandins, increased activity of the enzyme may also increase the metabolism of prostaglandins, thereby accounting for the reduction of prostaglandin-mediated congestion or intraprostatic oedema formation (*54*).

Intragastric administration of an *n*-hexane extract of the fruit to castrated rats for 60–90 days inhibited the increase in total weight of the prostate induced by estradiol and testosterone (*55*). Intragastric administration of a 90% ethanol extract to castrated rats (6 ml/kg body weight, weekly for 8 weeks) inhibited the increase in weight of the ventral prostate, seminal vesicles and coagulation glands induced by testosterone (*37*). Intragastric administration of a 90% ethanol extract of the fruit inhibited prostate growth stimulated by both estradiol and dihydrotestosterone in nude mice into which prostate tissue from humans with BPH had been transplanted (*56*). An *n*-hexane extract of the fruit (30 μg/ml) inhibited the proliferation of human prostate cells induced by basic fibroblast growth factor. Lupenone, hexacosanol and an unsaponified fraction of the extract markedly inhibited the proliferation of human prostate cells induced by basic fibroblast growth factor, but had only a minimal effect on basal cell proliferation (*57*).

### Effects on signal transduction

Addition of an *n*-hexane extract of the fruit (1–10 μg/ml) to Chinese hamster ovary cells completely inhibited the effects of prolactin on potassium conductance, protein kinase C activity and intracellular concentrations of calcium. These results suggest that the extract may inhibit prolactin-induced prostatic growth by interfering with the transduction signals involving the prolactin receptor (*58*). Lipidosterolic extracts of the fruit noncompetitively inhibited radioligand binding to human prostatic $\alpha_1$-adrenoceptors and agonist-induced [$^3$H]inositol phosphate formation (*59*).

## *Clinical pharmacology*

### Placebo-controlled clinical trials

Eleven double-blind, placebo-controlled studies have assessed the effects of lipidosterolic extracts of Fructus Serenoae Repentis in the symptomatic treatment of mild to moderate BPH (*26–33*, *60–62*). The number of patients in each study

ranged from 22 to 205, and the dosage of the extract was generally 160 mg twice daily for 1–3 months. All but one study (*61*) reported that the extract was significantly more effective than placebo in reducing the symptoms of mild to moderate BPH. In this study of 70 patients, which was also randomized, although a significant improvement in flow rate was seen in patients treated with either a hexane extract of the fruit (320 mg) or placebo daily for 3 months, no significant difference between the treatment groups was observed (*61*). However, most studies demonstrated an increase in urinary flow rate and a decrease in postvoid residual urine volume (*26*). In another study which was also randomized, 205 patients were treated with 320 mg extract or placebo daily for 3 months. The study concluded that the extract was superior to placebo in reducing the total symptom score (polyuria, nocturia, dysuria, and urgency and hesitancy of micturition), improving the quality of life score, and increasing urinary volume (*62*).

A study was performed on 176 patients with BPH who had been unresponsive to placebo treatment in previous clinical studies. After 30 days of treatment with an extract of the fruit (160 mg, twice daily), there was a significant reduction in dysuria, polyuria and nocturia in the treated group as compared with the placebo group. Patients treated with the extract had a significantly greater increase in mean peak urinary flow rate (28.9%), as compared with those that received the placebo (8.5%), and the overall efficacy of the extract was rated higher than that of the placebo by both patients and physicians (*33*).

Another double-blind, placebo-controlled study assessed the effect of a lipidosterolic extract in the reduction of prostate oedema and congestion in 18 patients with BPH. Histopathological analysis of enucleated prostate tissue from patients treated preoperatively with the extract (320 mg daily for 12 weeks) showed a significant decrease in prostate stromal oedema and congestion in treated patients, as compared with those in the placebo group ($P \leqslant 0.05$) (*63*).

## Controlled clinical trials

In a controlled clinical trial, 25 men with symptoms of urinary obstruction were randomized into two groups: 15 patients received no treatment, while 10 were treated with an *n*-hexane extract of Fructus Serenoae Repentis (320 mg extract daily). After 3 months, prostatic specimens were removed by suprapubic prostatectomy and were sectioned into three regions (i.e. periurethral, subcapsular and intermediate). In each region, the concentration of testosterone, dihydrotestosterone and epidermal growth factor was measured by radioimmunoassay. In the patients treated with the extract, a significant reduction ($P < 0.001$) in the concentration of dihydrotestosterone (50%) and epidermal growth factor (50%), and a significant increase ($P < 0.001$) in testosterone levels (125%), were observed in the periurethral region (*64*).

### *Clinical trials without controls*

Numerous clinical studies without controls of men with BPH have reported improvements in both objective and subjective variables after treatment with lipidosterolic extracts of the fruit (*15–28*). The largest trial of 1334 patients treated with 320 mg of a lipidosterolic fruit extract daily for 6 months showed an improvement in postvoid residual urine volume (50% decrease), nocturia (54% decrease) and polyuria (37% decrease) (*16*). The results of a prospective multicentre study in which 435 patients with BPH were treated with a lipidosterolic extract of the fruit (320 mg daily for 3 years) showed a steady improvement in micturition. The improvement was due to a marked decrease in symptoms and postvoid residual urine volume (50% decrease), and an increase in peak urinary flow rate (about 25%) (*17*). Another multicentre study analysed the effect of a lipidosterolic extract of the fruit (160 mg twice daily for 3 months) in 305 patients with mild to moderate BPH. After treatment, increases in maximal and mean urinary flow rates (of 25% and 27%, respectively) and a 35% improvement in the mean International Prostate Symptom Score were seen (*18*). Other studies have also reported improvements in symptoms and objective measurements of disease severity after 1–6 months of treatment with a lipidosterolic extract of the fruit (320 mg daily) (*19–28*). Generally, studies involving periodic evaluation over the course of treatment have demonstrated that improvements in both objective and subjective variables were progressive over time (*17*, *24–27*).

### Comparative trials

An *n*-hexane extract of Fructus Serenoae Repentis, finasteride and $\alpha_1$-receptor antagonists have been shown to be clinically effective in the treatment of BPH in comparative trials (*16*, *65–69*). One large international randomized, double-blind clinical trial compared the efficacy of the extract (320 mg daily) with that of finasteride (5 mg daily) in the treatment of 1098 patients with mild to moderate BPH. After 6 months of therapy, the International Prostate Symptom Score decreased from baseline by 37% in patients treated with the extract as compared with a decrease of 39% in patients who received finasteride. No significant difference was observed between the treatment groups in improvement of patient-rated quality of life scores and the primary end-point of objective symptom score. Both treatments resulted in improved peak urinary flow rates and a reduction in the size of the prostate. Peak urinary flow rate increased from 10.6 ml/s to 13.3 ml/s in patients treated with the extract, and from 10.8 ml/s to 14.0 ml/s in those who received finasteride. The size of the prostate was reduced by 6% in patients treated with the extract, and by 18% in those treated with finasteride. Serum prostate-specific antigen levels were reduced by 41% following finasteride treatment, but remained unchanged in patients treated with the extract (*16*).

Other smaller, shorter, randomized double-blind trials involving groups of 41–63 patients compared the efficacy of the fruit extract (320 mg daily) with the $\alpha_1$-receptor antagonists alfuzosin and prazosin (*68*, *69*). In a 3-week comparative trial with alfuzosin, the total mean symptom score using Boyarsky's rating scale improved by 27% and 39% in patients treated with the extract and alfuzosin, respectively. Although improvements in the peak urinary flow rates were greater in the alfuzosin-treated group, there was no significant difference between the treatments (*68*). In a 12-week randomized trial comparing the efficacy of a fruit extract (in 20 patients) and prazocin (in 21 patients), improvements in polyuria, mean urinary flow rate and postvoid residual urine volume were similar in both groups, but no statistical analysis of the data was provided by the investigators (*67*). Further large, well-designed, randomized trials of long duration are necessary to compare adequately the clinical efficacy of Fructus Serenoae Repentis and $\alpha_1$-receptor antagonists.

Four reviews of the randomized controlled clinical trials have indicated that lipidosterolic extracts of the fruit improve the symptoms of urinary tract disorders and urinary flow rates in men with mild to moderate BPH (*14*, *68*–*70*).

### Pharmacokinetics

The pharmacokinetics of Fructus Serenoae Repentis were investigated in a bioequivalence study that compared a new capsule formulation (320 mg/capsule) to a reference preparation (160 mg/capsule). Concentrations of the components of the extract were measured in plasma samples from 12 healthy fasting males (mean age 24 years) after oral administration of 320 mg extract (either one capsule of 320 mg or two capsules of 160 mg) (*71*). However, the methodology used in this study was questionable.

Tissue distribution was measured in rats after intragastric administration of a lipidosterolic extract supplemented with radiolabelled oleic acid, lauric acid or β-sitosterol. This investigation demonstrated that the uptake of the extract was much higher in the prostate than either the liver or genitourinary tissues (*72*).

### Toxicity

Clinical studies have shown that extracts of Fructus Serenoae Repentis are very well tolerated in humans (*16*, *69*). Minor gastrointestinal side-effects have been reported in most of the clinical trials, but results from standard blood chemistry tests were normal (*69*).

## Contraindications

Owing to its effects on androgen and estrogen metabolism, the use of Fructus Serenoae Repentis during pregnancy or lactation and in children under the age of 12 years is contraindicated.

## Warnings

Fructus Serenoae Repentis relieves the symptoms associated with BPH, but does not have an effect on the size of the prostate. If symptoms worsen or do not improve, or in cases of blood in the urine or acute urinary retention, contact a physician (*1*).

## Precautions

### *Pregnancy: teratogenic effects*

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during pregnancy.

### *Pregnancy: non-teratogenic effects*

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during pregnancy.

### *Nursing mothers*

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during lactation.

### *Paediatric use*

See Contraindications.

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

## Adverse reactions

Both short- and long-term clinical studies have found that extracts of Fructus Serenoae Repentis are very well tolerated. Occasional nausea, diarrhoea and other minor gastrointestinal complaints have been reported (*18*).

## Dosage forms

Crude drug, lipidosterolic extracts (*n*-hexane, 90% ethanol or fluid [carbon dioxide] supercritical extracts standardized to contain 70–95% free fatty acids and corresponding ethyl esters), and preparations thereof. Store in a tightly closed container in a cool, dry place.

## Posology

(Unless otherwise indicated)
Daily dosage: 1–2 g crude drug or 320 mg (as a single dose or 160 mg twice daily) of a lipidosterolic extract (*n*-hexane, 90% ethanol or supercritical

fluid [carbon dioxide] extract standardized to contain between 70 and 95% free fatty acids and corresponding ethyl esters) or equivalent preparations (*16–33, 60–62*).

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