EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Prunus africana* (Hook f.) Kalkm., cortex

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Prunus africana* (Hook f.) Kalkm., cortex
Herbal preparation(s)	Soft extract; DER: 114-222:1 extraction solvent: chloroform; (stabilised by 1.2 % of ethanol >99.9 %)
Pharmaceutical form(s)	Herbal preparations in solid dosage form for oral use
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Prunus africana* (Hook f.) Kalkm., cortex. It is a working document, not yet edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

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

- Herbal substance(s)

Prunus africana (Hook f.) Kalkm. (synonym: *Pygeum africanum* Hook f.) belongs to Rosaceae family

Pygeum bark consists of the whole or cut, dried bark of the stems and branches of *Prunus africana* (Hook f.) Kalkm. (synonym: *Pygeum africanum* Hook f.). The material complies with the monograph of the European Pharmacopoeia (Eur Pharmacopoeia 8.2 2015)

Selected vernacular names*: Pygeum*, African plum tree, African prune, armaatet, bitter almond, Bitteramandel, chati, inkhokhokho, inyangazoma-elimnyama, kiburabura, lemalan migambo,mueri, muiru, murugutu, mutimailu, mweria, mwiritsa, nuwehout, ol-koijuk, oromoti, red stinkwood, rooistinhout, tenduet, tendwet, twendet, umdumizulu, umkakase, umkhakhazi, umlalume (Bruneton 1995; Longo 1981; PDR 2007; The review of Natural Products 2005; ESCOP 2009 ; WHO monographs 2009).

The plant can be found in mountain forests of equatorial Africa (Angola, Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Malawi, Mozambique, Congo, South Africa, Uganda, Tanzania, Zambia and Zimbabwe (PDR 2007; Bruneton 1995).An evergreen tree, usually 10–25m high, with straight, cylindrical trunk and dense, rounded crown. Leaves deep green and glossy, alternate, 8–12cm long, long-stalked, simple, elliptic, bluntly pointed at apex, with shallow crenate margins; leathery, with midrib sharply impressed or channelled on upper surface and strongly prominent on underside. They smell as almonds when bruised. Leaf stalks and young branchlets often reddish. Flowers small, white or whitish cream, fragrant, in axillary racemes 3–8cm long; corolla lobes up to 2mm long. Fruits cherry-shaped, red to purplish-brown, 8–12mm in diameter; very bitter flesh and bony stone. Wood pale red, with strong cyanide smell when freshly cut, Owing to overexploitation and other factors, *Prunus africana* has been listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (*10*). darkening to rich dark red or mahogany-brown on exposure to air; straight-grained and even textured, strong and elastic, very hard and very heavy (PDR 2007; Bruneton 1995; Bombardelli & Morazzoni 1997).

Plant material of interest is the dried trunk bark

Red to blackish-brown, deeply square-fissured or corrugated with strong odour, characteristic almond smell, hydrocyanic acid-like odour (PDR 2007; The review of Natural Products 2005).

Constituents of pygeum bark

The major bark components are fat soluble compounds. The main characteristic constituents are phytosterols (approx. 0.05%), e.g. beta-sitosterol, beta-sitosterol 3-glucoside and beta-sitostenone, free C, -C 24 fatty acids, pentacyclic triterpenic acids are present (14%) (ursolic and oleanolic acid derivatives) and long chain aliphatic alcohols {n-docosanol, n-tetracosanol and their trans-ferulic acid esters) (Bombardelli &Morazzoni 1997, Fourneau et al. 1996; Bruneton 1995; WHO monographs).

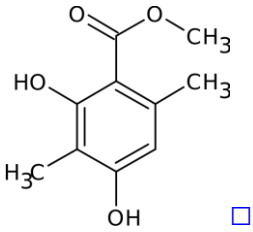
Major chemical constituents

The purported active constituents of a lipophilic extract of Cortex Pruni Africanae include docosanol (0.6%) and b-sitosterol (15.7%). Other major constituents include alkanols (tetracosanol [0.5%] and *trans*-ferulic acid esters of docosanol and tetracosanol), fatty acids (which are 12-24 carbons in length, 62.3%, comprising myristic, palmitic, linoleic, oleic, stearic, arachidic, behenic and lignoceric acids);

sterols (sitosterone [2.0%] and daucosterol) and triterpenes (ursolic acid [2.9%], friedelin [1.4%], 2-a-hydroxyursolic acid [0.5%], epimaslinic acid [0.8%] and maslinic acid) (Bruneton 1995; Uberti E et al. 1990; Catalano et al 1984). Tannins have also been found in the plant.

Qualitative and quantitative analysis for the major constituents, docosanol and beta-sitosterol, have been performed by gas chromatography–mass spectrometry while quantitative analysis of docosyl (*E*)-ferulate was performed by high performance liquid chromatography (Catalano et al 1984]

Through bioactivity directed fractionation of the dichloromethane extract of *Pygeum africanum* led to the isolation of N-butylbenzenesulfonamide (NBBS) which together with atraric acid showed) very strong anti-androgenic activities [Schleich et al. 2006i, 2006ii]. Atraric acid a phenolic ester with IUPAC name methyl 2,4-dihydroxy-3,6-dimethylbenzoate and molecular formula $C_{10}H_{12}O_4$ (occuring except of *P. africanum* also in *Evernia prunastri* - oakmoss) is well known for its anti-androgenic activity (Schleich et al. 2006i, 2006ii).



- ☐ Atraric acid

- .Herbal preparation(s)

Comminuted herbal substance.

- 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.

The request for information exchange concerning preparations from *Prunus africana* (Hook f.) Kalkm. , Pruni africanae cortex, Pygeum bark revealed that the extract is distributed in France and previously in other European countries (Italy, Spain, Poland, etc).

1.2. Search and assessment methodology

The assessment is based on the sources mentioned in the list of references. Publications in other languages than English (at least abstract in English or other language available) were precluded from assessment.

Search engines used: Google; key words: *Prunus africana* (Hook f.) Kalkm. , Pruni africanae cortex, Pygeum bark

Scientific databases: Scifinder, Scopus; search date 2014 and May 2015; key words: "pruni", "*Prunus africana"*, Pruni africanae, Pygeum

Medical databases: Pubmed, Cochrane library; key words: "*Prunus africana* (Hook f.) Kalkm. , Pruni africanae cortex, Pygeum bark "

Pharmacovigilance resources: Not applicable.

Data from EU and non-EU regulatory authorities:

Other resources: Library of the University of Athens (Pharmacy and Pharmacognosy library)

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Products on the market

- There are no product on the market in: Austria, Cyprus, Czech Republic, Estonia , Finland , Germany, Italy, Slovak Republic, Sweden, UK, while there are some combination products used as food supplements in Lithuania.
- Italy there was one product which is withdrawn with no well documented herbal preparation
- There are marketed products in France and Greece. France since 1969, 2009 (Overview of market, France, The Review of natural products (2005);

Well established use

Indication: Treatment in miction moderate disorders connected with BHP

i) Soft extract; Solvent: stabilized chloroform; DER : 114-222 : 1 (stabilized by 1.2 % of ethanol >99.9 %) since 1969

Indication: Treatment in miction moderate disorders connected with BHP

Posology

A capsule twice daily. A capsule contains 50 mg of extract,
Duration of use: 6 weeks (+ 2 weeks) it can be renewed

ii) Soft extract; Solvent: methylene chloride; DER : 200 : 1 , since 2009

i) A capsule twice daily. A capsule contains 50 mg of extract,
Duration of use: 6 weeks (+ 2 weeks) it can be renewed Soft extract; Solvent: methylene chloride ; DER : 200 (soft capsule) since 2009

Indication: Treatment in micturition moderate disorders connected with BHP

A capsule twice daily. A capsule contains 50 mg of extract
Duration of use: 6 weeks (+ 2 weeks) it can be renewed

Adverse reactions Rarely: digestive disorders (nausea, constipation or diarrhoea

The product soft extract; Solvent: stabilized chloroform; DER: 114-222: 1 (stabilised by 1.2 % of ethanol >99.9 %) since 1969, is fulfilling the criteria for traditional use

Greece

Lipo-sterolic extract of Pygeum africanum since 2009 (old type of registration) Capsule of 30mg

Indication: medicinal product for the relief of lower urinary tract symptoms related to BPH (such as nocturia, polyuria and urinary retention etc)

3 caps daily G04C
Duration of use: 4-6 weeks

Poland

1) There were used two strengths of the soft extract; Pruni africanae corticis extr. siccum (85-250:1), extr, solvent: chlorophorm Poland (Tadenan): 25mg, registered between 1985-1987 and then till 2004

Of 25 mg (caps(and of 50mg. 1985-2013.
Indication: Moderate micturition disorders caused by prostate hyperthophy.

2) tablets, authorized (or registered??) in 1987,

Prunus africana (=Pygeum africanum), DER (200:1), extraction solvent: methylene chloride, corresponds to 6 mg of beta sitosterol.

Each tablet content: It contains 46 mg of extract of *Prunus africana*, cortex in the amount equivalent to 6 mg of betasitosterol; extraction solvent methylene chloride.

Indication: In men, adjunctive treating of urination disorders at an early stage of prostatic hyperplasia (I-II Alken scale with frequent urination, the need to urinate at night, impeded urination, dropping).

Posology: 2 tablets (46mg x 2), twice daily, during a meals,

Duration: for at least 4 months (8 weeks). The treatment may be repeated if necessary.
Contraindications: Hypersensitivity to the active substance or excipients contained in a product or to plants of the family Rosaceae.

The product cannot be used in patients with diagnosed prostate cancer.
Special warnings: Use of the product does not relieve the patient from the constant consultation with the urologist. The product does not affect the size of the prostate and only relieves symptoms associated with its hypertrophy.

If symptoms worsen or do not improve or if you notice blood in your urine, sudden retention of urine, it needs immediate consultation.

Information on relevant combination medicinal products marketed in the EU/EEA

Czech Republic

Product registered 1984-1999 –withdrawn on request of the in 1999, the reason is not known, no pharmacovigilance action was taken on this product:

Trianol – capsules containing Pruni africanae extractum 25 mg/cps, no information on DER and extraction solvent is available/ No information on indication and posology is available anymore

Product registered 1996-2010 – withdrawn on request of the MAH in 2010, the reason is not known, no pharmacovigilance action was taken on this product: Tadenan - capsules containing Pruni africanae extractum 50 mg/cps, no information on DER and extraction solvent is available

Indication: Micturition disorders associated with benign prostatic hyperplasia

Posology: 1 capsule twice daily

Combination product registered 1992 - 2003 - withdrawn on request of the MAH in 2003, the reason is not known, no pharmacovigilance action was taken on this product:

Prostatonin – capsules containing Pruni africanae extractum, DER 180 – 220 : 1, extraction solvent methylene chloride 25 mg and Urticae radicis extractum 7 – 14 : 1, extraction solvent methanol 30% 300 mg/cps

Indication: for symptomatic treatment of early stages of benign prostatic hyperplasia

Posology: 2 capsules/day

The marketing authorisations of above mentioned products were granted in the old legislative frame

Information on other products marketed in the EU/EEA (where relevant)

Not applicable

2.1.2. Information on products on the market outside the EU/EEA

Not applicable

2.2. Information on documented medicinal use and historical data from literature

The hard wood of pygeum is valued in Africa. Powdered pygeum bark is used by Africans natives to treat urinary problems (The Plants review 2005; Bruneton 1995)

Prunus africana (Hook. f.) Kalkm. (syn. *Pygeum africanum* Hook f) commonly known as red stinkwood or bitter almond has traditionally been used for centuries by African traditional healers to treat genitourinary disorders. In the 1960s pygeum came to the attention of French scientists who began to investigate its benefits in the treatment of BPH. The commercial lipophilic extract of pygeum is the favourite phytomedicine used to treat prostate cancer, prostatitis and especially BPH in Europe

The phytosterols, especially beta-sitosterol, showed potentially antiinflammatory properties which could inhibit the formation of prostaglandins responsible for the swelling in the prostate gland. The pentacyclic triterpenoids are reported to block enzymatic activity associated with inflammation and swelling the prostate, while ferulic esters could help rid the prostate of cholesterol deposits which accompany BPH. Despite the activities of the compounds mentioned above, the active ingredient is considered to be n-docosanol The beneficial effects on lower urinary tract symptoms (LUTS) are ascribed to its protective action on the bladder. Clinical and pharmacological experiments have consistently confirmed the efficacy of pygeum extract in relieving the symptoms of BPH. A drawback of the clinical studies is that long-term studies (6 months or longer) using pygeum as a treatment for prostate disorders are still lacking. Mild gastro-intestinal irritation is a reported side effect. Findings on pygeum have been summarized in several extensive review articles (Cristoni et al. 2000; Ishani et al,. 2000; Steenkamp 2003; Stewart 2003;Shenouda et al. 2007; Wit & Ishani 2011).

Commission E Monograph (published 30.11.1985, revised 17.01.1991) *Bruneton 1995*

Pygeum is used as an anti-inflammatory, to increase prostatic secrations and to decrease certain hormones in the glandular area, which reduce the hypertrophy. Other actions of pygeum include increase in bladder elasticity and histological modifications of glandular cells.

ESCOP Monograph (Supplement 2009)

Pygeum bark (or a corresponding amount of extract) for: Symptomatic treatment of micturition disorders (dysuria, pollakiuria, nocturia, urine retention) in benign prostatic hyperplasia (BPH) stages I and II as defined by Aiken or stages II and III as defined by Vahlensieck.

The Review of natural products (2005)

In France, pygeum africanum extract (PAE) has become the primary course of treatment for enlarged prostate. Usual dosage of PAE is 100 mg/day in 6-8 week cycles. The highest activity was found in lipophilic extracts of the plant. Some of these extracts have been standardized to contain 14% triterpenes and 0.5% n-docosanol.

PDR for Herbal Medicines (Gruenwald et al 2007)

Fresh and dried seeds for: Irritable bladder and prostate complaints (this medication relieves only the symptoms associated with an enlarged prostate without reducing the enlargement).

WHO Monographs on selected medicinal plants Vol II (2009)

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.

In a recent review by Nicholson & Ricke 2011, about "Androgens and oestrogens in benign prostatic hyperplasia: Past, present and future" it is referred that plant extracts (pygeum bark) are extremely popular in the treatment of BPH, with American urologists estimating that up to 90% of newly referred patients with LUTS have tried or are using a form of alternative and complementary medicine, typically marketed as herbal prostate supplements. Extracts of the African evergreen tree P. africanum are a popular ingredient in herbal prostate supplements, with a mechanism related to androgen signaling in BPH. Studies of the P. africanum preparation, " have shown that it inhibits fibroblast proliferation and has anti-estrogenic and anti-inflammatory effects mediated by inhibition of leukotrienes. Further complicating the mechanism is the finding that in rabbits with experimentally induced partial BPH , high doses of P. africanum extract protect the ischemic detrusor muscle dysfunction by protecting bladder cell membranes from lipid peroxidation. A recent Cochrane review of 18 trials of P. africanum versus placebo revealed that it causes a moderate improvement in urinary symptom scores, increases urinary flow rates and men taking it are more than twice as likely to report overall symptoms to be improved (Wit & Ishani 2002]. It is likely that the clinical benefit experienced by BPH patients are due to the multiple mechanisms targeting hormonal, inflammatory and bladder components of male LUTS, and is highly dependent on the brand of the supplement and the active components.

Assessors' comment Oral use

On the basis of the information on traditional and current indications, and data from the overview of European market it is confirmed the existence of one marketed products, a herbal preparation (Soft extract; Solvent: stabilized chloroform; DER : 114-222 : 1) since 1969 is fulfilling the criteria of the safe use for a period of more than 30 years in the market. Moreover, according the data on clinical efficacy (see section 4.2) and the requirements for specified conditions of use to ensure a safe use, the following therapeutic indication is recommended for pygeum bark and the preparation(s) included in the monograph: "relief of lower urinary tract symptoms related to benign prostatic hyperplasia, after serious conditions have been excluded by a medical doctor".

Table 1: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form**	**Reference**
Soft extract; Solvent: stabilized chloroform; DER : 114-222 : since 1969 in France Liposterolic extracts of pygeum bark	Anti-inflammatory activity, to increase prostatic secretion and to decrease hormones in the glandular area, to reduce, the hypertrophy. Increase in bladder elasticity and histological	Doses 25-20mg up to 100 mg daily	ESCOP Monograph (Supplement 2009) WHO Monographs on selected medicinal plants Vol II (2009) PDR for Herbal Medicines

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Soft extract; DER (200:1), extraction solvent: methylene chloride, corresponds to 6 mg of beta sitosterol.	modifications of glandular cells.		(Gruenwald et al 2007) Bruneton 1995 Commission E Monograph (published 30.11.1985, revised 17.01.1991) Registered in Poland since 1987

2.3. Overall conclusions on medicinal use

On the basis of the information on traditional and current indications, and data from the overview of European market it is confirmed the existence of a marketed product, a herbal preparation (Soft extract; Solvent: stabilized chloroform; DER: 114-222 : 1) since 1969 which is fulfilling the criteria of the safe use for a period of more than 30 years in the market. Thus the requirements for the period of medicinal use according to Directive 2001/83/EC as amended with respect to "traditional use" regarded fulfilled for the indications.

Traditional herbal medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a medical doctor.

Moreover, according the data on clinical efficacy (see section 4.2) and the requirements for specified conditions of use to ensure a safe use, the following therapeutic indication is recommended for pygeum bark and the preparation(s) included in the monograph.

Table 2: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Soft extract; Solvent: stabilized chloroform; DER : 114-222 : 1 (stabilized by 1.2 % of ethanol >99.9 %) since 1969	Treatment in miction moderate disorders connected with BHP	A capsule twice daily. A capsule contains 50 mg of extract, Duration of use: 6 weeks (+ 2 weeks) it can be renewed	Since 1969 in France for WEU
Soft extract; Solvent: methylene chloride ; DER : 200 : 1 , since 2009	Treatment in miction moderate disorders connected with BHP	A capsule twice daily. A capsule contains 50 mg of extract, Duration of use: 6 weeks (+ 2 weeks) it can be	Since 2009 in France for WEU

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		renewed	
Capsules containing Pruni africanae extractum 25 mg/cps, capsules containing Pruni africanae extractum 25 mg/cps, no information on DER and extraction solvent is available/ No information on indication and posology is available anymore			1996-2010 Czech Republic
Caps of 30mg Lipo sterolic extract of *Pygeum africanum*	medicinal product for the relief of lower urinary tract symptoms related to BPH (such as nocturia, polyuria and urinary retention, etc)	3 times daily	Since 2009 in Greece
Soft extract; DER: (200:1), extraction solvent: methylene chloride, (corresponds to 6 mg of beta sitosterol)	In men, adjunctive treating of urination disorders at an early stage of prostatic hyperplasia (I-II Alken scale with frequent urination, the need to urinate at night, impeded urination, dropping).	Single dose 46mg x2 = 92 mg Daily dose up to 184mg Duration for at least 4 months (16 weeks)	Registered in Poland since 1987

Based on available literature references as well as recent clinical trials the following posologies are proposed:

The Review of natural products (2005); PDR for Herbal Medicines (Gruenwald et al 2007); ESCOP Monograph (Supplement 2009, information from France)

Soft extract; Solvent: stabilized chloroform; DER: 114-222 : 1 (stabilized by 1.2 % of ethanol >99.9 %) since 1969

Usual dosage of pygeum bark PAE is 50-100mg/day in 6-8 week cycles.

On the basis of the information on traditional and current dosages, information on duration of use from clinical studies (see section 4.2.2.) and the requirements for specified strength and specified posology, the following is recommended for pygeum bark and the preparations included in the monograph:

Posology

Adults and elderly men

50-100 mg daily

There is no relevant use in women, children and adolescents under 18 years of age.

Duration of use

Long-term use is possible, cycles of 6-8 weeks

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

In vitro experiments

Hormonal activity

A lipophilic extract from pygeum bark (200:1, methylene chloride; standardized to 13% sterols) concentration-dependently inhibited the activity of 5α-reductase from rat prostate cells (IC50: 0.78 mglml) and of aromatase from human placenta cells (1(50: 0.98 mg/ml). However, an earlier study demonstrated that a lipophlic extract had only slight inhibitory activity (1(50:63!Jglml) against 5α-reductase from the human prostate in comparison with the synthetic 5α-reductase inhibitor finasteride (1(50: 1 nglml) (Rhodes et al. 1993 in ESCOP 2009).

Bioactivity-directed fractionation of a selective dichloromethane extract from the stem bark of Pygeum africanum led to the isolation of the antiandrogenic compound atraric acid together with N-butylbenzenesulfonamide (NBBS). Their activity was examined by an androgen receptor responsive reporter gene assay (Schleich et al 2006i; 2006ii).

In tissue culture, ethanolic extracts (30%) of Pygeum africanum inhibited the growth of PC-3 and LNCaP cells; induced apoptosis and altered cell kinetics; down regulated ERa and PKC-a protein, and demonstrated good binding ability to both mouse uterine oestrogen receptors and LNCaP human androgen receptors (AR).

Recently, atraric acid (AA) and NBBS were isolated from a selective dichlormethane extract of P. africanum as two novel AR antagonistic compounds. The molecular mechanisms of AR inhibition were analyzed and showed that AA isolated from bark material of Pygeum africanum had anti-androgenic activity, inhibiting the transactivation mediated by the ligand-activated human AR. This androgen antagonistic activity is receptor specific and does not inhibit the closely related glucocorticoid or progesterone receptors. Mechanistically, AA inhibits nuclear transport of AR. Importantly, AA is able to efficiently repress the growth of both the androgen-dependent LNCaP and also the androgen-independent C4–2 Pca cells but not that of PC3 or CV1 cells lacking AR. In line with this, AA inhibits the expression of the endogenous prostate specific antigen gene in both LNCaP und C4–2 cells. Analyses of cell invasion revealed that AA inhibits the invasiveness of LNCaP cells through extracellular matrix. Thus, this study provided a molecular insight for AA as a natural anti-androgenic compound and may serve as a basis for AA derivatives as a new chemical lead structure for novel therapeutic compounds as AR antagonists, that can be used for prophylaxis or treatment of prostatic diseases (Papaioannou et al. 2009; Roell & Baniahmad 2011)

Effects on the prostate (androgen receptor (AR))

A herbal mixture containing extracts of the herbs Dendranthema morifolium, Ganoderma lucidium, Glycyrrhiza glabra, Isatis indigotica, Panax pseudo-ginseng, Rabdosia rubescens, Scutellaria baicalensis and Pygeum africanum) It has been used for a long time by prostate cancer patients as an alternative and/or subsidiary treatment of prostate cancer. In order to determine the toxic impact of particular

herbs in the mixture, it has been exposed the head and neck cancer cell lines FADU, HLaC79 and its Paclitaxel-resistant subline HLaC79-Clone1 as well as primary mucosal keratinocytes to increasing concentrations of the herbal mixture, as well as its single herbal components. Growth inhibition was measured using the MTT assay. Expression of P-glycoprotein (P-GP), multidrug resistance protein-1 (MRP-1), multidrug resistance protein-2 (MRP-2), breast cancer resistance protein (BCRP) and androgen receptor (AR) were examined by western blot analysis. Pygeum africanum extract clearly turned out as the main cytotoxic component of the herbal mixture prescription mixture, and initiated apoptosis in sensitive cell lines. All other extracts had only minor toxic effects. Western blot analysis revealed increased expression of P-GP in HLaC79-Clone1 cells, while HLaC79 and FADU cells were negative. All three cell lines were negative for MRP-1 and BCRP but positive for MRP-2. HLaC79 and its descendant HLaC79-Clone1 both expressed AR, as verified by western blotting and immunofluorescence staining. Primary mucosal keratinocytes were negative for all multidrug resistance markers as well as for AR. Growth inhibition rates of the single herbal extracts were compared with previously published results in prostate carcinoma cell lines. The relationship between expression levels of AR and multidrug resistance markers in relation to the measured toxicity of herbal extracts in our head and neck cancer cell system is critically discussed multidrug resistance markers as well as for AR. The relationship between expression levels of AR and multidrug multidrug resistance markers in relation to the measured toxicity of herbal extracts in our head and neck cancer cell system is critically discussed. In summary, it has been demonstrated that individual herbs such as Pygeum africanum extract used for treatment of prostatic diseases might also achieve growth inhibition in head and neck cancer cells, even if these cells are resistant to Paclitaxel. The growth inhibiting effect seems to be affected both by detoxification capacity of cells, as well as the expression of AR. The role of the AR in development and course of head and neck cancer remains to be revealed. (Schmidt et al. 2013).

Anti-inflammatory activity

A lipophilic extract from pygeum bark significantly inhibited the synthesis of S-lipoxygenase metabolites in human polymorphonuclear cells stimulated with the calcium ionophore A23187: 5-HETE (5-Hydroxyeicosatetraenoic acid) (p< 0.001 at 1 !Jg/ml), leukotriene B4 LTB4 (p<0.01 at 3 !Jg/ml), 20-hydroxy-LTB4 (p<0.001 at 3 !Jg/ml) and 20-carboxy-LTB4 (p<0.01 at 10 !Jg/ml) (ESCOP 2009)J.

In vivo experiments

Effects on the prostate

lntragastric administration of a lipophilic extract from pygeum bark to rats at 2 mg/kg body weight daily for 20-50 days stimulated the secretory activity of the prostate in normal rats and prevented the development of prostatic hyperplasia induced by injection of human prostate adenoma tissue [Thieblot et al. 1971, ESCOP]. Intraperitoneal administration of the extract at 1 and 10 mg/kg body weight daily for 20 days enhanced secretory activity of the prostate and seminal vesicles in castrated rats. However, the activity of testosterone on these glands was antagonized, as shown by a significant reduction in weight gain of these organs (p < O.O5). On the other hand, in castrated and adrenalectomized rats the extract potentiated the activity of testosterone on the target organs and increased the content of pituitary gonadotrophins (Thieblot et al. 1977, ESCOP 2009).

lntragastric administration of the extract to rats at 100 mg/kg daily for 3 days also increased prostate secretions (Clavert et al. 1986, ESCOP 2009).

TRAMP (transgenic adenocarcinoma of the mouse prostate) mice fed Pygeum africanum (ethanolic extracts (30%) of the plant) showed a significant reduction (P = 0.034) in prostate cancer incidence (35%) compared to casein fed mice (62.5%). Pygeum africanum, which is widely used in Europe and USA for treatment of BPH, has a significant role in regulation of prostate cancer both in vitro and in

vivo and therefore may be a useful supplement for people at high risk for developing prostate cancer (Shenuda et al. 2007).

Antispasmodic activity

A lipophilic extract of the crude drug administered intragastrically to rats inhibited spasms of the bladder induced by electroshock, phenylephrine, adenosine triphosphate and carbachol (World Health Organization). A reduction in carbachol-induced spasms of the bladder was observed after intragastric administration of a lipophilic extract of the crude drug to guinea-pigs (WHO). Intragastric administration of a lipophilic extract of the trunk bark to rabbits (100 mg/kg body weight) prevented the development of contractile dysfunction induced by partial obstruction of the bladder (Lowe & Ku 1996). A lipophilic extract of the crude drug improved the contractility of the detrusor muscle of the bladder in old rats (Riffaud & Lacolle 1990).

Effects on bladder function

Administration of a lipophilic extract from pygeum bark to rats reduced the response of the bladder to electrical stimulation, phenylephrine, adenosine triphosphate and carbachol. The extract also reduced bladder hyper-reactivity to carbachol in guinea pigs (ESCOP 2009).

After intragastric pre-treatment of rabbits with a lipophilic extract from pygeum bark at 1,10 and 100 mglkg body weight daily for 3 weeks, and further treatment for 2 weeks combined with partial bladder outlet obstruction, the bladders were excised, weighed and in vitro contraction studies were performed. The extract had no effect on bladder mass, but there was significant, dose-dependent preservation of the contractile responses of bladder strips ($p<O.OS$).

In a further experiment (intragastric pre-treatment of rabbits at 100 mg/kg/day for 3 weeks; partial urethral obstruction for 1-14 days) the extract had no effect on bladder weight but reduced on day 1 and prevented from day 3 the severity of contractile dysfunctions associated with partial outlet obstruction. Pre-treatment restored the activities of citrate synthase and calcium-ATPase to nearly normal from day 7 onwards after an initial significant reduction ($p<0.05$) of their activities.

In another study, after 2 weeks of mild or severe partial outlet obstruction the extract was intragastrically administered to rabbits at 100 mg/kg/day for 3 weeks. In contrast to the previous experiments, the bladder weight of the verum group with severe outlet obstruction was lower than in the placebo group but still significantly higher ($p<0.01$) than in the control group. Contractile dysfunction and reduction in compliance were reversed in the mild outlet obstruction group, while in the severe outlet obstruction group contractile dysfunction was improved. Recent studies indicate that focal ischemia/reperfusion (I/R) can cause the contractile dysfunctions induced in animal models of partial bladder outlet obstruction. A pretreatment with Pygeum africanum chloroform extract can prevent the rabbit bladder from developing the contractile and biochemical dysfunctions induced by partial outlet obstruction, possibly by protecting the bladder from ischemic injury. The current study was designed to determine whether pre-treating rabbits with a clinically relevant dose of chloroform extract could prevent the bladder from developing the contractile dysfunctions that are induced by bilateral ischemia followed by reperfusion. New Zealand White rabbits were separated into two groups. One group was pre-treated by oral gavage for 3 weeks with chloroform extract (3.0 mg/kg body wt./day). The second group was treated with vehicle (peanut oil). Five rabbits from each group were subjected to either bilateral ischemia for 1 or 3 h and than reperfused for either 1 h or 1 week. Five rabbits from each group were subjected to sham surgery and run with each of the experimental groups. The results of the current study show that chloroform extract pre-treatment at the clinically relevant dose of 3.0 mg/kg body wt./day protected the bladder from the contractile dysfunctions induced by bilateral ischemia followed by reperfusion. These data are consistent with the assertion that

chloroform extract therapy in both rabbits and humans acts by protecting the bladder smooth muscle against cellular damage caused by ischemia and reperfusion. In a related study, intragastric administration of the extract to rabbits (30 mglkglday for 3 weeks) after 2 weeks of partial outlet obstruction resulted in reduced bladder hypertrophy,improved contractile responses and reversal of the induced structural damage to cellular and subcellular membranes [Levin et al. 2002; 2005].

In a subsequent study rabbits received the extract intragastrically (100 mg/kg/day for 3 weeks) after 2 weeks of partial bladder outlet obstruction. Partial obstruction resulted in a significant increase in bladder weight compared to that of unobstructed animals (8.8 g versus 2.3 g; $p<0.05$). Obstructed rabbits in the verum group had significantly lower bladder weights than placebo-treated animals (4.2 g versus 8.8 g; $p<0.05$). The diminished contractile response to field stimulation and carbachol was restored to normal. Relative ratios for myosin heavy chain isoforms, altered at mRNA and protein levels by the obstruction, returned nearly to normal in the group treated with the extract ($p<O.Ol$) [Gomes et al. 2000].

In a 7-week experiment partial urethral obstruction was created in rats by stimulating prostate growth with DHT, administered subcutaneously at 1.25 mg/kg body weight during weeks 3 and 4. lntragastric administration of a lipophilic extract from pygeum bark (100 mg/kg/day for 2 weeks before, 2 weeks during and 3 weeks after DHT treatment) significantly reduced micturition frequency ($p<0.05$) and normalized urethral opening pressure and voiding volume, as well as the weight of the total prostate and of the ventral lobe, compared to controls ([Choo et al. 2000). A subsequent 6-week study in rats, during which DHT was administered in weeks 1 and 2, showed that co-treatment or post¬ treatment with the extract at 100mg/kg/day suppressed the effects on micturition frequency and volume, but that only co-treatment could correct a developing increase in prostatic weight ($p<0.05$) (Yoshimura et al. 2003).

Anti-inflammatory effects

A lipophilic extract from pygeum bark, administered intragastrically at 400 mg/kg body weight, markedly reduced carrageenan-induced paw oedema in rats.

When administered intraperitoneally at 10 and 100 mg/kg the extract inhibited the increased vascular permeability caused by histamine (ESCOP 2009).

Table 3: Overview of the main non-clinical data/conclusions on pygeum

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
lipophilic extract from pygeum bark (200:1, methylene chloride; standardized to 13% sterols)		In vitro	(Hartmann RW, Mark M, Soldati 1996)	inhibited the activity of 5α -reductase from rat prostate cells (IC50: 0.78 mg/ml) and of aromatase from human placenta cells (1(50: 0.98 mg/ml)
Lipophilic extract had only slight inhibitory activity (1(50:63!Jglml)		In vitro	(Rhodes et al. 1993; ESCOP 2009)	against 5α-reductase from the human prostate in comparison with the synthetic 5α-reductase inhibitor finasteride (1(50: 1 nglml)
Lipophilic extract and atraric acid		In vitro	Schleich et al 2006i; 2006ii	antiandrogenic compound atraric acid

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				together with N-butylbenzenesulfonamide (NBBS). Their activity was examined by an androgen receptor responsive reporter gene assay
A herbal mixture containing extracts of Pygeum africanum as well as the single Pygeum extract (Dendranthema morifolium, Ganoderma lucidum, Glycyrrhiza glabra, Isatis indigotica, Panax pseudo-ginseng, Rabdosia rubescens, Scutellaria baicalensis)	concentrations between 100 and 500 µg/ml, as well as at lower concentrations of10-50 µg/ml culture medium.	In vitro	Schmidt et al. 2013	Pygeum africanum extr appeared as the main cytotoxic compound (against cancer cell lines FADU, HLaC79 and its Paclitaxel-resistant subline HLaC79-Clone1 as well as primary mucosal keratinocytes) and initiated apoptosis in sensitive cell lines. Western blot analysis revealed increased expression of P-GP in HLaC79-Clone1 cells, while HLaC79 and FADU cells were negative. Pygeum africanum in low concentrations (50 µg/ml) exerted only a weak growth inhibition throughout carcinoma cell lines and primary mucosal keratinocytes.
ethanolic extracts of Pygeum africanum	ethanolic extracts (30%)	In vivo	Shenuda et al. 2007	Inhibited the growth of PC-3 and LNCaP cells; induced apoptosis and altered cell kinetics; down regulated ERa and PKC-a protein, and demonstrated good binding ability to both mouse uterine estrogen receptors and LNCaP human androgen receptors
A lipophilic extract		In vivo	Papaioannou et al. 2009; Roell & Baniahmad	significantly inhibited the synthesis of 5-lipoxygenase

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
			2011 ESCOP 2009	metabolites in human polymorphonuclear cells stimulated with the calcium ionophore A23187: 5-HETE (p<0.001 at 1 !Jg/ml), LTB4 (p<0.01 at 3 !Jg/ml),20-hydroxy-LTB 4 (p<0.001 at 3 !Jg/ml) and 20-carboxy-LTB4 (p<0.01 at 10 !Jg/ml)
	lntragastric administration to rats at 2 mg/kg body weight daily for 20-50 days	In vivo	(Thieblot et al. 1971) ESCOP]	stimulated the secretory activity of the prostate in normal rats and prevented the development of prostatic hyperplasia induced by injection of human prostate adenoma tissue
lipophilic extract from pygeum bark	lntragastric administration of the extract to rats at 100 mg/kg daily for 3 days	In vivo	(Clavert et al. 1986, ESCOP).	also increased prostate secretions
lipophilic extract	administered intragastrically to rats 100mg/kg body weight	In vivo	(Riffaud & Lacolle 1990), WHO 2007;	It inhibited spasms of the bladder induced by electroshock, phenylephrine, adenosine triphosphate and carbachol. A reduction in carbachol-induced spasms of the bladder was observed Also it prevented the development of contractile dysfunction induced by partial obstruction of the bladder. Also improved the

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				contractility of the detrusor muscle of the bladder in old rats
lipophilic extract from pygeum bark	After intragastric pre-treatment of rabbits with a lipophilic extract from pygeum bark at 1,10 and 100 mglkg body weight daily for 3 weeks, and further treatment for 2 weeks combined with partial bladder outlet obstruction, the bladders were excised, weighed and in vitro contraction studies were performed.	In vivo	Lowe & Ku 1996	The extract had no effect on bladder mass, but there was significant, dose-dependent preservation of the contractile responses of bladder strips ($p<0.05$).
Chlorophorm extract of pygeum	intragastrically administered to rabbits at 100 mg/kg/day for 3 weeks.	In vivo	Levin et al. 2002; 2005	The results showed that chloroform extract pre-treatment at the clinically relevant dose of 3.0 mg/kg body wt./day protected the bladder from the contractile dysfunctions induced by bilateral ischemia followed by reperfusion.
	study rabbits received the extract intragastrically (100 mg/kg/day for 3 weeks) after 2 weeks of partial bladder outlet obstruction	In vivo	(Gomes et al. 2000).	Partial obstruction resulted in a significant increase in bladder weight compared to that of unobstructed animals (8.8 g versus 2.3 g; $p<0.05$). Obstructed rabbits in the verum group had significantly lower bladder weights than

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				placebo-treated animals (4.2 g versus 8.8 g; p<0.05).
lipophilic extract from pygeum bark	In a 7-week experiment partial urethral obstruction was created in rats by stimulating prostate growth with DHT, administered subcutaneously at 1.25 mg/kg body weight during weeks 3 and 4. lntragastric administration of a lipophilic extract from pygeum bark (100 mg/kg/day for 2 weeks before, 2 weeks during and 3 weeks after DHT treatment)	In vivo	(Yoshimura et al. 2003). (Choo et al. 2000).	significantly reduced micturition frequency (p<0.05) and normalized urethral opening pressure and voiding volume, as well as the weight of the total prostate and of the ventral lobe, compared to controls A subsequent 6-week study in rats, during which DHT was administered in weeks 1 and 2, showed that co-treatment or post¬ treatment with the extract at 100mglkglday suppressed the effects on micturition frequency and volume, but that only co-treatment could correct a developing increase in prostatic weight (p<0.05)
A lipophilic extract from pygeum bark	administered intragastrically at 400 mg/kg body weight, markedly reduced carrageenan-induced paw oedema in rats. When administered intraperitoneally at 10 and 100 mg/kg	In vivo	(ESCOP 2009).	the extract inhibited the increased vascular permeability caused by histamine

3.1.2. Secondary pharmacodynamics

Antiproliferative effects

Growth factors seem to play a role in the pathogenesis of BPH, in particular basic fibroblast growth factor (b-FGF), which is present at an elevated level in BPH tissue. It has been shown that b-FGF, EGF (epidermal growth factor) and dihydrotestosterone DHT stimulate the growth of fibroblasts from the adult prostate (Bombardelli , Morazzoni 1997), while a lipophilic extract from pygeum bark at 1 ug/ml inhibited significantly the proliferation 3T3 fibroblasts of mouse stimulated by b-FGF and EGF (p<O.OS) (ESCOP 2009).

The activity of a lipophilic extract from pygeum bark on DNA synthesis was evaluated by measuring ['H]thymidine incorporation into rat prostatic stromal cells. The extract inhibite the proliferation of both non-stimulated cells (1(50: 14.4 !Jg/ml) and cells stimulated by the mitogenic growth factors EGF, insulin-like growth factor-1 and b-FGF (1(50 values of 4.6, 7.7, 12.6 !Jg/ml respectively) at similar concentrations to genistein, a known growth inhibitor in mitogenic studies. The proliferation induced by TPA (12-0-tetradecanoylphorbol-13-actate) and phorbol- 12,13-dibutyrate,direct activators of protein kinase C (PKC),was also concentration-dependently inhibited with 1(50 values of 12.4 and 8.1 !Jg/ml respectively, compared to an 1(50 of approximately 1 nM for the PKC inhibitor staurosporine [ESCOP 2009; Yablonsky et al. 1997].

As *Prunus africana* together with other plants (Withania somnifera, Warbugia ugandensis, and Plectrunthus barbatus) are used traditionally in Kenya for treatment of microbial infections and cancer Safety studies were carried using Cell Counting Kit 8 cell proliferation assay protocol. To evaluate extracts mechanisms of action, IEC-6 cells and RT-PCR technique was employed in vitro to evaluate Interleukin 7 cytokine. *Prunus africana* shuts down expression of IL 7 mRNA at 50 mg/ml. Mechanisms of action can largely be attributed to cytotoxicity, Gene silencing and immunopotentiation. *Prunus africana* shuts down expression of IL 7 completely at tested concentrations. It is possible that this is the mechanism by which P. africana works in traditional medicine by silencing certain genes. However this theory should be pursued further. P. africana (as well as W. somnifera, and P. barbatus) have IC50 cytoxicity levels much higher than 100 mg/ml when evaluated in IEC-6 cells (Mwitari et al 2013).

Antimicrobial activities

As *Prunus africana* together with orther plants (Withania somnifera, Warbugia ugandensis, and Plectrunthus barbatus) are used traditionally in Kenya for treatment of microbial infections. A study was conducted on the effect of organic extracts of these plants on both bacterial and fungal strains, and their mechanisms of action. Extracts were evaluated through the disc diffusion assay. Bacteria and yeast test strains were cultured on Mueller-Hinton agar and on Sabouraud dextrose agar for the filamentous fungi. A 0.5 McFarland standard suspension was prepared. Sterile paper discs 6 mm in diameter impregnated with 10 ml of the test extract (100 mg/ml) were aseptically placed onto the surface of the inoculated media. Chloramphenicol (30 mg) and fluconazole (25 mg) were used as standards. Discs impregnated with dissolution medium were used as controls. Activity of the extracts was expressed according to zone of inhibition diameter. methanol extract of P. africana was found have good activity while the ethyl acetate fraction had moderate activity against Staphylococcus aureus and Methicilin Resistance Staphylococcus aureus. MIC was determined at 0.78–100 mg/ml. (Mwitari et al 2013).

Antioxidant effects

A chloroform extract from pygeum bark was fractionated by partitioning between solvents of varying polarity and by column chromatography. The inhibitory activity of the extract and fractions from it on ferrous ion-induced stimulation of lipid peroxidation in microsomal preparations from rabbit livers was evaluated. The extract and fractions containing high levels of myristic acid markedly inhibited lipid peroxidation with a potency comparable to that of α-tocopherol (Hass et al. 1999).

3.1.3. Safety pharmacology

3.1.4. Pharmacodynamic interactions

3.1.5. Conclusions

Experimental preclinical data presenting influence on urinary function, anti-androgenic, antiinflammatory and antioxidant effects of pygeum bark confirm long tradition of their therapeutic use in benign prostatic hyperplasia. The published data on pharmacological activities support the traditional use of preparations containing pygeum bark lipophilic extract (chloroform extract) in the proposed indication.

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

No data are available on pygeum bark pharmacokinetics due to its complex phytochemical composition.

Due to lack of human data on pharmacokinetics, no general conclusions can be drawn.

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

3.3.1. Single dose toxicity

Acute toxicity / Single doses of the lipophilic (chloroform) extract administered intragastrically to mice and rats at up to 8 g/kg body weigh 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 & Morazzoni 1997).

3.3.2. Repeat dose toxicity

Repeated dose - chronic toxicity

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 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 E, Morazzoni 1997).

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 et al. 2000, 2002, ESCOP 2009).

3.3.3. Genotoxicity

In vivo and in vitro mutagenicity studies on the extract indicated a complete absence of mutagenic and clastogenic potential (ESCOP 2009].

Dichloromethane and 90 % methanol extracts of *Prunus africana* were investigated for mutagenic and antimutagenic effects in Salmonella/microsome and micronucleus tests. *Prunus africana* extracts tested in the Salmonella typhimurium TA98 strain was not mutagenic and did not modify the effect of the mutagen 4-nitroquinoline-oxide (4NQO) (Verschaeve et al. 2004; Elgorashi et al. 2003). 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 et al. 2004).

Dichloromethane and 90% methanol extracts were positive in the in vitro micronucleus test and in the alkaline Comet assay in human peripheral lymphocytes [Taylor et al 2003], however, in a later review article (Verschaeve & van Staden 2008) the authors are of the opinion that positive results in these cellular tests caused by plant extracts may sometimes be artificial.

3.3.4. Carcinogenicity

No studies on carcinogenicity were found in the literature.

3.3.5. Reproductive and developmental toxicity

At up to 80 mg/kg/day the extract had no effect on fertility in male rats or rabbits (ESCOP 2009).

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

Acute and chronic toxicity of the extract was low; signs of toxicity in liver, kidney and heart were observed only with very high doses. Genotoxicity studies gave variable results: the Ames test (strain TA98) gave uniformly negative results, whereas micronucleus test and the Comet assay gave both positive and negative results (Elgorashi et al. 2003; Reid et al. 2006; Taylor et al. 2003; Verschaeve & Van Staden 2008)

3.4. Overall conclusions on non-clinical data

Experimental preclinical data presenting influence on urinary function, anti-androgenic, antiinflammatory and antioxidant effects of pygeum bark confirm long tradition of their therapeutic use in benign prostatic hyperplasia. The published data on pharmacological activities support the traditional use of preparations containing pygeum bark in the proposed indications.

4. Clinical Data

4.1. Clinical pharmacology

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

No data available.

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

There are no data available on human pharmacokinetics.

4.2. Clinical efficacy

No data available.

4.2.1. Dose response studies

There are no specific data available on dose-response studies.

4.2.2. Clinical studies (case studies and clinical trials)

Trials were searched in computerized general and specialized databases (MEDLINE (1966 to 2000), EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting relevant manufacturers and researchers. Main results:

A total of 18 randomized controlled trials involving 1562 men met inclusion criteria and were analyzed. Only one of the studies reported a method of treatment allocation concealment, though 17 were double blinded. There were no studies comparing Pygeum africanum to standard pharmacologic interventions such as alpha-adrenergic blockers or 5-alpha reductase inhibitors.

A systematic review of randomized controlled studies with lipophilic extract from pygeum bark assessed 18 studies involving 1562 men with symptomatic BPH; 17 studies were double-blinded but only 1 reported a method of treatment allocation concealment. The mean study duration was 64 days and the daily dose of extract ranged from 75 to 200 mg. Data from 6 placebo-controlled studies involving474 participants were suitable for pooling to provide a weighted estimate of effectiveness and meta-analysis indicated moderate improvement in the combined outcome of urologic symptoms and flow measures; nocturia decreased by 19% and residual urine volume by 24°/., while peak urine flow increased by 23%. Although the duration of treatment was short, and study designs and types of reported outcome varied greatly, it was concluded that pygeum bark modestly but significantly ($p<0.001$ to $p<0.05$) improves urologic symptoms and flow measures (Ishani et al. 2000).

Other clinical reviews, which assessed open as well as controlled studies, involved a total of 1310 patients, daily doses of 75-200 mg of lipophilic extracts and treatment periods ranging from 15 to 120 days. They all concluded that pygeum bark improved the symptoms and objective measures of BPH and was well tolerated (Bombardelli E, Morazzoni 1997., ESCOP 2009, lshani et al. 2000).

Two different daily dosage regimens for a lipophilic extract from pygeum bark were compared in a randomized study. Out of 235 BPH patients on commencement 209 completed a 2-month double blind phase, receiving either 50 mg of the extract twice daily, morning and evening (group A, 101 patients) or 100 mg once daily in the evening (group B, 108 patients). The primary efficacy parameter was the International Prostate Symptom Score (IPSS), a 40% or greater reduction from baseline being considered a significant improvement. Both treatments had similar efficacy after 2 months:in group A the IPSS decreased by 38%,thequalityof life score improved by 28%and the maximum urinary flow rate increased by 16%; in group B the figures were 35%, 28% and 19%. In a subsequent 10-month open phase 174 patients took 100 mg of the extract once daily. After 12 months the overall iiPSS had decreased by 46% and the maximum urinary flow rate had increased by 15% Detailed (To compare the efficacy and safety of Pygeum africanum extract, 50 mg twice daily and 100 mg once daily. Methods. Patients with symptomatic benign prostatic hyperplasia (BPH) entered a 2-month randomized, parallel-group, double-blind, comparative phase (group A, 50 mg twice daily; group B, 100 mg once daily), followed by a 10-month, open phase (100 mg once daily). Main efficacy assessment parameters included International Prostate Symptom Score (IPSS), quality of life (QOL), and maximum urinary flow rate (Qmax). Results. Two hundred nine patients completed the comparative phase in compliance with the protocol; 174 were included in the open phase. Both treatments had similar efficacy. IPSS (baseline 17 in both groups) improved by 38% in group A and 35% in group B. QOL improved by 28% in both groups. Qmax increased by 1.63 mL/s (16%) in group A and 2.02 mL/s (19%) in group B. After 12 months, the IPSS fell from 16 (baseline) to 9 (−46%). Half of the patients had an IPSS below 8. Mean Qmax increased by 1.65 mL/s (15%). The safety profile was similar between groups and study phases. Conclusions. P. africanum extract at 50 mg twice daily and 100 mg once daily proved equally effective and safe at 2 months. Further improvements in efficacy with a satisfactory safety profile were documented after 12 months (Chatelain et al. 1999).

It was showed statistical results on clinical and flow-metric data for the first 500 patients treated with *Pygeum africanum* between 1981 and 1988. It can be confirmed that treatment with *P. africanum* improves subjective and objective symptomatology in patients with moderate prostatic growth and without prominent medium lobule, with less than 100cm3 of vesical residue and with a moderate initial clinic from the prostatic point of view (ESCOP 2009).

In an older work the effect of *Pygeum africanum* (25mg/capsule) was assayed on vesico-prostatic epithelium in: a) prostatic hypertrophy with high surgical risk; b) acute and chronic prostatitis; c) incipient prostatic hypertrophy not ready for surgical treatment. 50 patients were included who received 3 capsules daily for 45 days. The following conclusions were achieved: a) *Pygeum africanum* is useful in the treatment of acute and chronic prostatits, non-surgical adenomas and surgical adenomas with no possibility of surgery. b) In patients with adenoma, a regression is observed that improves urodynamic conditions. c) In a secondary way, it improves mictional disfunction (ESCOP 2009).

In a recent paper where were profiled the usage and effectiveness of various LUTS/ BPH drugs in real-life practice (TRIUMPH study). It was recorded the treatment and outcomes of 2351 newly-presenting LUTS/BPH patients in 6 European countries over a 1-year follow-up period. At each visit the clinician recorded the treatment, comorbidities, complications and drugs prescribed, and the patient completed an IPSS questionnaire. The results were analysed using change in IPSS as the primary outcome measure. Over the study period 74.9% of patients were prescribed medication, the majority (83% of

those medicated) were prescribed only a single drug. Tamsulosin was the most commonly prescribed drug in all countries (38% of medicated cases), although with national variation from 24% in Poland to 70% in Italy. The alpha-blockers were the most effective, with a mean reduction of 6.3 IPSS points. Finasteride was slightly less effective (4.1 points). Significant improvements were seen in 43% of patients on phytotherapy with *Pygeum africanum* compared to 57% of those on finasteride and 68% on alpha-blockers. The only combination therapy found to produce a statistically significant improvement over the use of individual drugs was finasteride + tamsulosin (8.1 points compared to 6.7 for tamsulosin alone and 4.2 for finasteride alone). All drug treatments showed some improvement over watchfulwaiting for most patients over the study period: the alpha-blockers were found to be the most effective. There were marked national differences in prescribing patterns, both in individual drug choice and in the use of combination therapies. The benefits reported for Pygeum africanum were also confirmed. However, the placebo effect is known to be strong with all types of LUTS medications, sometimes producing apparent improvement exceeding those of real drugs. This is especially the case for plant extracts, where the benefit over placebo for most preparations is uncertain. These phytotherapies, although giving statistically significant improvements in symptoms, were less effective than the alpha blockers or finasteride, and gave worthwhile benefits in less than half of those treated (Hutchinson et al. 2007).

Characteristics of excluded studies [Wilt & Ishani the Cochrane analysis 2011] Breza 1998 Diz 1973 Grasset 1974 Greiner 1970 Grévy 1970 Guilland-Vallée 1970 Guillemin 1970 Huet 1970 Lange 1970 Lhez 1970 Martínez-Piñeiro '73 Robineau 1976 Rometti 1970 No control group

In conclusion 12 Clinical trials were made with Soft extract; DER : 114-222 : 1 extraction solvent: chloroform; (stabilized by 1.2 % of ethanol >99.9 %)(Tadenan) 3 of them are available while all the other 9 are cited and evaluated in Wilt & Ishani the Cochrane analysis 2011. In total 825 European me (from frnace, italy, Poland, Netherlands) were participated, all 0f them with symptomatic BPH. The duration of the treatment was from 6-12 week (mainly 60 days) with an average dose of 72-100 mg (mainly 100mg, two tabs of 50mg each one). Different parmaters have been evaluated while in many case final conclusions were not clear.

Barlet 1990 Multicentre study. Double blinded (n=132). Treatment: *P. africanum* extract 100 mg twice daily (n=131). 60 days. European men with symptomatic BPH Significant improvement in nocturia ($p<0.007$) peak urine flow ($p<0.02$) residual volume ($p<0.02$) and overall symptoma ($p<0.001$) in the verum group 5 patients stopped their treatment due to gastrointestinal problems.

Blitz 1985 [ESCOP 2009 Wilt & Ishani the Cochrane analysis 2011] Double blinded Control: placebo Treatment: *P. africanum* extract 100 mg daily 60 days. N=57 French men Lost to follow-up: 0 men with symptomatic BPH Overall improvement in symptoms

Bongi 1972 Double blinded: [ESCOP 2009 Wilt & Ishani the Cochrane analysis 2011] Control: placebo Treatment: *P. africanum* extract 75 mg daily 60 days N=50 Italian men, residual volume < 200 ml. Age range: 49-84. Lost to follow-up: 0. men with symptomatic BPH Significant improvements in noctrurnal micturition frequency ($p<0.01$) dysuria ($p<0.05$) and volume of residual urine ($p<0.01$) in

Chatelain 1999 Double blinded Treatment 1 -A*: P. africanum* extract 50 mg x 2 daily (n=101). Treatment 2 -B: *P. africanum* extract 100 mg daily (n=108). 60 days**.** N=209 French men with symptomatic BPH, age > 50, IPSS 10 or >, PUF < 15 ml/s, residual volume < 150 ml. Mean age: 66 years. Lost to follow-up: 26 (11.1%). Symptom score (IPSS) International Prostate Symptom score Group A the IPSS decreased by 38%, the quality of life score improved by 28% and the max urinary flow rate increased by 16% in Group b the figs were 35%, 28% and 19%. After 12 months the overall IPSS had decreased by 465 and the maximum urinary low rate had increased by 15%

Donkervoort 1977 [Wilt & Ishani the Cochrane analysis 2011] Double blinded Control: placebo Treatment: P*. africanum* extract 75 mg daily 12 weeks. N=20 Dutch men Lost to follow-up: 4 (20%). Overall improvement in symptoms; Nocturia; peak urine flow

Dufour 1984 Double blinded Control: placebo (n=60). Treatment: *P. africanum* extract 100 mg daily (n=60). 6 weeks N=120 French men Lost to follow-up: 56 (47%). men with symptomatic BPH not in need of surgery. Significant improvement ($p<0.01$) in , difficulty in starting micturition and sensation of incomplete voiding of the bladder in the verum group.

Dutkiewicz 1996 Single-site study ESCOP 2009 Wilt & Ishani the Cochrane analysis 2011. Randomization: unclear Control: Cernilton 2 tablets three times daily x 2 weeks followed by 1 tablet three times daily up to 4 months (n=51). Treatment: Tadenan 2 tablets 50 mg (100mg) twice daily (38). 24 weeks. N=89 Polish men Age range: 50-68. Lost to follow-up: 0. men with symptomatic BPH at Alken stage I and II (no details given) Obstructive symptom score Irritative symptom score; peak urine flow; residual volume; prostate volume. Adverse events. From the evaluation of urodynamic and ultrasonographic parameters and subjective assessment, improvements compared to baseline were evident in peak urine fl;ow rate (+11%) residual urine volume (-22%), obstructive symptom score (-46%) and irritative symptom score (-40-%) Exclusions: No details provided

Frasseto 1986 Double blinded (Wilt & Ishani the Cochrane analysis 2011] Control: placebo (n=10). Treatment: *P. africanum* extract 75 mg daily (n=10). 60 days N=20 Italian men. Age range: 50-84, mean 67 years. Lost to follow-up: 0. men with symptomatic BPH "Dysuric symptoms" (nocturia, pollachiuria, reduced strength of flux). Adverse events. Prostate size evaluated by ultrasonography

Gagliardi 1983 Double blinded [Wilt & Ishani the Cochrane analysis 2011] Control: Anti-inflammatory (not identified) (n=20) Treatment: *P. africanum* extract 100 mg daily (n=20). 30 days. N=40 Italian. Age range: 50-84, mean 67 years. Lost to follow up: 1 (2.5%) men with symptomatic BPH Control: Anti-inflammatory (not identified) (n=20) Treatment: P. africanum extract (Tadenan) 100 mg daily (n=20). Treatment duration: 30 days. Peak flow rate; residual volume. Adverse events.

Maver 1972 [Wilt & Ishani the Cochrane analysis 2011] Double blinded Control: placebo (n=30). Treatment: *P. africanum* extract 100 mg daily (n=30). 60 days. N=60 Italian men Age range: 55-85, mean 66 years men with symptomatic BPH Nocturia; residual volume. Adverse events

Ranno 1986 [Wilt & Ishani the Cochrane analysis 2011] Double blinded Control: placebo (n=19). Treatment: *P. africanum* extract 100 mg daily (n=20). N=39 Italian men Mean age: 70 years. Lost to follow-up: 0 2 months.

Rigatti 1983 [Wilt & Ishani the Cochrane analysis 2011] Double blinded Control: NSAID (n=25). Treatment: P*. africanum e*xtract 100 mg daily (n=24). 60 days N=49 Italian men with symptomatic BPH. Lost to follow-up: 0 Residual volume.

Recently in a clinical trial was evaluated the efficacy and safety of an orally dosed herbal preparation containing a mixture of *Cucurbita pepo*, *Epilobium parviflorum*, *Pygeum africanum* and *Serenoa repens* extracts as well as , lycopene, in the management of symptoms of medically diagnosed benign prostate hypertrophy (BPH).

Each commercially available capsule-form herbal formulation containing *C. pepo* seed oil (160 mg), *E. parviflorum* extract (equivalent to 500 mg dry herb), lycopene (2.1 mg), *Prunus africana* (equivalent to 15 g dry stem, standardized to beta-sitosterol) and *S. repens* (equivalent to 660 mg of dry leaf per capsule) with the excipients lecithin, hydrogenated vegetable oil and beeswax and soya oil in a blue softgel capsule. This clinical trial was a short-term phase II randomized double-blind placebo controlled one, which was was conducted on 57 otherwise healthy males aged 40—80 years that presented with

medically diagnosed BPH. The trial participants were assigned to receive 3 months of treatment (1 capsule per day) with either the herbal preparation (n = 32) or a matched placebo capsule (n = 25).

The primary outcome measure was the international prostate specific score (IPSS) measured at baseline, 1, 2 and 3 months. The secondary outcomes were the specific questions of the IPSS and day-time and night-time urinary frequency.

There was a significant reduction in IPSS total median score in the active group of 36% as compared to 8% for the placebo group, during the 3-months intervention ($p < 0.05$). The day-time urinary frequency in the active group also showed a significant reduction over the 3-months intervention (7.0—5.9 times per day, a reduction of 15.6% compared to no significant reduction change for the placebo group (6.2—6.3 times per day) ($p < 0.03$). The night-time urinary frequency was also significantly reduced in the active group (2.9—1.8, 39.3% compared to placebo (2.8—2.6 times, 7%) ($p < 0.004$) (Coulson et al. 2013)

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

Not relevant as it is for use only of adults and elderly males.

Table 4: Clinical studies on humans

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
Barlet 1990 Multicentre study. Double blinded ESCOP 2009 Wilt & Ishani the Cochrane analysis 2011		Control: placebo (n=132). Treatment: P. africanum extract (chloroform extract 100 mg twice daily (n=131). 60 days.	(n=132). Treatment: P. africanum extract (chloroform extract) 100 mg twice daily (n=131). 60 days.	European men with symptomatic BPH			Significant improvement in nocturia ($p<0.007$) peak urine flow ($p<0.02$) residual volume ($p<0.02$) and overall symptoms ($p<0.001$) in the verum group
Blitz 1985 Double blinded		Control: placebo Treatment: P. africanum extract (chloroform extract 100 mg daily 60 days.	N=57 French men Lost to follow-up: 0	men with symptomatic BPH			Overall improvement in symptoms
Bongi 1972 Double blinded: ESCOP 2009 Wilt & Ishani the Cochrane		Control: placebo Treatment: *P. africanum* extract (chloroform extract) 75 mg daily 60 days	N=50 Italian men, residual volume < 200 ml. Age range: 49-84. Lost to follow-up: 0.	men with symptomatic BPH			Significant improvements in noctrurnal micturition frequency ($p<0.01$) dysuria ($p<0.05$) and volume of residual urine

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
analysis 2011							(p<0.01) in the verum group
Chatelain 1999 Double blinded ESCOP 2009 Wilt & Ishani the Cochrane analysis 2011		Treatment 1 -A: *P. africanum* extract (chloroform extract) 50 mg x 2 daily (n=101). Treatment 2 -B: *P. africanum* extract (chloroform extract) 100 mg daily (n=108). 60 days**.**	N=209 French men with symptomatic BPH, age > 50, IPSS 10 or >, PUF < 15 ml/s, residual volume < 150 ml. Mean age: 66 years. Lost to follow-up: 26 (11.1%).	men with symptomatic BPH		235 men were randomized, 223 completed the comparative phase, but only 209 men were valid for per-protocol analysis	Symptom score (IPSS) International Prostate Symptom score Group A the IPSS decreased by 38%, the quality of life score improved by 28% and the max urinary flow rate increased by 16% in Group b the figs were 35%, 28% and 19%. After 12 months the overall IPSS had decreased by 465 and the maximum urinary low rate had increased by 15%
Donkervoort 1977 Double blinded		Control: placebo Treatment: P. africanum extract (chloroform extract) 75 mg daily	N=20 Dutch men Lost to follow-up: 4 (20%).	men with symptomatic BPH			Overall improvement in symptoms; Nocturia; peak urine flow

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
		12 weeks.					
Dufour 1984 Double blinded ESCOP 2009 Wilt & Ishani the Cochrane analysis 2011		Control: placebo (n=60). Treatment: P. africanum extract (chloroform extract) 100 mg daily (n=60). 6 weeks.	N=120 French men Lost to follow-up: 56 (47%).	men with symptomatic BPH not in need of surgery.			Significant improvement ($p<0.01$) in , difficulty in starting micturition and sensation of incomplete voiding of the bladder in the verum group.
Dutkiewicz 1996 Single-site study ESCOP 2009 Wilt & Ishani the Cochrane analysis 2011.	Randomization: unclear	Control: Cernilton 2 tablets three times daily x 2 weeks followed by 1 tablet three times daily up to 4 months (n=51). Treatment: chloroform extract 2 tablets twice daily (38). 24 weeks.	N=89 Polish men Age range: 50-68. Lost to follow-up: 0.	men with symptomatic BPH at Alken stage I and II (no details given)		Obstructive symptom score Irritative symptom score; peak urine flow; residual volume; prostate volume. Adverse events.	From the evaluation of urodynamic and ultrasonographic parameters and subjective assessment, improvements compared to baseline were evident in peak urine fl;ow rate (+11%) residual urine volume (-22%), obstructive symptom score (-46%) and irritative

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
							symptom score (-40-%) Exclusions: No details provided
Frasseto 1986 Double blinded Wilt & Ishani the Cochrane analysis 2011		Control: placebo (n=10). Treatment: P. africanum extract (chloroform extract) 75 mg daily (n=10). 60 days	N=20 Italian men. Age range: 50-84, mean 67 years. Lost to follow-up: 0.	men with symptomatic BPH		"Dysuric symptoms" (nocturia, pollachiuria, reduced strenght of flux). Adverse events.	Prostate size evaluated by ultrasonography
Gagliardi 1983 Double blinded		Control: Anti-inflammatory (not identified) (n=20) Treatment: P. africanum extract (chloroform extract) 100 mg daily (n=20). 30 days.	N=40 Italian. Age range: 50-84, mean 67 years. Lost to followup: 1 (2.5%)	men with symptomatic BPH		Control: Anti-inflammatory (not identified) (n=20) Treatment: P. africanum extract (chloroform extract) 100 mg daily (n=20). Treatment duration: 30 days.	Peak flow rate; residual volume. Adverse events.
Maver 1972		Control: placebo	N=60 Italian men Age	men with		Nocturia;	

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
Double blinded		(n=30). Treatment: P. africanum extract (chloroform extract) 100 mg daily (n=30). 60 days.	range: 55-85, mean 66 years	symptomatic BPH		residual volume. Adverse events	
Ranno 1986 Double blinded		Control: placebo (n=19). Treatment: P. africanum extract (chloroform extract) 100 mg daily (n=20). 2 months.	N=39 Italian men Mean age: 70 years. Lost to follow-up: 0	men with symptomatic BPH	Nocturia; peak urine flow. Adverse events		
Rigatti 1983 Double blinded		Control: NSAID (n=25). Treatment: P. africanum extract (chloroform extract) 100 mg daily (n=24). 60 days	N=49 Italian men with symptomatic BPH. Lost to follow-up: 0.		Residual volume. Adverse events		
Barth 1981 Wilt & Ishani the Cochrane analysis		Control 1: placebo (n=46). Treatment 2: P. africanum extract (Docosanol) 100	N=215 European men, age > 50. Lost to follow-up: 67 (31%).	European men with symptomatic BPH			

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
2011 Double blinded		mg daily (n=50). Control 2: Sitosterin 30 mg (n=34). Treatment 2: P. africanum extract (Docosanol) 100 mg daily (n=37). Control 3: ERU* 300 mg (n=24). Treatment 3: P. africanum extract (Docosanol) 100 mg daily (n=24). 8 weeks.					
Bassi 1987 Double blinded ESCOP 2009 Wilt & Ishani the Cochrane analysis 2011		Control: placebo (n=20). Treatment: P. africanum extract (Pigenil) 100 mg daily (n=20). 60 days.	N=40 Italian men Mean age: 67 years. Lost to follow-up: 0.	men with symptomatic BPH			
Mandressi 1983 Wilt &	Double blinded: yes.	Control 1: placebo (n=20). Control 2:	N=60 Italian men . Age range: 50-80	men with symptomatic BPH		Patient self-rating of "Dysuric	

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
Ishani the Cochrane analysis 2011	Randomization: Identical packaging	Permixon 320mg daily (n=20). Treatment: P africanum extract Average (n=20).30 days. Lost to follow-up: unclear				symptoms" (pain on voiding) Nocturia. Adverse events. Dropouts due to side effects: none	
Krzeski 1993 Double blinded		Treatment 1: P. africanum 25 mg + Urtica dioica 300 mg (n=67). Treatment 2: half dose of above (n=67). 8 weeks.	**N**=134 Polish men Age range: 53-84, mean 64 years. Lost to follow-up: 14.2%.	men with symptomatic BPH (> 1 symptom)		Overall improvement in symptoms; nocturia; peak flow rate; residual volume. Adverse events	
Short-term phase II randomized double-blind placebo controlled one (Coulson et al. 2013	a short-term phase II randomized double-blind placebo control 3	A capsule with Mixture of C. pepo seed oil (160 mg), E. parviflorum (equiv to 500 mg herb), lycopene (2.1 mg), *Prunus africana* (equiv to 15 g dry stem,	57 otherwise healthy males aged 40—80 years that presented with medically diagnosed BPH. with herbal mix (n = 32) or a matched placebo capsule (n = 25).		The primary outcome measure was the international prostate specific score (IPSS) measured at baseline, 1, 2 and 3 months. The secondary	The day-time urinary frequency in the active group showed significant reduction over the 3-months intervention (7.0—5.9 times	There was a significant reduction in IPSS total median score in the active group of 36% as compared to 8% for the placebo group, during the 3-months intervention ($p < 0.05$).

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
	months	standardized to bsitosterol) and S. repens (equivalent to 660 mg of dry herb) with excips: lecithin, hydrogenated vegetable oil and beeswax and soya oil in a blue softgel capsule. Oral administration for 3 months (12 weeks) / 1 caps per day			outcomes were the specific questions of the IPSS and day-time and night-time urinary frequency	per day, a reduction of 15.6% compared to no significant reduction change for the placebo group (6.2—6.3 times per day) ($p < 0.03$). The night-time urinary frequency was also significantly reduced in the active group (2.9—1.8, 39.3% compared to placebo (2.8—2.6 times, 7%) ($p < 0.004$)	

4.4. Overall conclusions on clinical pharmacology and efficacy

A total of 18 randomized controlled trials involving 1562 men met inclusion criteria and were analyzed. Only one of the studies reported a method of treatment allocation concealment, though 17 were double blinded. There were no studies comparing *Pygeum africanum* to standard pharmacologic interventions such as alpha-adrenergic blockers or 5-alpha reductase inhibitors.

The mean study duration was 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 afr*icanum 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 *Pygeum afr*icanum 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 *Pygeum africanum* were mild and comparable to placebo. The overall dropout rate was 12% and was similar between *Pygeum africanum* (13%), placebo (11%) and other controls (8%).

Fourteen trials were excluded because they did not include a control group Wilt & Ishani the Cochrane analysis 2011 (Anonymous 1973; Breza 1998; Diz 1973; Grasset 1974; Greiner 1970; Grévy 1970; Guilland-Vallée 1970; Guillemin 1970; Huet 1970; Lange 1970; Lhez 1970; Martínez-Piñeiro ’73; Robineau 1976; Rometti 1970). The majority of studies examined *Pygeum africanum* alone versus placebo alone (n = 11) Wilt & Ishani the Cochrane analysis 2011 (Barlet 1990; Bassi 1987; Blitz 1985; Bongi 1972; Donkervoort 1977; Dufour 1984; Frasseto 1986; Maver 1972; Ranno 1986; Rizzo 1985). Two trials comparing *Pygeum africanum* against an anti-inflammatory drug Wilt & Ishani the Cochrane analysis 2011 (Gagliardi 1983; Rigatti 1983).

One study comparing *Pygeum africanumto* placebo included an additional treatment arm of *Pygeum africanum* in combination with a steroid (Giacobini 1986). Two studies compared *Pygeum africanum* alone to one or more herbal agents and versus placebo (Barth 1981;Mandressi 1983), one trial compared *Pygeum africanum* to another herbal agent (Dutkiewicz 1996), one trial compared different daily dosage forms of *Pygeum africanum* (Chatelain 1999), and one trial compared two different doses of *Pygeum africanum* in combination with another herbal extract (Krzeski 1993).

12 Clinical trials were made with Soft extract; DER : 114-222 : 1 extraction solvent: chloroform; (stabilized by 1.2 % of ethanol >99.9 %) [Wilt & Ishani the Cochrane analysis 2011]. In total 825 European men (from frnace, italy, Poland, Netherlands) were participated, all 0f them with symptomatic BPH. The duration of the treatment was from 6-12 week (mainly 60 days) with an average dose of 72-100 mg (mainly 100mg, two tabs of 50mg each one). Different parameters have been evaluated while in many case final conclusions were not clear.

The final conclusions showed that a standardized preparation of *Pygeum africanum* 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 doses and preparations and rarely reported outcomes using standardized validated measures of efficacy. Additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. These trials should be of sufficient size and duration to detect important differences in clinically relevant endpoints and use standardized urologic symptom scale scores (Wilt & Ishani the Cochrane analysis 2011).

None of the "active comparison" arms have been conclusively demonstrated to be effective in treating symptomatic benign prostatic hyperplasia

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

5.3. Adverse events, serious adverse events and deaths

Adverse events, serious adverse events and deaths have not been reported so far.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

No data available.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special Warnings and precautions for use

To ensure a safe use the following statement should be labelled:

If adverse reactions occur, a doctor or a qualified health care practitioner should be consulted.

5.5.4. Drug interactions and other forms of interaction

Drug interactions from clinical trials or case studies have not been reported so far.

5.5.5. Fertility, pregnancy and lactation

No fertility data available.

Not relevant in use for pregnancy and lactation.

5.5.6. Overdose

None reported.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

There are no data available from most clinical trials. The common use of pygeum bark proves not to be harmful. Some reported side effects concerning gastrointestinal reactions due to the pygeum bark preparations intake are acceptable.

No adverse events, serious adverse events or deaths as well as no drug interactions from clinical trials or case studies have been reported so far

6. Overall conclusions (benefit-risk assessment)

Pygeum bark and herbal preparation (Soft extract; DER: 114-222 : 1 extraction solvent: chloroform; (stabilized by 1.2 % of ethanol >99.9 %) thereof has been in medicinal use since 1969 in France, so for at least 30 years with at least 15 years in the European Union. The long-standing medicinal use as well pharmacological data make the use in the proposed indication plausible.

There are no sufficient data from well-designed clinical trials to support well-established use in this indication. Therefore the medicinal use of pygeum has to be regarded as traditional in the sense of Dir. 2004/24/EC. However, the outcome of the clinical trials supports the plausibility in the proposed indication.

Indication:

Traditional herbal medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a medical doctor.

Posology

Adults and elderly

Single dose 25- 50mg / Daily dose up to 100mg

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'). 6-12 weeks

Method of administration: Oral use

Administration of pygeum bark preparations can be regarded as safe and justified, when using therapeutic doses. Rarely: digestive disorders (nausea, constipation or diarrhoea) have been referred

Acute and chronic toxicity of the extract was low; signs of toxicity in liver, kidney and heart were observed only with very high doses. Genotoxicity studies gave variable results: the Ames test (strain TA98) gave uniformly negative results, whereas micronucleus test and the Comet assay gave both positive and negative results (Elgorashi et al. 2003; Reid et al. 2006; Taylor et al. 2003; Verschaeve & Van Staden 20080

Due to the lack of adequate on genotoxicity, a European Union list entry is not supported

No constituent with well-known therapeutic activity or active marker can be recognised by the HMPC

Annex

List of references