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

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*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 forms for oral use
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Table of contents

1. Introduction

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

- Herbal substance(s)

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

Pygeum africanum 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 existing monograph of the European Pharmacopoeia (European Pharmacopoeia 1886: 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 1999; DerMarderosian & Beutler 2005; Gruenwald *et al.* 2007; ESCOP 2009; WHO 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 (Gruenwald *et al.* 2007; Bruneton 1999). An evergreen tree, usually 10–25 m high, with straight, cylindrical trunk and dense, rounded crown. Leaves deep green and glossy, alternate, 8–12 cm 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 3–8 cm long; corolla lobes up to 2 mm long. Fruits cherry-shaped, red to purplish-brown, 8–12 mm 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. 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 (Gruenwald *et al.* 2007; Bruneton 1999; Bombardelli & Morazzoni 1997; DerMarderosian & Beutler 2005).

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 (DerMarderosian & Beutler 2005; Gruenwald *et al.* 2007).

Chemical Constituents

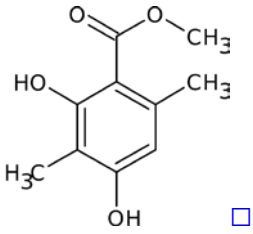
The major components in the bark are fat soluble compounds: the main characteristic constituents are phytosterols (approximately 0.05%), e.g. beta-sitosterol, beta-sitosterol 3-glucoside and beta-sitostenone, free C, -C 24 fatty acids, pentacyclic triterpenic acids are present (14%) (ursolic and oleanolic acid derivatives) and long chain aliphatic alcohols (*n*-docosanol, *n*-tetracosanol and their trans-ferulic acid esters) (Bruneton 1999; Fourneau *et al*. 1996; Bombardelli & Morazzoni 1997, WHO 2009).

The proposed active constituents of a lipophilic extract of Pruni africanae cortex include docosanol (0.6%) and beta-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 1999). 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 (please see below) showed anti-androgenic activities (Schleich *et al*. 2006a, 2006b). 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 pygeum africanum also in *Evernia prunastri* - oakmoss) is well known for its anti-androgenic activity (Schleich *et al*. 2006a, 2006b).



☐ Atraric acid

- Herbal preparation(s)

The request for information exchange concerning preparations from *Prunus africana* (Hook f.) Kalkm., Pruni africanae cortex, pygeum africanum bark revealed that a soft extract (DER 114-222:1), extraction solvent: chloroform; (stabilised by 1.2% of ethanol >99.9%) is distributed in France and previously in other European countries (Italy, Spain, Poland, etc).

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

Not applicable

1.2. 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

Other resources: Library of the National Kapodistrian 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 is 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 specified herbal preparation.

In Czech Republic, a product registered 1984-1999 –withdrawn on request in 1999, the reason is not known, no pharmacovigilance action was taken on this product: Capsules containing Pruni africanae extractum 25 mg/capsules, 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: Capsules containing Pruni africanae extractum 50 mg/capsules, no information on DER and extraction solvent is available.

Indication: Micturition disorders associated with benign prostatic hyperplasia. Posology: 1 capsule twice daily.

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

Moreover, there are the following marketed products in France, Greece and Poland:

France

Well established use

Indication: Treatment in miction moderate disorders connected with BHP

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

   Indication: Treatment in miction moderate disorders connected with benign prostatic hyperplasia (BPH). Posology: A capsule twice daily. A capsule contains 50 mg of extract. Duration of use: 6 weeks (+ 2 weeks) it can be renewed.

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

   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)

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

Greece

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

   Indication (G04C): medicinal product for the relief of lower urinary tract symptoms related to BPH (such as nocturia, polyuria and urinary retention, etc). Posology: 3 capsules daily. Duration of use: 4-6 weeks

Poland

4) Two strengths of a soft extract were used; Pruni africanae corticis extractum siccum (DER 85-250:1), extraction solvent: chloroform.

   25 mg registered between 1985-1987 and then till 2004 of 25 mg capsules and of 50 mg 1985-2013 and then withdrawn.
   Indication: Moderate micturition disorders caused by prostate hyperthophy.

5) tablets, registered in 1987-2003

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 *beta*-sitosterol; extraction solvent methylene chloride. (1987-2003 PL)

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 (46 mg x 2), twice daily, during a meals. Duration: for at least 4 months. The treatment may be repeated if necessary. Contraindications: Hypersensitivity to the active substance or excipients contained in a product or to plants of the Rosaceae family.

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.

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Soft extract; Solvent: stabilised chloroform; DER 114-222:1 (stabilised by 1.2% of ethanol >99.9%)	Treatment in miction moderate disorders connected with BHP	Capsules One capsule twice daily. One capsule contains 50 mg of extract. Duration of use: 6 weeks (+ 2 weeks) it can be renewed	Since 1969 in FR WEU

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Soft extract; Solvent: methylene chloride; DER 200:1	Treatment in miction moderate disorders connected with BHP	Capsules One capsule twice daily. One capsule contains 50 mg of extract. Duration of use: 6 weeks (+ 2 weeks) it can be renewed	Since 2009 in FR WEU
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)	Capsules One capsule 3 times daily. One capsule contains 30 mg of extract. Duration of use: 4-6 weeks	Since 2009 in EL, old type of registration
Soft extract; DER 200:1, extraction solvent: methylene chloride, (46 mg of extract 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).	Tablets Two tablets twice daily. One tablet contains 46 mg of extract. Duration for at least 4 months	1987-2003 in PL
Soft extract; DER 85-250:1, extraction solvent: chloroform.	Moderate micturition disorders caused by prostate hyperthophy.	Capsules Posology not available	1985-1987, 1987-2004 (then withdrawed) in PL
		Capsules Posology not available	1985-2013 (then withdrawn) in PL

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

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

Czech Republic

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: Capsules containing a combination of 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/capsules

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 africanum is valued in Africa. Powdered pygeum africanum bark is used by Africans natives to treat urinary problems (Bruneton 1999; DerMarderosian & Beutler 2005)

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 africanum came to the attention of French scientists who began to investigate its benefits in the treatment of BPH. The lipophilic extract of pygeum africanum bark has been used among the phytomedicines for BPH's symptoms in Europe.

Pygeum africanum bark is used as an anti-inflammatory agent to increase prostatic secretions and to decrease certain hormones in the glandular area, which consequent reduction of hypertrophy. Other actions of pygeum africanum bark 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 BPH stages I and II as defined by Aiken or stages II and III as defined by Vahlensieck.

The Review of natural products (DerMarderosian & Beutler 2005)

In France, pygeum africanum extract has become the primary course of treatment for enlarged prostate. Usual dosage of pygeum africanum extract 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 standardised 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 (LUTS) of 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 pygeum africanum

are a popular ingredient in herbal prostate supplements, with a mechanism related to androgen signalling in BPH.

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form Posology Duration of use**	**Reference**
Liposterolic extracts of pygeum africanum 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 modifications of glandular cells	Doses 25-50 mg up to 100 mg daily	ESCOP 2009 WHO 2009 Gruenwald *et al.* 2007 DerMarderosian & Beutler 2005 Bruneton 1999

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: stabilised 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 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.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Soft extract; Solvent: stabilised chloroform; DER 114-222:1 (stabilised by 1.2% of ethanol >99.9%) since 1969	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. The product is a traditional herbal medicinal product for use in the specified indication exclusively	*Adults and elderly men*: 50 mg two times daily. There is no relevant use in women, children and adolescents under 18 years of age. Duration of use: long-term use is possible	Since 1969 FR

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	based upon long-standing use.		

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

The phytosterols, especially beta-sitosterol, showed potentially anti-inflammatory 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 of the prostate. The beneficial effects on LUTS are ascribed to its protective action on the bladder.

***In vitro* experiments**

Hormonal activity

A lipophilic extract from pygeum africanum bark (200:1, methylene chloride; standardised to 13% sterols) concentration-dependently inhibited the activity of 5α-reductase from rat prostate cells (IC_{50}: 0.78 mg/ml) and of aromatase from human placenta cells IC_{50}: 0.98 mg/ml) (Hartmann *et al.* 1996 in ESCOP 2009). However, an earlier study demonstrated that a lipophlic extract had only slight inhibitory activity (IC_{50}: 63 µg/ml) against 5α-reductase from the human prostate in comparison with the synthetic 5α-reductase inhibitor finasteride (IC_{50}: 1 ng/ml) (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.* 2006a; 2006b) and revealed the highest antiandrogenic activity.

In tissue culture, ethanolic extracts (30%) of pygeum africanum inhibited the growth of PC-3 (prostate cancer-3) and LNCaP (human prostatic cancer cells) cells; induced apoptosis and altered cell kinetics; down regulated ER-α (oestrogen receptor α) and PKC- α (protein kinase C alpha) protein, and demonstrated good binding ability to both mouse uterine oestrogen receptors and LNCaP human androgen receptors (AR) (Shenouda *et al.* 2007).

Recently, atraric acid (AA) and NBBS were isolated from a selective dichloromethane extract of pygeum africanum as two novel AR antagonistic compounds. The molecular mechanisms of AR inhibition were analysed 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 was receptor specific and did not inhibit the closely related glucocorticoid or progesterone receptors. Mechanistically, AA inhibited nuclear transport of AR. Importantly, AA was able to efficiently repress the growth of both the androgen-dependent LNCaP and also the androgen-independent C4–2 PCa cells (prostate cancer cells exhibiting androgen-infdependent growth) but not that of PC-3 or CV1 cells (kidney cell line) lacking AR. In line with this, AA inhibited the expression of the endogenous prostate specific antigen gene in both LNCaP und C4–2 cells. Analyses of cell invasion revealed that AA inhibited the invasiveness of LNCaP cells through extracellular matrix.

According to the authors, 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.* 2010; Roell & Baniahmad 2011).

Anti-inflammatory activity

A lipophilic extract from pygeum africanum bark (not further confirmed) significantly inhibited the synthesis of 5-lipoxygenase metabolites in human polymorphonuclear cells stimulated with the calcium ionophore A23187: 5-HETE (5- Hydroxyeicosatetraenoic acid) ($p<0.001$ at 1 µg/ml), leukotriene B4 LTB4 ($p<0.01$ at 3 µg/ml), 20-hydroxy-LTB4 ($p<0.001$ at 3 µg/ml) and 20-carboxy-LTB4 ($p<0.01$ at 10 µg/ml (ESCOP 2009).

***In vivo* experiments**

Influence on the prostate

Intragastric administration of a lipophilic extract from pygeum africanum 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 in ESCOP 2009). 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 antagonised, as shown by a significant reduction in weight gain of these organs ($p<0.05$). On the other hand, in castrated and adrenalectomies rats the extract potentiated the activity of testosterone on the target organs and increased the content of pituitary gonadotrophins (Thieblot *et al*. 1977 in ESCOP 2009).

Intragastric administration of the extract to rats at 100 mg/kg daily for 3 days also increased prostate secretions (Clavert *et al*. 1986 in 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%) (Shenouda *et al*. 2007).

Influence on bladder function

A lipophilic extract of the crude drug administered intragastrically to rats inhibited spasms of the bladder induced by electroshock, phenylephrine, adenosine triphosphate and carbachol (WHO 2009). 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 2009). 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).

After intragastric pre-treatment of rabbits with a lipophilic extract from pygeum africanum bark at 1, 10 and 100 mg/kg 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 ($p<0.05$) (Lowe & Ku 1996).

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 (Chen. *et al*. 1999).

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 pre-treatment 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 weight/day). The second group was treated with vehicle (peanut oil). Five rabbits from each group were subjected to either bilateral ischemia for 1 hour or 3 hours and then reperfused for either 1 hour 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 weight/day protected the bladder from the contractile dysfunctions induced by bilateral ischemia followed by reperfusion. According to the authors 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 mg/kg/day 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*. 1996; 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 ($p<0.01$) (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. Intragastric administration of a lipophilic extract from pygeum africanum bark (100 mg/kg/day for 2 weeks before, 2 weeks during and 3 weeks after DHT (dihydrotestosterone) treatment) significantly reduced micturition frequency ($p<0.05$) and normalised 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 100 mg/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 africanum 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 (Marcoli *et al*. 1986 in ESCOP 2009).

Table 4: Overview of the main non-clinical data/conclusions on pygeum africanum bark

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
lipophilic extract from pygeum bark (200:1, methylene chloride; standardised to 13% sterols)		*In vitro*	Hartmann *et al*. 1996 in ESCOP 2009	Inhibition of 5α -reductase from rat prostate cells (IC_{50}: 0.78 mg/ml) and of aromatase from human placenta cells ($1C_{50}$: 0.98 mg/ml)
Lipophilic extract had only slight inhibitory activity		*In vitro*	Rhodes *et al*. 1993 in ESCOP 2009	Inhibition of 5α-reductase from the human prostate (IC_{50}: 63 µg/ml) in comparison with the synthetic 5α-reductase inhibitor finasteride (IC_{50}: 1 ng/ml)
Lipophilic extract and pure atraric acid together with N-butylbenzenesulfonamide		*In vitro*	Schleich *et al.* 2006a; 2006b	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 of 10-50 µg/ml culture medium	*In vitro*	Schmidt *et al*. 2013	*Pygeum africanum* extract 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.
Ethanolic extracts of pygeum africanum	Ethanolic extracts (30%)	*In vivo*	Shenouda *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 oestrogen receptors and LNCaP human androgen receptors
A lipophilic extract		*In vivo*	ESCOP 2009	significantly inhibited the synthesis of 5-lipoxygenase metabolites in human polymorphonuclear cells stimulated with the calcium ionophore A23187: 5-HETE ($p<0.001$ at 1 ng/ml), LTB4 ($p<0.01$ at 3 ng/ml),20-hydroxy-LTB 4 ($p<0.001$ at 3 ng/ml) and 20-

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				carboxy-LTB4 ($p<0.01$ at 10 ng/ml)
Lipophilic extract from pygeum bark	Intragastric administration to rats at 2 mg/kg body weight daily for 20-50 days	*In vivo*	Thieblot *et al*. 1971 in ESCOP 2009	prevented the development of prostatic hyperplasia induced by injection of human prostate adenoma tissue
Lipophilic extract from pygeum bark	Intraperitoneal administration to castrated rats at a and 10 mg/kg body weight daily for 20 days	*In vivo*	Thieblot *et al*. 1977 in ESCOP 2009	stimulated the secretory activity of the prostate and seminal vesicules, significant reduction in weight gain of these orgnas, potentiated the activity of testosterone on the target organs
Lipophilic extract from pygeum bark	Intragastric administration of the extract to rats at 100 mg/kg daily for 3 days	*In vivo*	Clavert *et al*. 1986 in ESCOP	Increased prostate secretions
Lipophilic extract from pygeum bark	Administered intragastrically to rats 100 mg/kg body weight	*In vivo*	WHO 2009	It inhibited spasms of the bladder induced by electroshock, phenylephrine, adenosine triphosphate and carbachol.
A lipophilic extract of the crude drug improved the contractility of the detrusor muscle of the bladder in old rats (Riffaud & Lacolle 1990).	intragastric administration to guinea-pigs	*In vivo*	(WHO 2009)	A reduction in carbachol-induced spasms of the bladder was observed Prevention of development of contractile dysfunction induced by partial obstruction of the bladder, in old rats
Lipophilic extract from pygeum bark	In old rats (Riffaud & Lacolle 1990).	*In vivo*	Riffaud & Lacolle 1990	Improvement of the contractility of the detrusor muscle of the bladder of the animals
Lipophilic extract from pygeum bark	Intragastric pre-treatment of rabbits with a at 1,10 and 100 mg/kg body weight daily for 3 weeks, and further treatment for 2 weeks combined with partial bladder outlet obstruction	*In vivo* *In vitro*	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 ($p<0.05$).

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Chlorophorm extract of pygeum bark	Intragastrically administered to rabbits at 100 mg/kg/day for 3 weeks	*In vivo*	Levin *et al*. 1996	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
Chlorophorm extract of pygeum bark	One group was pre-treated by oral gavage for 3 weeks with chloroform extract (3.0 mg/kg body weight/day). The second group was treated with vehicle (peanut oil). relevant dose of 3.0 mg/kg body weight /day	*In vivo*	Levin *et al*. 2002	The results show that the used chloroform extract pre-treatment protected the bladder from the contractile dysfunctions induced by bilateral ischemia followed by reperfusion.
Chlorophorm extract of pygeum bark	intragastric administration of the extract to rabbits (30 mg/kg/day for 3 weeks) for 2 weeks	*In vivo*	Levin *et al*. 2005	This experiment resulted in reduced bladder hypertrophy, improved contractile responses and reversal of the induced structural damage to cellular and subcellular membranes
Lipophilic extract from pygeum bark	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 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. Intragastric 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 normalised 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 100 mg/kg/day suppressed the effects on micturition frequency and volume.

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
A lipophilic extract from pygeum bark	Administered intragastrically at 400 mg/kg body weight, markedly reduced carrageenan-induced paw oedema in rats. intraperitoneally at 10 and 100 mg/kg	*In vivo*	Marcoli *et al*. 1986; ESCOP 2009	The extract inhibited the increased vascular permeability caused by histamine
A lipophilic extract from pygeum bark	Administered orally/intragastrically 100 mg/kg/day body weight, in rats/rabbits	*In vivo*	Wang *et al*. 2010; Yongzhi 2008	Protective effect against ischemic damage to the bladder. Suppression effectively the oxidative stress in diabetic bladder and reduced levels of hydroxyproline, TGF-beta1, and bFGF.
A lipophilic extract from pygeum bark	Administered 100 mg/kg/day body weight, in rabbits		Chen 1999	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.

3.1.2. Secondary pharmacodynamics

Antiproliferative effects

The effect of pygeum africanum (PA) extract on the proliferation of cultured human prostatic myofibroblasts and fibroblasts was investigated. Primary cultures of prostatic stromal cells were obtained from histologically confirmed human BPH by enzymatic digestion. Cell proliferation was measured by 5-bromo-2'-deoxy-uridine (BrdU) incorporation assays, and cytotoxicity by luminescent quantification of adenylate kinase activity. Cultured cells were labelled by an antivimentin antibody, and most of them by an α−smooth-muscle-actin antibody, revealing the presence of fibroblasts and myofibroblasts. BrdU incorporation tests showed that proliferation of cultured human stromal cells, stimulated by foetal calf serum, by basic fibroblast growth factor and by epidermal growth factor, was dose dependently inhibited by PA extract (5–100 µg/ml). Except at 100 µg/ml, no acute cytotoxicity of the extract was detected after 24 hours of culture. Similarly, the extract dose dependently inhibited the proliferation of Madin–Darby canine kidney epithelial cells, but to a lesser extent; whatever the dose of extract, no acute toxicity was evident on this cell line. The pygeumafricanum extract inhibited the proliferation of cultured human prostatic myofibroblasts and fibroblasts. It was proposed that cultured human prostatic cells offer a reliable model for preclinical screening of therapeutic agents, and to study the mechanisms underlying the inhibition of proliferation (Boulbès *et al*. 2006).

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 ($p<0.05$) (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 inhibited the proliferation of both non-stimulated cells IC_{50}: 14.4 µg/ml and cells stimulated by the mitogenic growth factors EGF, insulin-like growth factor-1 and b-FGF (IC_{50} values of 4.6, 7.7, 12.6 µg/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 IC_{50} values of 12.4 and 8.1 µg/ml respectively, compared to an IC_{50} of approximately 1 nM for the PKC inhibitor staurosporine (Yablonsky *et al*. 1997; ESCOP 2009; Quiles *et al.* 2010).

As *Prunus africana* together with other plants (*Withania somnifera*, *Warbugia ugandensis*, and *Plectrunthus barbatus*) are used traditionally in Kenya for treatment of 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. *P. 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. According to the authors 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 IC_{50} cytoxicity levels much higher than 100 mg/ml when evaluated in IEC-6 cells (Mwitari *et al.* 2013).

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*) 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, 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. According to the authors, 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).

Antimicrobial activities

The previous referred plant combination (pygeum together with *Withania*, *Warbugia*, and *Plectrunthus barbatus*) are used also 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).

Oxidative stress in early diabetes induced bladder

In the diabetic rat bladder, early treatment with *P. africana* could effectively suppress oxidative stress (Wang 2010), also bladders of diabetic rats had reduced levels of hydroxyproline, TGF beta1, and bFGF following extract administration (Yongzhi 2008)

3.1.3. Safety pharmacology

No data available

3.1.4. Pharmacodynamic interactions

No data available

3.1.5. Conclusions

Experimental preclinical data presenting influence on urinary function, anti-androgenic, anti-inflammatory and antioxidant effects of pygeum africanum bark gives some rationale for the long tradition of their therapeutic use in benign prostatic hyperplasia. The published data on pharmacological activities support the traditional use of preparations containing pygeum africanum 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 available

Due to lack of 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

Single doses of the lipophilic (chloroform) 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 & Morazzoni 1997).

3.3.2. Repeat dose 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 (Andro & Riffaud 1995).

No adverse reactions were observed after daily intragastric administration of the extract to mice at 60 mg/kg or rats at 600 mg/kg bodyweight for 11 months (Bombardelli & 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 (Andro & Riffaud 1995; 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 were of the opinion that positive results in these cellular tests caused by plant extracts may sometimes be artificial.

Assessor's conclusion

In conclusion, the 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; especially 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 (Elgorashi et al. 2003;Taylor et al. 2003; Verschaeve 2004; Verschaeve & Van Staden 2008). 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).

3.3.4. Carcinogenicity

No studies on carcinogenicity were found in the literature.

3.3.5. Reproductive and developmental toxicity

The pygeum bark extract at doses up to 80 mg/kg/day had no effect on fertility in male rats or rabbits (Andro & Riffaud 1995). The assays did not follow the International standards, hence were taken into consideration.

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

2004; Verschaeve & Van Staden 2008; ESCOP 2009). Thus, the use of the extracted is accepted as safe.

3.4. Overall conclusions on non-clinical data

Experimental preclinical data presenting influence on urinary function, anti-androgenic, anti-inflammatory and antioxidant effects of pygeum africanum bark gives some rationale for the long tradition of their therapeutic use in benign prostatic hyperplasia. The published data on pharmacological activities support the traditional use of preparations containing pygeum africanum bark in the proposed indication.

Tests on carcinogenicity have not been performed. Adequate tests on genotoxicity and reproductive toxicity have not been performed.

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)

Ishani *et al.* 2000: Trials were searched in computerised general and specialised 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 randomised controlled trials involving 1562 men met inclusion criteria and were analysed. Only one of the studies reported a method of treatment allocation concealment, though 17 were double blinded. 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 quite short of only 64 days and not longer, and the daily dose of extract ranged from 75 to 200 mg. Data from 6 placebo-controlled studies involving 474 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 $p<0.05$) improved urologic symptoms and flow measures.

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 & Morazzoni 1997, Ishani *et al*. 2000; ESCOP 2009,).

Chatelain *et al*. 1999: Two different daily dosage regimens for a lipophilic extract from pygeum bark were compared in a randomised study. Out of 235 BPH patients on commencement 209 completed a 2-month double blind phase (quite short again), 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%, the quality of 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 IPSS had decreased by 46% and the maximum urinary flow rate had increased by 15%.

Methods: Patients with symptomatic benign prostatic hyperplasia (BPH) entered a 2-month randomised, 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: 209 patients completed the comparative phase in compliance with the protocol; One hundred seventy four 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. *Pygeum africanum* extract at 50 mg twice daily and 100 mg once daily proved equally effective and safe at a short period of 2 months and it was never repeated in any longer period study. Further improvements in efficacy with a satisfactory safety profile were documented after 12 months.

ESCOP 2009: In an older work the effect of *Pygeum africanum* (25 mg/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. Fifty patients were included who received 3 capsules daily for a short period of 45 days. The following conclusions were achieved: a) *Pygeum africanum* is useful in the treatment of acute and chronic prostatitis, 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 dysfunction.

Hutchinson *et al*. 2007: 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 watchful waiting 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.

Wilt and Ishani, 2011: The Cochrane meta-analysis (Wilt and Ishani, 2011) recently summarised 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 quite short of about 64 days (range 30 - 122 days). Compared to men receiving placebo, *P. africana* provided a moderately 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* reported 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%).

Excluded studies had no control group : Breza 1998, Diz 1973, Grasset 1974, Greiner 1970, Grévy 1970, Guilland-Vallée 1970, Guillemin 1970, Huet 1970, Lange 1970, Lhez 1970, Martínez-Piñeiro 1973, Robineau 1976, Rometti 1970.

In conclusion 12 clinical trials were made with soft extract; DER 114-222:1 extraction solvent: chloroform; (stabilised by 1.2% of ethanol >99.9%) 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 men (from France, Italy, Poland, Netherlands) were participated, all of them with symptomatic BPH. The duration of the treatment was short from 6-12 week (mainly 60 days) with an average dose of 72-100 mg (mainly 100 mg, 2 tablets of 50 mg each one). Different parameters have been evaluated while in many cases final conclusions were not at all clear.

Barlet 1990: Multicentre study. Double blinded (n=132). Treatment: *Pygeum africanum* extract 100 mg twice daily (n=131). Duration of 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 symptom ($p<0.001$) in the verum group 5 patients stopped their treatment due to gastrointestinal problems.

Blitz *et al.* 1985 (ESCOP 2009; Wilt & Ishani the Cochrane analysis 2011): Double blinded. Control: placebo. Treatment: *Pygeum africanum* extract 100 mg daily. Duration of the study 60 days. Lost to

follow-up: 0. Patients were French men (n=57) with symptomatic BPH. Outcome: overall improvement in symptoms.

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

Donkervoort *et al.* 1977 (Wilt & Ishani the Cochrane analysis 2011): Double blinded. Control: placebo. Treatment: *Pygeum africanum* extract 75 mg daily 12 weeks. Patients were Dutch men with symptomatic BPH (n=20). Lost to follow-up: 4 (20%). Outcomes: overall improvement in symptoms, nocturia, peak urine flow.

Dufour *et al.* 1984: Double blinded. Control: placebo (n=60). Treatment: *Pygeum africanum* extract 100 mg daily (n=60). Duration of the study 6 weeks (42 days). Lost to follow-up: 56 (47%). Patients were French men with symptomatic BPH not in need of surgery (n=120). Significant improvement ($p<0.01$) in difficulty in starting micturition and sensation of incomplete voiding of the bladder in the verum group.

Dutkiewicz 1996: (ESCOP 2009; Wilt & Ishani the Cochrane analysis 2011): Single-site study. Randomisation: 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: commercial lipophilic extract 2 tablets 50 mg (100 mg) twice daily. Duration of the study 24 weeks. Age range: 50-68. Lost to follow-up: 0. Polish men with symptomatic BPH at Alken stage I and II (no details given) (n=89). Outcomes: obstructive symptom score, irritative symptom score, peak urine flow, residual volume, prostate volume, adverse events. From the evaluation of urodynamic and ultra-sonographic parameters and subjective assessment, improvements compared to baseline were evident in peak urine flow rate (+11%) residual urine volume (-22%), obstructive symptom score (-46%) and irritative symptom score (-40-%) Exclusions: No details provided.

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

Gagliardi 1983 (Wilt & Ishani the Cochrane analysis 2011): Double blinded. Control: Anti-inflammatory (not identified) (n=20). Treatment: *Pygeum africanum* extract 100 mg daily (n=20). Duration of the study 30 days. Age range: 50-84, mean 67 years. Lost to follow up: 1 (2.5%). Italian men with symptomatic BPH (n=40). Outcomes: peak flow rate, residual volume, adverse events.

Maver 1972 (Wilt & Ishani the Cochrane analysis 2011): Double blinded. Control: placebo (n=30). Treatment: *Pygeum africanum* extract 100 mg daily (n=30). Duration of the study 60 days. Age range: 55-85, mean 66 years. Italian men with symptomatic BPH (n=60). Outcomes: nocturia, residual volume, adverse events.

Ranno *et al.* 1986 (Wilt & Ishani the Cochrane analysis 2011): Double blinded. Control: placebo (n=19). Treatment: *Pygeum africanum* extract 100 mg daily (n=20). Italian men with symptomatic BPH (n=39). Mean age: 70 years. Lost to follow-up: 0. Treatment duration: 2 months.

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

Coulson *et al*. 2013: Recently in a clinical trial the efficacy and safety was evaluated 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, standardised 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 soft gel capsule. This clinical trial was a short-term phase II randomised double-blind placebo controlled one, which 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).

Descazeaud *et al*. 2015: In France, pygeum africanum extract (PAE) is among the well-known herbal medicines used in BPH (treatment for enlarged prostate) from the French Authorities (HAS transparency commission 2011 Journal) together with *Serenoa repens* 2015 containing herbal medicines) and the French association of urologists (AFU) admit is as safe and plausible (Descazeaud *et al*. 2015).

The guidance to physicians regarding LUTS associated with BPH, written in cooperation with the French society of Urology (AFU) (Descazeaud 2015) indicated BPH 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.

In a review by **Andro & Riffaud 1995**, in total 12 double-blind, placebo-controlled studies on *P. africana* are summarised. These studies used objective measurements (maximum flow, voided volume, residual volume, nocturia, daytime frequency) to determine the efficacy of *P. africana* extract in alleviating BPH symptoms. Within the 12 reviewed studies, 358 evaluated patients received the proposed chloroform extract of *P. africana* whereas 359 received placebo. All 12 studies demonstrated efficacy of the extract compared to placebo - the review concluded that “pygeum africanum bark extract is well-tolerated treatment for mild and moderate symptomatic BPH”, butin almost all cases the duration of the studies was short (mainly 60 days).

The placebo effect regarding miction problems can be quite large for men suffering from BPH (Dufour 1984) and a difference of objective measures within 2 months between extract and placebo group in a double-blind setting is a short period (Gravas *et al*. 2015).

Assessor’s comment: Although the placebo effect regarding miction problems can be quite large for men suffering from BPH and a study period of 2 months is short, the clinical studies could be taken into consideration for the plausibility of the use of Pruni africanae cortex.

In an older review of Andro & Riffaud 1995, results from an open-label study with a several-year follow-up were included, stating only some weak clinical and urodynamic improvements (Moya-Prats 1989).

Table 5: Clinical studies on humans

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Barlet 1990 Multicentre study. (in Wilt & Ishani 2011; ESCOP 2009)	Multicentered Double blinded	Treatment: Pygeum africanum extract (chloroform extract 100 mg twice daily). 60 days	Control: placebo (n=132) (n=131)	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	No data available in Wilt & Ishani 2011; ESCOP 2009	Multicentered double blinded clinical study with unclear overall dropout rate and short duration (60 days).
Blitz 1985 (in Wilt & Ishani 2011)	Double blinded	Control: placebo Treatment: Pygeum africanum extract (chloroform extract 100 mg daily 60 days	N=57 French men Lost to follow-up: 0	men with symptomatic BPH	Improvement of BPH measured symptoms without clear data about potential risks	No data available in Wilt & Ishani 2011	Double blinded clinical study with insufficient size (N=57) and short duration (60 days)
Bongi 1972 (in Wilt & Ishani 2011; ESCOP 2009)	Double blinded	Control: placebo Treatment: Pygeum 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 nocturnal micturition frequency ($p<0.01$) dysuria ($p<0.05$) and volume of residual urine ($p<0.01$) in the verum group	No data available in Wilt & Ishani 2011; ESCOP 2009	Double blinded clinical study with insufficient size (N=50) and short duration (60 days).
Chatelain *et al.* 1999 (in Wilt & Ishani 2011; ESCOP 2009)	Double blinded	Treatment 1 -A: Pygeum africanum extract (chloroform extract) 50 mg x 2 daily (n=101). Treatment 2 -B: Pygeum africanum extract (chloroform extract) 100	N=209 French men with symptomatic BPH, age > 50, IPSS 10 or >, PUF<15 ml/s,	men with symptomatic BPH	International Prostate Symptom score Group A the IPSS decreased by 38%, the quality of life score improved by 28% and the maximum urinary	235 men were randomised, 223 completed the comparative phase, but only 209 men	Double blinded study with overall dropout rate (11.1%) and short duration (60 days).

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		mg daily (n=108). 60 days.	residual volume <150 ml. Mean age: 66 years Lost to follow-up: 26 (11.1%)		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%	were valid for per-protocol analysis	
Donkervoort *et al.* 1977 (in Wilt & Ishani 2011)	Double blinded	Control: placebo Treatment: Pygeum africanum extract (chloroform extract) 75 mg daily 12 weeks	N=20 Dutch men Lost to follow-up: 4 (20%)	men with symptomatic BPH	Overall improvement in symptoms; Nocturia; peak urine flow	No data available_in Wilt & Ishani 2011	Insufficient size of study (N=20) with very high overall dropout rate (20%) and short duration.
Dufour *et al.* 1984 (in Wilt & Ishani 2011; ESCOP 2009)	Double blinded	Control: placebo (n=60). Treatment: Pygeum 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	No data available in Wilt & Ishani 2011; ESCOP 2009	Double blinded clinical study with insufficient size (N=120), very high overall dropout rate (47%) and very short duration (6 weeks only) to be further evaluated.
Dutkiewicz 1996 (in Wilt & Ishani 2011; ESCOP 2009)	Randomisation: unclear Single-site study	Control: Cernilton 2 tablets three times daily x 2 weeks followed by 1 tablet three times daily	N=89 Polish men Age range: 50-68 Exclusions: No details	Men with symptomatic BPH at Alken stage I and	From the evaluation of urodynamic and ultra-sonographic parameters and subjective	Obstructive symptom score Irritative	Double blinded clinical trial with unclear dropout rate scale scores

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		up to 4 months (n=51). Treatment: chloroform extract 2 tablets twice daily 24 weeks	provided	II (no details given)	assessment, improvements compared to baseline were evident in peak urine flow rate (+11%) residual urine volume (-22%), obstructive symptom score (-46%) and irritative symptom score (-40-%)	symptom score; peak urine flow; residual volume; prostate volume. Adverse events.	with varying posologies (6 tablets daily for 2 weeks) followed by 3 tabs daily for another 16 weeks.
Frasseto *et al.* 1986 (in Wilt & Ishani 2011)	Double blinded	Control: placebo (n=10). Treatment: Pygeum 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	Prostate size evaluated by ultrasonography. Dysuric symptoms" (nocturia, pollachiuria, reduced strength of flux).	No data available in Wilt & Ishani 2011	Small Double blinded study (N=20) with short duration (60 days).
Gagliardi 1983 (in Wilt & Ishani 2011)	Double blinded	Control: Anti-inflammatory (not identified) (n=20) Treatment: Pygeum 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	Peak flow rate; residual volume. Adverse events	No data available in Wilt & Ishani 2011	Insufficient size of double blind study (N=40) with too short duration (30 days).
Maver 1972 (in Wilt & Ishani 2011)	Double blinded	Control: placebo (n=30). Treatment: Pygeum africanum extract (chloroform extract) 100 mg daily (n=30).	N=60 Italian men Age range: 55-85, mean 66 years	men with symptomatic BPH	Nocturia; residual volume. Adverse events	No data available in Wilt & Ishani 2011	Insufficient size of the study (N=60) with high overall dropout rate (20%) and short

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		60 days					duration (60 days) to detect important clinical relevance.
Ranno *et al.* 1986 (in Wilt & Ishani 2011)	Double blinded	Control: placebo (n=19). Treatment: Pygeum 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	No data available in Wilt & Ishani 2011	Small Double blinded study (N=39) and short duration (60 days).
Rigatti *et al.* 1983 (in Wilt & Ishani 2011)	Double blinded	Control: NSAID (n=25). Treatment: Pygeum africanum extract (chloroform extract) 100 mg daily (n=24). 60 days	N=49 Italian men with symptomatic BPH. Lost to follow-up: 0.	Symptomatic BPH	Residual volume, adverse events	No data available in Wilt & Ishani 2011	Insufficient size of the study (N=49) with short duration (60days).
Barth 1981 (in Wilt & Ishani 2011)	Double blinded	Control 1: placebo (n=46). Treatment 2: Pygeum africanum extract (Docosanol) 100 mg daily (n=50). Control 2: Sitosterin 30 mg (n=34). Treatment 2: Pygeum africanum extract (Docosanol) 100 mg daily (n=37). Control 3: ERU* 300 mg	N=215 European men, age > 50. Lost to follow-up: 67 (31%),	European men with symptomatic BPH	No outcome reported	No data available in Wilt & Ishani 2011	Clinical study with unexplained high overall dropout rate (31%) and short duration (56 days).

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		(n=24). Treatment 3: Pygeum africanum extract 100 mg daily (n=24). 8 weeks.					
Bassi 1987 (ESCOP 2009; Wilt & Ishani 2011)	Double blinded	Control: placebo (n=20). Treatment: Pygeum africanum extract 100 mg daily (n=20). 60 days.	N=40 Italian men Mean age: 67 years. Lost to follow-up: 0	men with symptomatic BPH	No clear final outcome	No data available in Wilt & Ishani 2011; ESCOP 2009	Insufficient size of the study (N=40) with short duration.(60 days)
Mandressi 1983 (in Wilt & Ishani 2011)	Double blinded: yes. Randomisation: Identical packaging	Control 1: placebo (n=20). Control 2: Permixon 320 mg daily (n=20) Treatment: Pygeum africanum extract Average (n=20).30 days. Lost to follow-up: unclear	N=60 Italian men. Age range: 50-80	men with symptomatic BPH	Patient self-rating of "Dysuric symptoms" (pain on voiding) Nocturia. Adverse events. Dropouts due to side effects: none	No data available in Wilt & Ishani 2011	Insufficient size of the study (N=60) with unclear dropout rate and very short duration (30 days).

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.

4.4. Overall conclusions on clinical pharmacology and efficacy

Wilt & Ishani the Cochrane analysis 2011: A total of 18 randomised controlled trials involving 1562 men met inclusion criteria and were analysed. 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 too short of mainly 64 days (range, 30 to 122 days), while several of the existing clinical studies did not report adequate results in a method that permitted proper meta-analysis.

Compared to men receiving placebo, pygeum africanum 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)]).

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 (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 197373; Robineau 1976; Rometti 1970 – all cited in Wilt & Ishani 2011).

Twelve Clinical trials were made with Soft extract; DER 114-222:1 extraction solvent: chloroform; (stabilised by 1.2% of ethanol >99.9%) (Wilt & Ishani the Cochrane analysis 2011). In total 825 European men (from France, Italy, Poland, Netherlands) were participated, all of 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 100 mg, 2 tablets of 50 mg each one). Different parameters have been evaluated while in many case final conclusions were not clear.

The final conclusions showed that preparation of pygeum africanum bark may be a useful treatment option for men with lower urinary symptoms consistent with BPH. 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 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 standardised urologic symptom scale scores.

None of the “active comparison” arms have been conclusively demonstrated to be effective in treating symptomatic BPH.

5. Clinical Safety/Pharmacovigilance

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

No data available

5.2. Patient exposure

Aside from market presence and data from studies, there are no concrete data concerning 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

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

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 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.

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 as it is for use only for adults and elderly males.

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

The common use of pygeum africanum bark proves not to be harmful. Thirteen of the eighteen studies provided information on specific adverse events. Adverse events due to pygeum africanum bark were generally mild in nature and comparable in frequency to placebo. The most frequently reported adverse events were gastrointestinal and occurred only among seven men in five trials. Overall, few side effects of gastrointestinal reactions due to the pygeum africanum bark preparations intake have been reported.

No 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 africanum bark and herbal preparation (Soft extract; DER 114-222:1 extraction solvent: chloroform; (stabilised 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 africanum bark has to be regarded as traditional in the sense of Directive 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 BPH after serious conditions have been excluded by a medical doctor.

Posology*; Adults and elderly*: Single dose 50 mg / Daily dose 100 mg

No adequate fertility data available.

There is no relevant use in women, adolescents and children, as it is for use only for adults and elderly males.

Duration of use: Long-term use is possible (see section 4.4 ‘Special warnings and precautions for use’).

Method of administration: Oral use

Acute and chronic toxicity of the extract was low; signs of toxicity in liver, kidney and heart were observed only with very high doses.

No studies on carcinogenicity were found in the literature

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).

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

Due to the lack of adequate data 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