12 July 2016
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Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph *Prunus africana* (Hook f.) Kalkm., cortex (EMA/HMPC/680626/2013)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Prunus africana* (Hook f.) Kalkm., cortex as released for public consultation on 15 December 2015 until 15 March 2016.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	***Prunus africana* (=*Pygeum africanum*) (soft extract; DER 114-222:1) should be listed under "well-established use" instead of the existing THMP listing due to the fact that the 2 conditions for well-established use (proven clinical efficacy and 10 years on the market) are met** **10-year EU market presence** *P. africana* (Soft extract; DER 114-222:1) has been on the market for more than 10 years (e.g. product "Tadenan", authorised in France since 1969) within the EU, thus qualifying for the criteria of Article 10a of the Community Code. It should be emphasised that in France, *P. africana* extract (PAE) has become the primary course of treatment for enlarged prostate for the French Authorities HAS transparency commission 2011 Journal/http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-05/tadenan_-_ct-10090.pdf as well as another phytotherapy agent (Serenoa repens) 2015 Journal/ http://www.has-sante.fr/portail/upload/docs/evamed/CT-13775_PERMIXON_PIS_RI_Avis1_CT13775.pdf or alpha1-blockers 2015, Journal/ http://www.has-sante.fr/portail/upload/docs/evamed/CT-14410_UROREC_PIS_RI_Avis2_CT14410.pdf and the French association of urologists (AFU) (Descazeaud 2015, Journal/Prog Urol, 25: 404—412). **Proven clinical efficacy of P. africana extract for the treatment of BPH in**	**Not endorsed as** A total of 18 randomised controlled trials involving 1562 men met inclusion criteria were analysed and taken into consideration. Only one of these studies reported a method of treatment allocation concealment, though 17 were double blinded. Among them there were no studies comparing pygeum africanum bark to standard pharmacologic interventions such as alpha-adrenergic blockers or 5-alpha reductase inhibitors. The mean study duration was short of mainly 64 days (range, 30 to 122 days). Many studies did not report results in a method that permitted meta-analysis. Compared to men receiving placebo, pygeum africanum bark provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures as assessed by an effect size defined by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome (-0.8 SD [95% confidence interval (CI), -1.4 to -0.3 (n = 6 studies)]). Fourteen trials were excluded because they did not

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	randomised, controlled clinical studies See specific comments within section “4.1 Therapeutic indications”.	include a control group. The final conclusions showed that preparation of pygeum africanum bark may be a useful treatment option for men with lower urinary symptoms consistent with benign prostatic hyperplasia. However, the reviewed studies were small in size, were of short duration, used varied preparations and rarely reported outcomes using standardised validated measures of efficacy. Additional placebo-controlled trials are needed as well as studies that compare pygeum africanum bark to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. So it is an agreement to endorse only TU for pygeum africanum bark herbal preparation in the EU Monograph

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition	AESGP	**Well-established use** We propose moving the following herbal preparation under 'well-established use' instead of 'Traditional use': *Prunus africana* (=*Pygeum africanum*) soft extract (DER 114-222:1), extraction solvent chloroform (stabilised by 1.2% of ethanol>99.9%).	Not endorsed. Please see above.
3 Pharmaceutical form	AESGP	**Well established use** We propose moving *P. africana* the soft extract (DER 114-222:1) under 'well-established use' instead of 'Traditional use': Herbal preparations in solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	Not endorsed. Please see above.
4.1 Therapeutic indications	AESGP	**Well established use** We propose the following well-established use therapeutic indication for the soft extract (DER 114-222:1) "Herbal medicinal product for the symptomatic treatment of benign prostatic hyperplasia (e.g. increased frequency of urination, nocturia, incomplete miction, weak urine stream)." *Reasons* The efficacy and safety of *P. africana* has been shown in several double-blind randomised controlled clinical trials (RCTs) Also, the proposed indication has been confirmed in, meta-analyses and consensus reviews:	Not endorsed. Please see above.

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		Clinical evidence A 1995 review (Andro 1995, Journal/Curr Therapeutic Res, 56: 796-817) summarises (in their Table IV) 12 double-blind, placebo-controlled studies on *P. africana*. These studies use objective measurements (maximum flow, voided volume, residual volume, nocturia, daytime frequency) to determine the efficacy of *P. africana* exract in alleviating BPH symptoms. Within the 12 reviewed studies, 358 evaluated patients received the indicated *P. africana* extract whereas 359 received placebo. All 12 studies demonstrate efficacy of the extract compared to placebo - the review concludes that "P. africanum bark extract is an effective and exceptionally well-tolerated treatment for mild and moderate symptomatic BPH". Although the placebo effect regarding miction problems can be quite large for men suffering from BPH (Dufour 1984, Journal/Ann Urol, 18: 193195), a significant difference of objective measures within 2 months between extract and placebo group in a double-blind setting should be taken as proof for efficacy: In medical practice it is common to judge effectiveness of a BPH medication within 6 weeks of treatment initiation (Gravas 2015, Journal/European Association of Urology (EAU), 1-70; Tadenan SPC 2016). The Cochrane metaanalysis (Wilt 2011; edited, no change to conclusions, Journal/Cochrane Database Syst Rev, CD001044) recently summarized RCTs with *P. africana* extract which used clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements, which are relevant markers still valid today. A total of 18 RCTs (17 double blind) involving 1562 men met the Cochrane inclusion criteria. The mean study duration was 64 days	

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		(range 30 - 122 days). Compared to men receiving placebo, *P. P. africana* provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures as assessed by an effect size defined by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome (-0.8 SD [95% confidence interval (CI), -1.4 to -0.3 (n = 6 studies)]). Men using *P. africana* were more than twice as likely to report an improvement in overall symptoms (RR=2.1, 95% CI = 1.4 to 3.1). Nocturia was reduced by 19%, residual urine volume by 24% and peak urine flow was increased by 23%. Adverse effects due to *P. africana* were mild and comparable to placebo. The overall dropout rate was similar between *P. africana* (13%), placebo (11%) and other controls (8%). The author conclusion was: "A standardised preparation of *P. africana* may be a useful treatment option for men with lower urinary symptoms consistent with benign prostatic hyperplasia". The argument that long-term data is lacking for *P. africana* is not valid The review (Andro 1995, Journal/Curr Therapeutic Res, 56: 796-817) also includes results from an open-label study with a several-year follow-up, confirming lasting clinical and urodynamic improvements - see also (Moya-Prats 1989, Journal/Urodiruimica Aplicada, 1: 150-155). **Recommendation to physicians and patients** The guidance to physicians regarding LUTS associated with BPH, written in cooperation with the French society of Urology (AFU) (Descazeaud 2015, Journal/Prog Urol, 25: 404—412) indicates BPH	

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		treatment options within its table 5 on page 409. These include alpha blockers and 5-alpha-reductase inhibitors or alternatively phytotherapy with plant extracts: specifically 50 mg/day *P. africana* extract or 160 mg/day *S. repens* extract. The transparency commission of the French Health Agency which evaluates human medicines, reviewed all clinical BPH data and concluded that *P. africana* (TADENAN) and *S. repens* (PERMIXON) are first line treatments for the management of BPH. “When a drug therapy is necessary “alpha blockers, inhibitors of 5-alpha reductase or plant extracts can be used. There is no satisfactory methodology test to establish the superiority of one of the three therapeutic classes”. For *P. africana*: (HAS transparency commission 2011, Journal/http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-05/tadenan_-_ct-10090.pdf). For *S. Repens* (HAS transparency commission 2015, Journal/ http://www.has-sante.fr/portail/upload/docs/evamed/CT-13775_PERMIXON_PIS_RI_Avis1_CT13775.pdf). For alpha1 blockers eg. Silodozine (HAS transparency commission 2015, Journal/ http://www.has-sante.fr/portail/upload/docs/evamed/CT-14409_SILODYX_PIS_RI_Avis2_CT14409.pdf The WHO monograph on *P. africana* states the following uses “supported by clinical data”: “Treatment of lower urinary tract symptoms of benign prostatic hyperplasia (BPH) stages I and II, as defined by Alken (e.g. nocturia, polyuria and urinary retention), in cases where diagnosis of prostate cancer is negative” (WHO 2004, Journal/http://apps.who.int/medicinedocs/en/d/Js4927e/24.html#Js4927e.24).	

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		In addition, the classification of *Prunus Africana* as well-established use should be consistent with the decision taken for the EU monograph on *Serenoa repens*, given that the indication, target population, and clinical safety and efficacy are the same.	
4.2 Posology & method of administration	AESGP	**Well established use** Posology *Adults and elderly* Single dose: 50 mg; Daily dose: 100 mg, administered as 50 mg twice a day (morning and evening). There is no relevant use in women, adolescents and children. Duration of use: Long-term use is possible (see section 4.4 'Special warnings and precautions for use'). Method of administration: Oral use	Not endorsed. Please see above.
4.3 Contra indications	AESGP	**Well established use** Hypersensitivity to the active substance or any of the contained excipients	WEU not endorsed. Please see above.
4.4 Special warnings	AESGP	**Well established use** *Warning and precautions* The action of the extract of *Prunus africana* on BPH does not exempt from the usual medical surveillance. The drug cannot replace surgery If complaints worsen or if symptoms such as fever, spasms or blood in the urine, painful urination or urinary retention occur during the use of the medicinal product, a doctor should be consulted immediately.	WEU not endorsed. Please see above.

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4.5 Interactions with other medicinal products	AESGP	**Well established use** None reported	WEU not endorsed. Please see above.
4.6 Fertility	AESGP	**Well established use** No effects of male fertility (Andro 1995, Journal/Curr Therapeutic Res, 56: 796-817; WHO 2004, Journal/http://apps.who.int/medicinedocs/en/d/Js4927e/24.html#Js4927e.24). Not relevant in use during pregnancy and lactation.	Not endorsed as there is no reference to the international standards for such an assay.
4.7 Effect on ability to drive	AESGP	**Well established use** No studies on the effect on the ability to drive and use machines have been performed. No effects have been reported.	WEU not endorsed. Please see above.
4.8 Undesirable effects	AESGP	**Well established use** Rarely: digestive disorders (nausea, constipation or diarrhoea) If other adverse reactions occur, a doctor or a qualified health care practitioner should be consulted.	WEU not endorsed. Please see above.
4.9 Overdoses	AESGP	**Well established use** No case of overdosage has been reported.	WEU not endorsed. Please see above.
5.1 Pharmaco-dynamics	AESGP	**Well established use** *P. africana* extract targets both growth factor-mediated prostate	Not endorsed.

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properties		growth as well as of bladder function on a molecular level (Edgar 2007, Journal/Neurourol Urodyn, 26: 458-463; discussion 464). The central mode of action on the prostate is the inhibition of the androgen receptor (Roell 2011, Journal/Mol Cell Endocrinol, 332: 1-8). Specifically, N-butylbenzene-sulfonamide (NBBS) isolated from *P. africana* was found to have androgen antagonistic activity by inhibiting the translocation of the human androgen receptor to the cell nucleus (Papaioannou 2010, Journal/Invest New Drugs, 28: 729-743). The extract suppressed the effects of dihydrotestosterone on micturition, and co-treatment with extract regressed a developing increase in prostatic weight in rats (Yoshimura 2003, Journal/Urology, 61: 474-478). In humans, the 15-20 days of extract caused a marked reduction of prostate enlargement (Mathe 1995, Journal/Biomed Pharmacother, 49: 341-343). The extract has antiproliferative, tissue-protective effects, as judged from the following publications: *P. africana* extract (25 µg/ml) was shown to inhibit proliferation of human cultured prostatic fibroblasts and myofibroblasts stimulated or not by growth factors (Boulbes 2006, Journal/BJU Int, 98: 1106-1113). In addition, the oral intake of *P. africana* could result in sufficient serum level of actives substances to induce inhibition of cultured myofirbroblasts prostatic cells proliferation, with consistant chages in related transcriptomic profile (Larre 2012, Journal/Asian J Androl, 14: 499-504). Also murine 3T3 fibroblasts, induced by basic Fibroblast Growth Factor (bFGF), were inhibited by the extract (Paubert-Braquet 1994,	

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		Journal/Biomed & Pharmacother, 48: 43s-47s). Similarly the growth factors EGF, bFGF, and IGF-I but not KGF were shown to be inhibited by *P. africana* extract in their mitogenic action on prostatic fibroblasts in culture (Yablonsky 1997, Journal/J Urol, 157: 2381-2387). Another publication describes antiproliferative and apoptotic effects of *P. africana* extract on cultured prostate stromal cells from patients with benign prostatic hyperplasia (Quiles 2010, Journal/Prostate, 70:1044-1053). Of note these data were convincing enough to get a revision of the pharmacological properties the approved Summary Product Characteristics (SPC) of TADENAN in France, with the following sentences granted by the French MA commission in January 12th, 2010: Chapter 5. Pharmacological properties, part 5.1 pharmacodynamic properties: “Moreover, Prunus Africana extract has shown antiproliferative effect on fibroblasts and myofibroblasts from cell culture of human prostate”. The indicated extract also had a protective effect against ischemic damage to the bladder (Chen 1999, Journal/Mol Urol, 3: 5-10; Levin 2005, Journal/Phytomedicine, 12: 17-24). In the diabetic rat bladder, early treatment with *P. africana* could effectively suppress oxidative stress (Wang 2010, Journal/Int Urol Nephrol, 42: 401-408), also bladders of diabetic rats had reduced levels of hydroxyproline, TGF beta1, and bFGF following extract administration (Yongzhi 2008, Journal/Neurourol Urodyn, 27: 254-259). Treatment of rabbits with partial outlet obstruction with *P. africana*	

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		extract resulted in a dose dependent improvement in bladder ultrastructure in parallel with improved bladder compliance and contractile responses of isolated strips to stimulation (Levin 1996, Journal/J Urol, 156: 2084-2088; Levin 2002, Journal/J Urol, 167: 2253-2259). Furthermore, *P. africana* extract has anti-inflammatory properties following oral administration in a rat paw oedema model (Marcoli 1986, Journal/Farmaci & terapia, 3: 135-137). An extensive review of the pharmacodynamics literature can be found in the *P. africana* assessment report, as well as in the WHO monograph on P. africana. (WHO 2004, Journal/http://apps.who.int/medicinedocs/en/d/Js4927e/24.html#Js4927e.24).	
5. 2 Pharmacokinetic properties	AESGP	**Well established use** No data available due the complex phytochemical composition of the extract.	Not required.
5.3 Preclinical safety data	AESGP	**Well established use** Acute, single doses of *P. africana* extract administered intragastrically to mice and rats at up to 8 g/kg body weight were well tolerated (ESCOP 2009). Neither mortality nor signs of adverse effects were observed after oral administration of single doses of extract to mice at 1-6 g/kg body weight and to rats at 1-8 g/kg (Bombardelli 1997, Journal/Fitoterapia,, 68: 205-218). Short-term (1 month) and long-term (6 months) intragastric administration of the extract to dogs at 375 mg/kg/day and to rats at	Partially endorsed for TU only Tests on reproductive toxicity and carcinogenicity have not been performed. While it was added that genotoxicity studies have given variable results: the Ames test (strain TA98) gave uniformly negative results, whereas micronucleus test and the Comet assay gave both positive and negative results, especially the in vitro micronucleus test in

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		750 mg/kg/day caused no adverse effects on haematological, biochemical or anatomical/pathological parameters (ESCOP 2009). No adverse reactions were observed after daily intragastric administration of the extract to mice at 60 mg/kg or rats at 600 mg/kg bw for 11 months (Bombardelli 1997, Journal/Fitoterapia,, 68: 205-218). Oral administration of the extract to rats at up to 1 g/kg body weight daily for 8 weeks did not cause clinical or pathological signs of toxicity, but moderate rises were observed in serum alanine aminotransferase (ALAT) and blood urea nitrogen levels. At 3.3 g/kg daily for 6 days the extract caused marked clinical signs of toxicity, organ damage and a 50% mortality rate; the main lesions were hepatocellular degeneration and necrosis, diffuse nephrosis and myocardial degeneration, lymphocytic necrosis and neuronal degeneration. The morphological damage in these tissues caused a corresponding rise in blood biochemical parameters namely, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, creatine kinase and blood urea nitrogen. The target organs of toxicity of this extract are the liver, kidney and heart. Overt toxicity occurred only after the administration of multiple doses of 3.3 g/kg body weight. These findings confirmed the safety of the extract at therapeutic dosages, since signs of toxicity were observed only at very high dose levels (Gathumbi 2000, Journal/Onderstepoort J Vet Res, 67: 123-128; Gathumbi 2002, Journal/Phytother Res, 16: 244-247; ESCOP 2009). In vivo and in vitro mutagenicity studies on the extract indicated a complete absence of mutagenic and clastogenic potential (ESCOP 2009).	human lymphocytes, extracts from *P. africana* significantly lowered the effect of the mutagen mitomycin C (MMC), where the extract alone was not genotoxic (Elgorashi et al. 2003; Reid et al. 2006; Taylor et al. 2003; Verschaeve 2004; Verschaeve & Van Staden 2008)

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		P. Africana extract was negative in the Ames test (strain TA98) (Elgorashi 2003, Journal/Toxicol Lett, 143: 195-207; Verschaeve 2004, Journal/Toxicol In Vitro, 18: 29-35). In the in vitro micronucleus test in human lymphocytes, extracts from *P. africana* significantly lowered the effect of the mutagen mitomycin C (MMC), where the extract alone was not genotoxic (Verschaeve 2004, Journal/Toxicol In Vitro, 18: 29-35).	
References	AESGP	Andro, M.-C. and J.-P. Riffaud, 1995. Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. Curr Therapeutic Res. 56, 796-817 Bombardelli, E., et al., 1997. *Prunus africana* (Hook. f) Kalkm. Fitoterapia,. 68, 205-218 Boulbes, D., et al., 2006. Pygeum africanum extract inhibits proliferation of human cultured prostatic fibroblasts and myofibroblasts. BJU Int. 98, 1106-1113 Chen, M. W., et al., 1999. Effects of Unilateral Ischemia on the Contractile Response of the Bladder: Protective Effect of Tadenan (Pygeum africanum Extract). Mol Urol. 3, 5-10 Descazeaud, A., et al., and Comité des troubles mictionnels de l'homme de l'Association française d'urologie (CTMH-AFU), 2015. Guide de prise en charge en médecine générale des symptômes du bas appareil urinaire de l'homme liés à une hyperplasie bénigne de la prostate. Prog Urol. 25, 404-412 Dufour, B., et al., 1984. Étude contrôlée des effets de l'extrait de	All provided references were taken into consideration and were included in the AR and LoR

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		pygeum africanum* sur les symptômes fonctionnels de l'adénome prostatique. [Controlled study of the effects of Pygeum africanum extract on the functional symptoms of prostatic adenoma Ann Urol (Paris).18,:193-5 Edgar, A. D., et al., 2007. A critical review of the pharmacology of the plant extract of Pygeum africanum in the treatment of LUTS. Neurourol Urodyn. 26, 458-463; discussion 464 Elgorashi, E. E., et al., 2003. Screening of medicinal plants used in South African traditional medicine for genotoxic effects. Toxicol Lett. 143, 195-207 ESCOP, 2009. E/S/C/O/P Monographs. Second Edition Supplement 2009. In: Book E/S/C/O/P Monographs. Second Edition Supplement 2009. Vol., ed.^eds. Thime Gathumbi, P. K., et al., 2002. Toxicity of chloroform extract of *Prunus africana* stem bark in rats: gross and histological lesions. Phytother Res. 16, 244-247 Gathumbi, P. K., et al., 2000. Biochemical and haematological changes in rats administered an aqueous extract of *Prunus africana* stem-bark at various dosage levels. Onderstepoort J Vet Res. 67, 123-128 Gravas, S., et al., 2015. Guidelines on the Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO). European Association of Urology (EAU). 1-70 HAS transparency commission, 2011. Commission de la Transparence,	

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		Avis 27 avril 2011; Tadenan (HAS transparency commission Tadenan, 2011-04-27). http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-05/tadenan_-_ct-10090.pdf HAS transparency commission 2015. Commission de la Transparence avis 18 mars 2015; Permixon, (Serenoa repens) http://www.has-sante.fr/portail/upload/docs/evamed/CT-13775_PERMIXON_PIS_RI_Avis1_CT13775.pdf HAS transparency commission, 2015. Commission de la Transparence Silodyx avis 21 octobre 2015 (silodozine) http://www.has-sante.fr/portail/upload/docs/evamed/CT-14409_SILODYX_PIS_RI_Avis2_CT14409.pdf HMPC, 2015. European Union herbal monograph on Serenoa repens (W. Bartram) Small, fructus. http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Herbal_monograph/2016/01/WC500199750.pdf Larré, S., et al., 2011. Biological effect of human serum collected before and after oral intake of Pygeum africanum on various benign prostate cell cultures. Asian J Androl. 14, 499-504 Levin, R. M., et al., 2002. Effect of oral Tadenan treatment on rabbit bladder structure and function after partial outlet obstruction. J Urol. 167, 2253-2259 Levin, R. M., et al., 1996. Effects of tadenan pretreatment on bladder physiology and biochemistry following partial outlet obstruction. J Urol. 156, 2084-2088	

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		Levin, R. M., et al., 2005. Low-dose tadenan protects the rabbit bladder from bilateral ischemia/ reperfusion-induced contractile dysfunction. Phytomedicine. 12, 17-24 Marcoli, M. and L. D'Angelo, 1986. Anti-inflammatory action of Pygeum africanum extract in the rat. Farmaci & terapia. 3, 135-137 Mathé, G., et al., 1995. A Pygeum africanum extract with so-called phyto-estrogenic action markedly reduces the volume of true and large prostatic hypertrophy. Biomed Pharmacother. 49, 341-343 McConnell, J. D., et al., 2003. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med. 349, 2387-2398 Moya-Prats, PP., et al., 1989. Valoracion estadistica de 500 pacientes con hipertrofia prostática benigna, tratados con Pygeum africanum, y valorados estadísticamente desde el punto de vista clínico y flujométrico. Urodiruimica Aplicada. 1, 150-155 (Cited in the List of references supporting the assessment of *Prunus africana* (Hook f.) Kalkm., cortex.) Papaioannou, M., et al., 2010. NBBS isolated from Pygeum africanum bark exhibits androgen antagonistic activity, inhibits AR nuclear translocation and prostate cancer cell growth. Invest New Drugs. 28, 729-743 Paubert-Braquet, M., 1994. Inhibition of bFGF and EGF-induced proliferation of 3T3 fibtroblasts by extract of Pygeum africanum (Tadenan) Biomed & Pharmacother. 48, suppl 1,43s-47s Quiles, M. T., et al., 2010. Antiproliferative and apoptotic effects of the	

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		herbal agent Pygeum africanum on cultured prostate stromal cells from patients with benign prostatic hyperplasia (BPH). Prostate. 70, 1044-1053 Roell, D. and A. Baniahmad, 2011. The natural compounds atraric acid and N-butylbenzene-sulfonamide as antagonists of the human androgen receptor and inhibitors of prostate cancer cell growth. Mol Cell Endocrinol. 332, 1-8 Stroup, S. P., et al., 2012. Trends in adverse events of benign prostatic hyperplasia (BPH) in the USA, 1998 to 2008. BJU Int. 109, 84-87 Tacklind, J., et al., 2012. Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst Rev. 12, CD001423 Tadenan Summary Product characeteristics, 2016. Tadenan Verschaeve, L., et al., 2004. Investigation of the antimutagenic effects of selected South African medicinal plant extracts. Toxicol In Vitro. 18, 29-35 Verschaeve, L. and J. Van Staden, 2008. Mutagenic and antimutagenic properties of extracts from South African traditional medicinal plants. J Ethnopharmacol. 119, 575-587 Wang, D., et al., 2010. Pygeum africanum: effect on oxidative stress in early diabetes-induced bladder. Int Urol Nephrol. 42, 401-408 WHO, 2004. Cortex Pruni Africanae. http://apps.who.int/medicinedocs/en/d/Js4927e/24.html - Js4927e.24 Wilt, T. and A. Ishani, 2011; edited, no change to conclusions.	

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		Pygeum africanum for benign prostatic hyperplasia. Cochrane Database Syst Rev. CD001044 Yablonsky, F., et al., 1997. Antiproliferative effect of Pygeum africanum extract on rat prostatic fibroblasts. J Urol. 157, 2381-2387 Yongzhi, L., et al., 2008. Expression of transforming growth factor beta1 gene, basic fibroblast growth factor gene and hydroxyproline in diabetes-induced bladder dysfunction in a rat model. Neurourol Urodyn. 27, 254-259 Yoshimura, Y., et al., 2003. Effect of Pygeum africanum tadenan on micturition and prostate growth of the rat secondary to coadministered treatment and post-treatment with dihydrotestosterone. Urology. 61, 474-478.	