EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2012
EMA/HMPC/461156/2008
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Urtica dioica* L., *Urtica urens* L., their hybrids or their mixtures, radix

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Nettle root consist of the whole, cut or powdered dried root and rhizomes *of Urtica dioica* L. *Urtica urens* L, their hybrids or mixtures of these.
Herbal preparation(s)	Comminuted herbal substance Liquid extract, extraction solvent ethanol Dry extract, extraction solvent methanol Dry extract, extraction solvent ethanol
Pharmaceutical forms	Herbal preparation in solid or liquid dosage forms or as an herbal tea for oral use.
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1. Introduction

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

- Herbal substance(s)

Definition of the herbal substance:

German Pharmacopoeia (Deutsches Arzneibuch - DAB 10, 1993), ESCOP monographs (ESCOP 1996, 2003), WHO monograph (WHO 2002):

Nettle root consists of the whole, cut or powdered dried root and rhizomes of *Urtica dioica* L., *Urtica urens* L., their hybrids or mixtures of these.

British Herbal Pharmacopoeia (BHP) (BHP 1996), British Herbal Compendium (Bradley 2006):

Nettle root consist of the dried rhizomes and roots of *Urtica dioica* L.

Phytotherapie in der Urologie (Schilcher & Wülker 1992):

Plant sources: Mainly *Urtica dioica* L.*,* common nettle, but occasionally also *U. urens* L., small nettle and/or their hybrids. Plant part: the whole subterranean part (rhizome and radix).

Description of the herbal substance:

German Pharmacopoeia (Deutsches Arzneibuch - DAB 10, 1993)

British Herbal Pharmacopoeia (BHP 1996)

Phytotherapie in der Urologie (Schilcher & Wülker 1992)

Hagers Handbuch der Pharmazeutischen Praxis. Drogen L-Z. (Blaschek et al. 1998)

WHO monographs (WHO 2002)

- Herbal preparation(s)

The following preparations were reported in literature or have been available on the market (see details on DERs and concentration of extraction solvents under the paragraph 2.2.' Information on traditional/current indications and specified substances/preparations').

Herbal tea:

Comminuted herbal substance for infusions

Powdered herbal substance

Extracts:

Liquid extract, extraction solvent water

Liquid extract, extraction solvent ethanol

Dry extract, extraction solvent methanol

Dry extract, extraction solvent ethanol

Dry extract extraction solvent: diethyl ether

Constituents:

Based on Blaschek 1998; ESCOP 2003; Mills 2003; Blumenthal 2000; Bruneton 1999; Wichtl 2002; Bradley 2006:

Lectins: 0.05-0.6% *Urtica dioica* agglutinin (UDA). UDA is a small monomeric protein with a molecular weight of 8.5 kDa, consisting of 89 amino acid residues including two 43-amino acid, glycine- and cysteine-rich domains. UDA is a mixture of at least 6 similar isolectins.

Polysaccharides: Approximately 0.85%. Five polysaccharides have been isolated (RP1-RP5), of which two are glucans with [1→4]-linked glucose units but differing in MW (15 and 50 kDa), degree of branching and acidity; two are rhamnogalacturonans of MW 18 and 210 kDa; and the fifth is an acidic arabinogalactan of MW 70 kDa consisting of a [1→3]-linked galactan chain with arabinose side chains.

Lignans: 1,4-Butandiol-type lignans: 0.004% secoisolariciresinol-9-O-β-D-glucoside; 8.O.4'-Arylether-type lignans: 0.002% 7'(*E*)-7-O-β-D-glucopyranosyl-4,4',7,9,9'-pentahydroxy-3,3'-dimethoxy-8.O.4'-lignan, 0.001% 7'(*E*)-4,4',7,9,9'-pentahydroxy-3,3'-dimethoxy-8.O.4'-lignan Monoepoxylignans: 0.003% neo-olivil, 0.004% neo-olivil-4-O-β-D-glucoside, 0.001% 9-acetyl-neo-olivil , 0.006% 9-acetyl-neo-olivil-4-O-β-D-glucoside, 0.006% 9'-acetyl-neo-olivil-4-O-β-D-glucoside, 0.007% 9,9'-bisacetyl-neo-olivil, 0.01% 9,9'-bisacetyl-neo-olivil-glucosid. *Urtica dioica* roots contain lignans in higher amount than *Urtica urens* roots.

Sterols: 0.2-1% β-sitosterol, 0.032-0.2% β-sitosterol-3-O-β-glucoside (in *Urtica dioica* roots the ratio of the former two compounds is between 2:1 and 1:1, in case of *Urtica urens* roots the ratio is 4:1), 0.003% (6'-O-palmitoyl)-sitosterol-3-O-β-D-glucoside, 0.001% 7β –hydroxysitosterol, 0.001% 7α-hydroxysitosterol, 0.0005% 7β -hydroxysitosterol-β-D-glucoside, 0.0005% 7α-hydroxysitosterol-β-glucoside, 0.0015% 24*R*-ethyl-5α-cholestane-3β,6α-diol, stigmasterol, campesterol, stigmast-4-en-3-on, hecogenin.

Phenylpropanes: 0.002% Homovanillyl alcohol and its 4'-glucoside (0.003%)

Ceramides: Two groups of ceramides, consisting of a sphingoid base (2-amino-1,3,4-trihydroxy-8-octadecene) with an amido link from the amino group to an unbranched C_{20}-C_{25} fatty acid or corresponding 2-hydroxy fatty acid, have been identified.

Hydroxy fatty acids: (10*E*,12*Z*)-9-hydroxy-10-12-octadecadienoic acid, (9*Z*,11*E*)-13-hydroxy-9,11-octadecadienoic acid and the isomeric 9,10,13-trihydroxy-11-octadecenoic and 9,12,13-trihydroxy-10-octadecenoic acids

Fatty alcohol: 14-Octacosanol

Monoterpenes: Three monoterpene diols and their monoglucosides

Triterpenes: 0.002% Oleanolic acid and ursolic acid

Phenols: p-hydroxy-benzaldehyde

Tannins

Coumarins: 0.0001-0.01% scopoletin in *Urtica dioica* roots, 0.0001% scopoletin in *Urtica urens* roots

Monosaccharides, oligosaccharides: Fructose, galactinol, galactose, glucose, myo-inositol, maltose, raffinose, stachyose

Amino acids: Alanine, β-alanine, arginine, asparagine, asparaginic acid, glutamine, glutaminic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, methylhistidine, phenylalanine, serine,

threonine, tyrosine, valine (0.05%). In *Urtica dioica* roots, the free amino acid fraction contains 10% gamma-aminobutyric acid.

Silicic acid: 0.3-0.6%

Adenosine: 0.002%

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

Not applicable.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA 32	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ 5 authorized combination products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combination products
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Food-supplement
Latvia	☒ MA 1	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ in combination
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Food-supplement
Poland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ in combination
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	in combination
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

Table 1. Products on the market

Active substance	**Indication**	**Posology**	**Legal status (MA since)**
Urticae radix herbal tea	Symptomatic treatment of benign prostatic hyperplasia at stages I and II as defined by Alken or stages II and III as defined by Vahlensieck.	for use in adults and adolescents over 16 years 2-3 times daily 1 sachet of 2.3 g containing 2.068g Urticae radix in 150 ml of boiling water, let 10 min extract and drink	1992
Urticae radix powdered herbal substance		1.32 g of powdered herbal substance 3 – 4 times daily.	2001
liquid extract from Urticae radix (1:1), extraction solvent: ethanol 30% V/V oral liquid		3 times daily 40 drops or 4 x daily 30 drops oral liquid containing 100% liquid extract Once a day 5 ml oral liquid containing 100% liquid extract	at least since 1976, at least 1990
dry extract from Urticae radix (7-14:1), extraction solvent: methanol 20% V/V film-coated tablet, coated tablet, hard capsules,		Once a day 1 film-coated tablet containing 460 mg dry extract Twice a day 1 coated tablet containing 250 mg dry extract 3 times daily 1 hard capsule containing 150 mg dry extract At the beginning of treatment for the first 3 months and in stage II Twice a day 2 hard capsules	1991, 2000 1991
dry extract from Urticae radix (7.1-14.3:1), extraction solvent: methanol 20% V/V coated tablet, film-coated tablet,		3 times daily 1 coated tablet containing 161 mg dry extract Once a day 1 film-coated tablet containing 459 mg dry extract	at least since 1976
dry extract from Urticae radix (6-11:1), extraction solvent: methanol 20% V/V film-coated tablet		Once a day 1 film-coated tablet containing 600.1 mg dry extract	2001, 2003
dry extract from Urticae radix (12-16:1), extraction solvent: ethanol 70% V/V coated tablet, hard capsule		Twice a day 1 coated tablet containing 150.5 mg dry extract Twice a day 1 hard capsule containing 189 mg dry extract	at least since 1976

Table 1. Products on the market (continued)

Active substance	Indication	Posology	Legal status (MA since)
dry extract from Urticae radix (15-20:1), extraction solvent: ethanol 80% V/V film-coated tablet	Symptomatic treatment of benign prostatic hyperplasia at stages I and II as defined by Alken or stages II and III as defined by Vahlensieck.	1 film-coated tablet containing 285 mg dry extract once a day	2001
dry extract from Urticae radix (5.4-6.6:1), extraction solvent: ethanol 80% V/V hard capsules		3 times daily 1 hard capsule containing 240 mg dry extract At the beginning of treatment 2 hard capsules twice a day 3 times daily 1 hard capsule containing 240 mg dry extract	1993, 1994
dry extract from Urticae radix (6.7-8.3:1), extraction solvent: ethanol 20% V/V soft capsule		3 times daily 1 soft capsule containing 240 mg dry extract	at least since 1976, 1996, 1997,
dry extract from Urticae radix (7-9:1), extraction solvent: ethanol 60% V/V film-coated tablet		twice a day 2 film-coated tablets containing 125 mg dry extract each	1992
dry extract from Urticae radix (8-12:1), extraction solvent: ethanol 60% m/m coated tablet		once a day 1 coated tablet containing 475 mg dry extract	1998, 1999
dry extract from Urticae radix (15.75-19.25:1), extraction solvent: ethanol 80% V/V hard capsule		At the beginning of treatment 3 times daily 1 hard capsule containing 115 mg dry extract After amelioration of discomfort and for long-term treatment 1 hard capsule twice a day	1991

1.3. Search and assessment methodology

The assessment report on nettle root is based on the following literature:

- Articles supplied by ESCOP (1996, 2003) and AESGP.
- Monographs on nettle: Hagers Handbuch (Blaschek W. et al. 1998), Commission E Monograph (Blumenthal 1998), WHO (2002).
- Review articles: Veit M et al. 1998, Chrubasik JE. et al. 2007.
- Articles and references retrieved from data bases (Pubmed, Toxnet) or internet sources (e.g. Google) until March 2011.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Nettle root was mentioned as herbal medicine first by Paracelsus and Matthiolus (Madaus 1938). In folk medicine, nettle herb and leaves were of higher importance than nettle root. In the Russian folk medicine, the powder of the root and seed was used against dropsy, diarrhoea and worms. In the Lithuanian folk medicine, the infusion of the aerial parts and roots was applied to treat atrophy (Madaus 1938). The Eclectics used leaf and root as a blood purifier, styptic, stimulating tonic and diuretic to treat diarrhoea, dysentery, discharges, chronic diseases of the colon and chronic skin eruptions (Mills 2003). Syrup made from the juice of root or leaves was said to relieve bronchial and asthmatic troubles (Mills, 2003). In African medicine, nettle root is used to treat diarrhoea and as an anthelmintic to expel intestinal worms (Blumenthal 1998).

Nettle root was first used in urinary tract disorders in the 1950s. The Commission E approved the use of nettle root for problems in urination in benign prostatic adenoma stages I and II (Commission E Monograph 1986). The British Herbal Pharmacopoeia reported prostatic action (BHP 1996). According to the wording of the British Herbal Compendium, nettle root is suitable for the symptomatic treatment of micturition disorders in the early stages of benign prostatic hyperplasia (BPH) (Bradley 2006). The French Herbal Remedies Notice to Applicants for Marketing Authorization allows two uses of nettle root: as an adjunctive treatment for the bladder outlet obstruction symptoms of prostatic origin, and to enhance the renal elimination of water (Bruneton 1999). ESCOP indicates its use for symptomatic treatment of micturition disorders (nocturia, pollakisuria, dysuria, urine retention) in BPH at stages I and II as defined by Alken or stages II and III as defined by Vahlensieck (ESCOP 2003). In the USA, it is used similarly, although as a dietary supplement its indications for use are limited to non-therapeutic “structure and function” claims (Blumenthal 1998).

Other use in the folk medicine:

Healing plants (Rápóti & Romvári 1974): Decoction of the root is taken orally against enteritis (diarhoeae), externally as shampoo against loss of hair and dandruff formation.

Lutomsky J. and Speichert (1983): against renal calculus

Jaspersen-Schib R. (1989): mild diuretic

Herbal Drugs and Phytopharmaceuticals (Bisset 1994): In folk medicine the use of nettle herb has been reported, e.g. as diuretic, but also as an adstringent and gargle because of its tannin content.

Hagers Handbuch (Berger 1960, Kern 1979, Blaschek et al. 1998): In folk medicine nettle root has been used as diuretic, as a component in ‘blood-purifying’ combination-preparations, against dropsy, for prostatitis in early stage, for rheumatic disorders, for gout similar to nettle herb. Externally nettle root has been used against dandruff in hair-lotion/wash.

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

All the products which have been on the market for more or less than 30 years have the same indication:

Symptomatic treatment of benign prostatic hyperplasia at stages I and II as defined by Alken (1973) or stages II and III as defined by Vahlensieck (1996).

Preparations which have been on the market for more than 30 years:

- Liquid extract (1:1), extraction solvent: ethanol 30% V/V
- Dry extract (DER: 7.1-14.3:1), extraction solvent: methanol 20% V/V
- Dry extract (DER: 6.7-8.3:1), extraction solvent: ethanol 20% V/V
- Dry extract (DER: 12-16:1), extraction solvent: ethanol 70% V/V

Other preparations which have been on the market for less than 30 years:

- Comminuted herbal substance (products on the market since 1992)
- Powdered herbal substance (products on the market since 2001)
- Dry extract (DER: 7-14:1), extraction solvent: methanol 20% V/V (products on the market since 1991/2000)
- Dry extract (DER: 6-11:1), extraction solvent: methanol 20% V/V (product on the market since 2001, 2003)
- Dry extract (DER: 7-9:1), extraction solvent: ethanol 60% V/V (product on the market since 1992)
- Dry extract (DER: 8-12:1), extraction solvent: ethanol 60% m/m (product on the market since 1998/1999)
- Dry extract (DER: 15-20:1), extraction solvent: ethanol 80% V/V (product on the market since 2001)
- Dry extract (DER: 5.4-6.6:1), extraction solvent: ethanol 80% V/V (product on the market since 1993, 1994)
- Dry extract (DER: 15.75-19.25:1), extraction solvent: ethanol 80% V/V (product on the market since 1991)

Preparations in the literature:

- Chopped drug for infusions (Commission E Monograph 1986, Bisset 1994)
- Liquid extract (1:1), extraction solvent: water (Blaschek et al. 1998)
- Liquid extract (1:1), extraction solvent: ethanol 16% (ESCOP 2003, Engelmann et al. 1996)
- Liquid extract (1:5), extraction solvent: ethanol 40% (ESCOP 1996, 2003)
- Liquid extract (1:1), extraction solvent: ethanol 45% V/V (prepared according to PF X) (ESCOP 1996, 2003; Blaschek et al. 1998 and Goetz 1989)
- Dry extract (DER: 7-14:1), extraction solvent: methanol 20% V/V (Blaschek et al. 1998; ESCOP 2003)
- Dry extract (DER: 5.4-6.6:1) extraction solvent: ethanol 20% V/V (Veit et al. 1998, Klein-Bischoff et al. 2007)
- Dry extract (DER: 8.3-12.5:1), extraction solvent: ethanol 60% m/m (Blaschek et al. 1998).
- Dry extract (DER: 20:1), extraction solvent: diethyl ether (Safarinejad 2005)

Preparations accepted in the monograph with traditional use:

- Comminuted herbal substance
- Liquid extract (1:1), extraction solvent: ethanol 30% V/V

- Dry extract (DER: 7.1-14.3:1), extraction solvent: methanol 20% V/V
- Dry extract (DER: 6.7-8.3:1), extraction solvent: ethanol 20% V/V
- Dry extract (DER: 12-16:1), extraction solvent: ethanol 70% V/V

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

Posology for preparations which have been on the market for more than 30 years (at least since 1976):

a) Dry extract (DER: 7-14:1), extraction solvent: methanol 20% V/V
Three times daily 1 coated tablet containing 161 mg dry extract

Once a day 1 film-coated tablet containing 459 mg dry extract

b) Dry extract (DER: 6.7-8.3:1), extraction solvent: ethanol 20% V/V
Three times daily 1 soft capsule containing 240 mg dry extract

c) Dry extract (DER:12-16:1), extraction solvent: ethanol 70% V/V
Twice a day 1 coated tablet containing 150.5 mg dry extract
Twice a day 1 hard capsule containing 189 mg dry extract

d) Liquid extract (1:1), extraction solvent: ethanol 30% V/V
Three times daily 40 drops or 4 times daily 30 drops

Posology for preparations which have been on the market for less than 30 years:

- Comminuted herbal substance (products on the market since 1992)

Two-3 times daily 1 sachet of 2.3 g containing 2.068g of Urticae radix

- Powdered herbal substance

1.32 g of powdered herbal substance 3–4 times daily (products on the market since 2001)

- Dry extract (DER: 7-14:1), extraction solvent: methanol 20% V/V

Once a day 1 film-coated tablet containing 460 mg of dry extract (products on the market since 2000)

Twice a day 1 coated tablet containing 250 mg of dry extract (products on the market since 2000).

Three times daily 1 hard capsule containing 150 mg of dry extract, 2 hard capsules twice a day at the beginning of treatment for the first 3 months and in stage II (products on the market since 1991).

- Dry extract (DER: 6-11:1), extraction solvent: methanol 20% V/V (products on the market since 2001/2003)

Once a day 1 film-coated tablet containing 600 mg of dry extract

- Dry extract (DER: 7-9:1), extraction solvent: ethanol 60% V/V (products on the market since 1992)

Twice a day 2 film-coated tablets containing 125 mg of dry extract

- Dry extract (DER: 8-12:1), extraction solvent: ethanol 60% m/m (products on the market since 1998/1999)

Once a day 1 coated tablet containing 475 mg of dry extract

- Dry extract (DER: 15-20:1), extraction solvent: ethanol 80% V/V

Once a day 1 film-coated tablet containing 285 mg of dry extract (product on the market since 2001)

Three times daily 1 hard capsule containing 115 mg of dry extract at the beginning of treatment. After amelioration of discomfort and for long-term treatment 1 hard capsule twice a day (product on the market since 1991)

- Dry extract (DER: 5.4-6.6:1), extraction solvent: ethanol 80% V/V

Three times daily 1 hard capsule containing 240 mg of dry extract. At the beginning of treatment 2 hard capsules twice a day (product on the market since 1993).

Three times daily 1 hard capsule containing 240 mg of dry extract (product on the market since 1994).

- Liquid extract (1:1), extraction solvent: ethanol 30% V/V (product on the market at least since 1990)

Once a day 5 ml oral liquid containing 100% liquid extract

Posology for preparations in the literature:

Herbal tea:

Daily dose: 4-6 g of the herbal substance as an infusion (Commission E Monograph 1986, Schilcher & Wülker 1992; Bisset 1994; Jaspersen-Schib 1989, Schilcher H 1989, ESCOP 1996, 2003; Blaschek et al. 1998)

Preparation of a herbal tea: 1.5 g of the coarsely powdered herbal substance is put into cold water, heated to boiling for ca. 1 min, then covered and allowed to stand for 10 min, and finally strained. 1 Teaspoon = ca. 1.3 g" (Bisset 1994; Blaschek et al. 1998)

Extracts:

- Liquid extract (1:1), extraction solvent: water (Blaschek et al. 1998)
  Six ml daily
- Liquid extract (1:1), extraction solvent: ethanol 16% (ESCOP 2003, Engelmann et al. 1996)
  Two times 3 ml daily (equivalent to 4.68 g of the fluid extract)
- Liquid extract (1:5), extraction solvent: ethanol 40% (ESCOP 1996, 2003)
  Five ml daily
- Liquid extract (1:1), extraction solvent: ethanol 45% V/V prepared according to PF X (ESCOP 1996, 2003; Blaschek et al. 1998 and Goetz 1989)
  At the beginning 30 drops daily, later in most of the cases the dose increased to 150 drops daily.
- Dry extract (DER: 7-14:1), extraction solvent: methanol 20% V/V (Blaschek et al. 1998; ESCOP 2003)
  Two times 300 mg daily
- Dry extract (DER: 5.4-6.6:1), extraction solvent: ethanol 20 % V/V (PU 240) (Veit et al. 1998, Klein-Bischoff et al. 2007)
  Two times 2 capsules daily, 1 capsule contains 240 mg of the dry extract
- Dry extract (DER: 8.3-12.5:1), extraction solvent: ethanol 60% m/m (Blaschek et al. 1998)
  Two times 120 mg daily

Duration of use

Based on clinical studies long-term use is possible.

Preparations and their posology in the monograph:

a) Herbal tea: 1.5 g of the comminuted herbal substance as a decoction 3-4 times daily.

b) Dry extract (DER 7.1-14.3:1), extraction solvent methanol 20% V/V
160 mg dry extract 3 times daily or 460 mg dry extract once a day

c) Dry extract (DER 6.7-8.3:1), extraction solvent ethanol 20% V/V
240 mg dry extract 3 times daily

d) Dry extract (DER 12-16:1), extraction solvent ethanol 70% V/V
150-190 mg dry extract twice a daily

e) Liquid extract (1:1), extraction solvent ethanol 30% V/V
Maximum 5 ml daily divided into 3 or 4 single doses

(Comment: The quantity in ml is based on the corresponding product from 1990.)

Duration of use

Long-term use is possible.

3. Non-Clinical Data

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

Aromatase inhibition

A potential role of oestrogens in the development of BPH has been emphasised by animal studies (Habenicht 1991). The biological action of oestrogens may be blocked either by oestrogen receptor antagonists or by suppressing oestrogen synthesis, e.g. by inhibition of aromatase.

An extract from Urticae radix (DER 10:1, 30% methanol) inhibited concentration dependently (ED_{50} = 3.58 mg/ml) the aromatase enzyme, which converts testosterone into estradiol (Hartmann 1996). The nettle root extract WS1031 (DER 8–13:1, 60% ethanol) inhibited aromatisation of androstenedione *in vitro* (IC_{50} 338 µg/ml). The active principle was found in a heptane fraction, suggesting that lipophilic compounds are responsible for the action (Chrubasik 2007). (10*E*, 12*Z*)-9-hydroxy-10,12-octadecadienoic acid isolated from an aqueous-methanolic root extract and its derivative (10*E*,12*Z*)-9-oxo-10,12-octadecadienoic acid inhibited aromatase activity *in vitro*, however, the heptane fraction was more effective than the single component (Bartsch 1992; ESCOP 2003; Kraus 1991). In a human placenta microsomal *in vitro* model, the EC_{50} values of the fractions of an (DER 8.3-12.5:1, 60% ethanol) extract were determined as follows: Urticae radix extract 338 µg/ml, heptane soluble fraction of the extract 9 µg/ml, ethylacetate soluble fraction of the extract 41 µg/ml, buthanol soluble fraction of the extract 109 µg/ml, water soluble fraction of the extract >200 µg/ml (Blaschek 1998). In this extract, besides common fatty acids, 9-hydroxy-10,12-octadecadienoic acid was identified as a major active constituent. This compound is possibly only formed during or after extract preparation by the oxydation of linoleic acid. The EC_{50} values of γ-linolenic acid and 9-hydroxy-10,12-octadecadienoic acid were 10 µg/ml and 11 µg/ml, respectively (Koch 2001; Blaschek 1998). A comparable aromatase inhibition of the ethanolic nettle extract LI166 (DER 8–12:1, 60% ethanol) and a synthetic aromatase inhibitor was achieved, however at a concentration 250 fold higher than that of

the synthetic one (Chrubasik 2007). On the other hand, aromatase inhibition by 5 other compounds isolated from methanol extract of nettle root (secoisolariciresinol, oleanolic and ursolic acid, (9*Z*,11*E*)-13-hydroxy-9,11-octadecadienoic acid, and 14-octacosanol) was only weak (Ganßer 1995a). The aqueous nettle extract BNO1250 (DER 10:1, 30% methanol; 0.75 and 7.5 mg/ml) inhibited estradiol formation in a time and dose-dependent manner (a cytotoxic effect could be excluded). Jarry et al. (1999) suggested that besides the inhibition of the enzyme activity, inhibition of aromatase gene expression may be involved in the nettle root effect (Chrubasik 2007).

Different nettle root extracts were found to inhibit the aromatase, as did some isolated compounds. However, nettle root contains only low quantities of these components and the active principle for a clinically relevant aromatase inhibition still needs to be defined (Chrubasik 2007). Although nettle extracts are weak inhibitors of aromatase compared to synthetic preparations, a pharmacological effect might be expected from the lipophilic compounds accumulated in fatty tissues where androgens are aromatised (Mills 2003).

Interaction with 5-α-reductase and androgen receptor binding

Increased plasma level of dihydrotestosterone (DHT) is associated with the development of BPH. Thus, the inhibitors of 5-α-reductase, the enzyme which converts testosterone to DHT, and inhibitors of androgen receptor binding are viable alternatives in the treatment of BPH.

Methanolic Urticae radix extract (UR102, DER 10:1, 30% methanol) inhibited 5-α-reductase only at high concentrations (≥ 12 mg/ml, ED_{50} 14.7 mg/ml) (Hartmann 1996). The ethanolic extract WS1031 (DER 8–13:1, 60% ethanol) had no impact on the conversion of testosterone into DHT (Chrubasik 2007).

An ethanolic extract of nettle roots (DER 7-14:1, 20% methanol) did not inhibit the binding of DHT to the rat androgen receptor (Blaschek 1998). In human prostate adenoma cells, the 5-α-reductase inhibitory IC_{50} value of this methanol nettle root extract (DER 7-14:1, 20% methanol) was >500 000 ng/ml, compared with the 1 ng/ml IC_{50} value of finasterid (Rhodes 1993). Urticae radix extract BAZ (DER 5:1, 20% methanol) at a concentration up to 0.5 mg/ml did not inhibit 5-α-reductase in vitro or the binding of radioactively labelled dihydrotestosterone to the rat prostatic androgen receptor, and also did not inhibit testosterone- or dihydrotestosterone-stimulated prostate growth in castrated rats in doses 276 and 1380 mg extract/day (Rhodes 1993). This extract mildly inhibited DHT binding to cytosolic androgen receptors in the prostate (ESCOP 1996; Mills 2003), but did not affect microsomal 5-α-reductase activity (Chrubasik 2007).

Effect on the SHBG (sex hormone binding globulin) binding capacity and sex hormones

SHBG is a plasma transport protein which binds androgens and oestrogens. In the blood only about 2% of testosterone is circulating free, while approximately 44% and 54% are bound to SHBG and other plasma proteins, respectively (Koch 2001). Advancing age is accompanied by the change of the androgen:oestrogen equilibrium and increased SHBG level. Increased binding capacity of SHBG to testosterone and dihydrotestosterone results in hyperplasia, as a compensation for the decrease in hormones and increase in 5-α-reductase activity (ESCOP 2003). Two possibilities have been suggested to compensate these changes: (i) interaction with blood levels of free (active) steroid hormones by displacing them from their SHBG binding sites and (ii) prevention of the interaction of prostate receptors with SHGB (Chrubasik 2007).

Already in 1983 it was reported that an ethanol-water nettle root extract inhibited the binding of [^{3}H]-DHT to SHBG (Koch 2001). Since then, several extracts, fractions and compounds were tested for their activities on SHBG. A significant (average 67%) suppression of the SHBG binding capacity in the

presence of an Urtica root **extract preparation (DER 5:1, 20% methanol)** was shown *in vitro* after preincubation in human serum (ESCOP 1996; Mills 2003). An aqueous extract (extraction at 80°C) of Urticae radix inhibited dose-dependently (0.6-10 mg/ml) binding of radioactively labelled SHBG to solubilized receptors from human prostatic tissue, however **an 70% ethanol Urticae radix extract;** isolated *U. dioica* agglutinin, and stigmasta-4-en-3-one **were not active** (Hryb 1995). The lignan secoisolariciresinol, as well as a mixture of isomeric (11E)-9,10,13-trihydroxy-11-octadecenoic acid and (10E)-9,12,13-trihydroxy-10-octadecenoic acids reduced binding activity of human SHBG. So did the mixture of the latter two compounds after methylation, moreover, methylation increased activity about 10-fold (Ganßer 1995b). The affinity to human SHBG of the lignans (+)-neoolivil, (-)-secoisolariciresinol, dehydrodiconiferyl alcohol, isolariciresinol, pinoresinol, and 3,4-divanillyltetrahydrofuran identified in nettle roots was tested in an *in vitro* assay. In addition, the main intestinal transformation products of plant lignans in humans, enterodiol and enterolactone, together with enterofuran were checked for their activity. All lignans except (-)-pinoresinol developed a binding affinity to SHBG in the assay. The affinity of (-)-3,4-divanillyltetrahydrofuran was outstandingly high. The metabolite of (-)-3,4-divanillyltetrahydrofuran (enterofuran) showed higher binding affinity to SHBG than the metabolite of secoisolariciresinol (enterodiol, enterolactone) (Schöttner 1997).

Anti-inflammatory and immunomodulating activity

Although the aetiology of non-bacterial chronic prostatitis is poorly understood, it is well recognised that this condition is frequently associated with BPH and may even be a causative factor in the pathogenesis of this ailment (Koch 2001). Immunohistological analysis of lymphocyte subpopulations revealed marked qualitative and quantitative differences between normal and BPH tissue. Cytokines released from leukocytes not only possess pro-inflammatory properties but may also induce cell proliferation (Koch 2001). Therefore, anti-inflammatory and immunological interventions may provide approaches for the treatment of BPH.

A polysaccharide fraction obtained from an aqueous extract of nettle root was shown to be active in the lymphocyte transformation test. This fraction was found to be active in the carrageenan rat paw oedema model as well (ESCOP 1996). The methanolic extract BAZ (DER 5:1, 20% methanol) was shown to inhibit the alternative pathway of complement activation which involves various serine proteinases (Wagner 1994). Isolated polysaccharides (e.g. rhamnogalacturanes, a type II arabinogalactane) produced a dose-dependent reduction of haemolysis in the classical and alternative complement test. From these results an anti-inflammatory and immunomodulating effect was deduced (ESCOP 1996; Chrubasik 2007). Isolated *Urtica dioica* lectins were found to stimulate the proliferation of human lymphocytes in the lymphocyte transformation test (ESCOP 1996). The 1T fraction of UDA stimulated the proliferation of lymphocytes by 543%, UDA 2T by 341% (Blaschek 1998). UDA stimulated concentration dependently the interferon secretion of human lymphocytes (Peumans 1984). The presence of human leukocyte elastase in the seminal plasma has been demonstrated to be a biochemical marker of clinically silent prostatitis (Wolff 1991). This enzyme catalyses the degradation of many extracellular matrix and plasma proteins. Ethanolic nettle root extract WS1031 (DER 8–13:1, 60% ethanol) inhibited bovine leukocyte elastase (IC_{50} 68 µg/ml), which reflects anti-inflammatory activity (Chrubasik 2007). During a pharmacological screening programme for human leukocyte elastase inhibitors, the nettle root extract WS1031 (DER 8–13:1, 60% ethanol) was found to potently suppress enzyme activity with a calculated IC_{50} value of 3.6 µg/ml (Koch 2001).

A crude extract from nettle root containing 4 different polysaccharides was shown to possess anti-inflammatory activity comparable to indomethacin in the rat paw oedema test 5 hours after oral administration (Wagner 1994). The effect oral nettle root extract LI166 (DER 8–12:1, ethanol 60%; 250–750 mg/kg) and of root components (40 mg/kg of a particular polysaccharide fraction, which consisted of four different polysaccharides administered orally or a mixture of two polysaccharides

intravenously) were investigated in the carrageenan-induced rat paw oedema test and indicated an anti-inflammatory potential (Chrubasik 2007).

Effect on muscle contractility

In concentrations of 100–800 µg/ml, a methanol extract (DER unknown, 50% methanol) did not affect circular muscle spontaneous contractions or longitudinal muscle contractions on isolated guinea pig ileum induced by acetylcholine and barium chloride (Chrubasik 2007).

Effect on growth of BPH-tissue cells

Different growth factors and their receptors and some enzymes (besides aromatase and 5-α-reductase) may be involved in the pathogenesis of BPH. The inhibition of these receptors and enzymes may be a therapeutic approach of BPH.

According to Farnsworth's hypothesis biological effects of androgens on the prostate are mediated not only through binding to steroid receptors in the nucleus, but also through interaction with receptors on the plasma membrane of target cells; as one of these sites Na/K-ATPase has been recognised (Koch 2001). Organic solvent extracts of *Urtica dioica* root (0.1 mg/ml) gave 28-82% inhibition of Na/K-ATPase activity of human BPH-tissue cells. Steroidal compounds of the root, such as stigmast-4-en-3-one, stigmasterol, and campesterol, inhibited the enzyme activity by 23-67% at concentrations ranging from 10^{-3} to 10^{-6} M. These results suggest that some hydrophobic constituents such as steroids inhibit the membrane Na/K-ATPase activity of the prostate which may subsequently suppress prostate-cell metabolism and growth (Hirano 1994; Mills 2003).

Five subfractions from the **20% methanolic extract** of Urticae radix gave a statistically significant proliferation inhibition of cultured BPH-tissue cells in concentrations ranging from 10 to 1500 µg/ml (ESCOP 1996; Mills 2003). The lectin fraction UDA 1T gave 53% inhibition of the binding of epidermal growth factor (EGF) to EGF-receptors in cultivated cells from human prostatic tissue (ESCOP 1996; Blaschek 1998). UDA from an *Urtica dioica* root extract showed a dose-dependent inhibition of EGF-binding to human A431 epidermal cancer cell membranes (ESCOP 1996). Incubation of prostatic stromal fibroblasts with 0.01% nettle root extract BAZ **(DER 5:1, 20% methanol)** reduced cell proliferation by 50%. The proliferation rate was affected by DHT. High extract doses were even toxic, probably due to osmotic conditions (Chrubasik 2007).

Fractions of the methanolic extract BAZ (DER 5:1, 20% methanol) inhibited cell growth of cultivated human hyperplastic prostate cells from biopsy samples *in vitro* to various degrees. Electronmicroscopic examination did not reveal specific changes and testosterone metabolism remained unaffected. EGF receptor concentrations were reduced when particular fractions were employed but the effect on receptor expression did not correlate with ultrastructural changes (Chrubasik 2007). Already low concentrations of the methanolic extract BAZ (DER 5:1, 20% methanol) (dose range tested: 10 ng–100 µg/ml) inhibited cell growth of incubated fibroblastic and epithelial cells by about 20%. Higher concentrations were not more effective. Since microsomal 5α-reductase activity was not affected, an androgen-independent mechanism was suggested (Chrubasik 2007).

A concentration-dependent and significant anti-proliferative effect of BAZ extract (DER 5:1, 20% methanol) was documented only on epithelial cancer cells (LNCaP), whereas stromal cell growth remained unaltered. The inhibition was time dependent, with a maximum growth reduction of 30% at a concentration of 1.0E−6 mg/ml on day 5 compared to the untreated control. No cytotoxic effect was observed (Konrad 2000). Chemical analysis of this extract revealed a carbohydrate content about 21%. Therefore, a polysaccharide-enriched subfraction was prepared which suppressed growth of LNCap cells maximally by about 50% at concentrations of 10-1000 fg/ml. The authors report that this

fraction even at a concentration of 10^{-16} mg/ml caused a significant reduction of proliferation when compared with controls (Lichius 1999).

Cells from normal and BPH biopsies were incubated with different concentrations of the methanol extract BAZ (DER 5:1, 20% methanol). Prostate metabolism remained unaffected, but homogenous granules showed a relevant decrease in nettle root extract-treated cells (Chrubasik 2007). UDA inhibited the binding of EGF/bFGF (basic fibroblast growth factor) to HeLa cells, binding of EGF to membranes of A431 cells, and EGF receptor tyrosine kinase activity (Wagner 1994). Using the human epidermoid cancer cell line A431 with its high expression of EGF receptors at the cell surface, UDA was found to inhibit the binding of ^{125}I-labelled EGF to the receptor. The effect was more pronounced than with wheat germ agglutinin, which possesses the same sugar specificity and the mannose-specific agglutinin Conconavalin A. The inhibitory effect of UDA could be antagonised by chitotriose, an oligosaccharide with affinity for the EGF receptor site (Wagner 1995).

An average decrease of 30% of prostate volume and decrease of serum testosterone levels after a 100-day treatment with 90 mg of a BAZ extract (DER 5:1, 20% methanol) per kg body weight was shown in 10 dogs suffering from BPH (ESCOP 1996). In a later study over 100 days, it was confirmed that hecogenin acetate is a co-active constituent. Doses 0.5 and 5 mg/10 kg resulted in sonographic prostate volume reductions of 14% and 29%, respectively (Chrubasik 2007). The same extract did not inhibit testosterone and dihydrotestosterone stimulated growth of the prostate in castrated rats (Rhodes 1993). In a BPH-model (directly implanting a urogenital sinus) into the ventral prostate gland of an adult mouse) five differently prepared stinging nettle root extracts were tested. The 20% methanolic extract was the most effective with a 51.4% inhibition of the induced growth. The aqueous extract also inhibited growth, although not significantly (26.5%). There was no correlation between the amounts of sitosterin and scopoletin with the growth-inhibiting effect, however, a correlation was assumed with the lectin fraction UDA, lectin and saccharyde content of the extract (Lichius 1997; Blaschek 1998).

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

No data available.

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

Acute toxicity

In rats the oral LD_{50} was suggested to be higher than 30g/kg and intraperitoneal LD_{50} to be higher than 3 g/kg (detailed data unpublished, property of the manufacturer Kanoldt) (Chrubasik et al. 2007).

Reproduction and chronic toxicity

No data available.

Mutagenic potential

An extract (not characterised) of Urticae radix was tested using two *Salmonella typhimurium* strains (TA 98 and TA 100) using the plate incorporation test and extract doses up to 5000 µg/plate. None of the tested strains showed increased reversion to prototrophy either in the absence or presence of rat liver metabolic activation system. Significant increases in the number of revertant colonies were introduced by the known mutagens and carcinogens sodium azide, 2-nitrofluorene, 2-aminoanthracene when tested under the same conditions (Chrubasik et al. 2007).

3.4. Overall conclusions on non-clinical data

The reputed beneficial effect of nettle root on BPH seems to be supported by *in vitro* and *in vivo* pharmacological studies. Only a few components of the active principle have been identified and the mechanism of action is still unclear. Phytosterols, lignans, polysaccharides and the lectin UDA (0.2-0.6%) are considered to be among the active principles. Phytosterol components are thought to be the least important since their content in nettle products is very low (0.01%). It seems likely that sex hormone binding globulin (SHBG), aromatase, epidermal growth factor and prostate steroid membrane receptors are involved in the anti-prostatic effect, but it is less likely that 5-α-reductase or androgen receptors are involved. The oral nettle root extract (DER 8–12:1, ethanol 60%, 250-750 mg/kg) and its polysaccharide fraction were shown to exert anti-inflammatory activity in the carrageenan-induced rat paw oedema. The methanolic (20% V/V) extract (DER 5:1) and its particular fractions inhibited cell proliferation *in vitro*. Isolated lectins (UDA) were shown to be promising immunomodulatory agents, having also anti-viral and fungistatic effects. However, despite these *in vitro* studies it is unclear whether the *in vitro* or animal data are a surrogate for clinical effects.

4. Clinical Data

Prostate Hyperplasia, Benign (Leveillee RJ et al. 2010)

Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is a histologic diagnosis characterised by proliferation of the cellular elements of the prostate. Cellular accumulation and gland enlargement may result from epithelial and stromal proliferation, impaired programmed cell death (apoptosis), or both. BPH involves the stromal and epithelial elements of the prostate arising in the periurethral and transition zones of the gland. The hyperplasia presumably results in enlargement of the prostate that may restrict the flow of urine from the bladder.

BPH is considered a normal part of the aging process in men and is hormonally dependent on testosterone and dihydrotestosterone (DHT) production. An estimated 50% of men demonstrate histopathologic BPH by age 60. This number increases to 90% by age 85; thus, increasing gland size is considered a normal part of the aging process. Worldwide, approximately 30 million men have symptoms related to BPH.

The voiding dysfunction that results from prostate gland enlargement and bladder outlet obstruction (BOO) is termed lower urinary tract symptoms (LUTS). These entities overlap; not all men with BPH have LUTS, and, likewise, not all men with LUTS have BPH. Approximately half of men diagnosed with histopathologic BPH demonstrate moderate-to-severe LUTS. Clinical manifestations of LUTS include urinary frequency, urgency, nocturia (getting up at night during sleep to urinate), decreased or intermittent force of stream, or a sensation of incomplete emptying.

Prostate volume may increase over time in men with BPH. In addition, peak urinary flow, voided volume, and symptoms may worsen over time in men with untreated BPH. The risk of acute urinary retention (AUR) and the need for corrective surgery increases with age.

Complications occur less commonly but may include AUR, impaired bladder emptying, or the need for corrective surgery.

In the past, chronic end-stage BOO often led to renal failure and uremia. Although this complication is much less common now, chronic BOO secondary to BPH may lead to urinary retention, renal insufficiency, recurrent urinary tract infections, gross hematuria, and bladder calculi.

Diagnosis: The diagnosis of benign prostatic hyperplasia (BPH) can often be suggested based on history alone. Special attention to the onset and duration of symptoms, general health issues

(including sexual history), fitness for any possible surgical intervention, severity of symptoms and how they are affecting quality of life, medications, and previously attempted treatments is essential to making the correct diagnosis. Symptoms often attributed to BPH can be caused by other disease processes, and a history and physical examination are essential in ruling out other etiologies of LUTS.

Severity of the symptoms can be evaluated with the help of **symptoms scores**:

The ***International Prostate Symptom Score (IPSS)*** has become the international standard. It is derived from the American Urological Association (AUA) 7 score described by Barry and his colleagues in the early 1990s. This is a questionnaire designed to be completed by the patient. Symptom scores range between 0 and 35, and are classified as “mild” (0-7) “moderate” (8-19), or “severe” (20-35).

Other questionnaires used in research studies include the Boyarsky Index and the Madsen-Iversen score. Both are completed by clinicians, and may not therefore capture the patient’s perspective.

It should be noted that the AUA symptom index is not a specific indicator of the presence of BPH. When this questionnaire was completed by elderly women, it was found that their responses and scores were indistinguishable from those of a sample of men of similar age.

The US Agency for Health Care Policy and Research Guidelines uses symptom severity to allocate treatment. Patients with moderate symptoms might benefit from pharmacotherapy, while patients with severe symptoms may derive most benefit from prostatectomy.

Quality-of-life assessment

The impact of urinary symptoms on the quality of life is generally evaluated by means of question 8 of the IPSS. However, this question measures the extent to which patients tolerate their symptoms rather than evaluating their quality of life. A number of health-related, quality-of-life instruments have been used for clinical research.

Objective measures: Peak urinary flow rate (Q_{max}) may be the best non-invasive indicator of bladder outlet obstruction. There is uncertainty about what rates of flow indicate obstruction. Some urologists use a 15 ml/second cut-off: however, a study of over 2,000 men revealed that most men over 60 fall below this level. Another study of asymptomatic elderly men found that all those aged over 80 had maximum flow rates below 9 ml/second. Estimation of the volume of residual urine is useful for assessing the degree of obstruction and risk of kidney damage.

Prostate-specific antigen (PSA) measurement

Before selecting the proper treatment for men with LUTS, every urologist will perform a digital rectal examination (DRE) and most will measure the serum value of PSA (prostate-specific autigen).

In cases where the architecture of the prostatic gland is disrupted, PSA will ‘leak’ into the circulation.

This occurs when prostatic carcinoma is present but also in BPH, prostatitis and after urinary retention.

PSA is not considered as being cancer-specific, but organ-specific.

Two other important factors, age and race, must also be considered when evaluating PSA values in men with LUTS. African-Americans with no evidence of prostate carcinoma have higher PSA values after their fourth decade of life, and therefore age-specific reference ranges must be adapted and interpreted according to race and ethnicity.

PSA and prostate volume have an age dependent, log-linear relationship and PSA has a good predictive value for assessing prostatic volume.

The chance of having prostate cancer is strongly related with the serum value of PSA. For many years the value of 4 ng/mL was considered as the upper normal limit of PSA but lately a lower threshold of PSA for recommending prostate biopsy in younger men has shown to improve the clinical value of this test.

PSA and prostatic volume can be used to evaluate the risks of either a need for surgery or developing acute urinary retention. These parameters were also related with long-term changes in symptom scores and flow rates.

4.1. Clinical Pharmacology

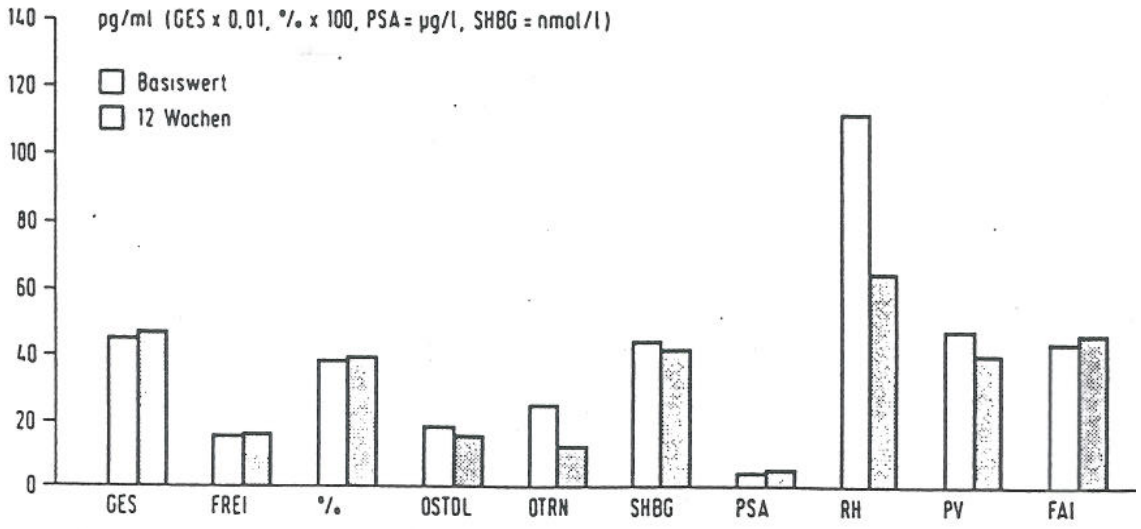
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Changes in serum parameters in clinical studies:

In 3 studies with dried native extract of nettle root (DER: 7-14:1; extraction solvent methanol 20% V/V) in a preparation containing an equal amount of diluent SHBG (sex hormone binding globulin), testosterone, 5-alfa-DHT, estradiol and oestron serum levels were measured (Fischer & Wilbert 1992; Vontobel et al. 1985; Bauer et al. 1988).

SHBG levels decreased significantly in the three studies. Sexual hormone parameters did not change significantly (Fischer & Wilbert 1992; Vontobel et al. 1985). In the study conducted by Bauer et al. (1988) a significant difference ($p<0.05$) was found between the values of PSA, oestradiol, oestron and SHBG at the beginning of the therapy and after 12 weeks (See Figure 1.).

Figure 1. Bauer et al. (1988): Results of the ERU study. Values of the serum parameters at baseline and after 12 weeks treatment



(n=253) GES: Total-testosterone, FREI: free testosterone, %=percentage of free testosterone, OSTDL: oestradiol; OTRN=oestron; RH: residual urine, PV: prostate volume; FAI=quotient of testosterone/SHBG. Significance < 0.05 in OSTDL; OTRN; PSA; RH; PV (Basiswert=baseline value Wochen=weeks):

Assessor's comment: Bauer et al. (1988) did not publish any further specific data (only a figure). A final evaluation of the significance of the data from this publication is not possible.

In the study published by Safarinejad (2005) serum PSA and testosterone levels were unchanged after a 6-month therapy. The composition of the investigated extract is not mentioned in the article.

Assessor's comment: Since the recent study of Safarinejad (2005) is a placebo-controlled one and the duration was longer than in previous studies, the results of this study were considered more relevant in the development of the monograph.

Histological prostate cell changes

Thirty-one men aged between 58 and 62 years with BPH at stages I and II were treated daily for 20 weeks with 1200 mg of dried nettle root extract preparation (DER:3.5-7:1; 20% V/V methanol). From fine needle aspiration biopsies of prostate at 4 weekly intervals, **morphologically significant changes in prostatic adenoma cells were detected** that may relate to competitive inhibition of SHBG binding capacity by the extract (Ziegler 1982).

Prostatic cells taken by needle biopsy from 33 BPH patients treated with nettle root extract for about 6 months were investigated by fluorescence microscopy. Compared with normal prostatic cells, a decrease in homogenous granules was detected in hyperplasic cells from the BPH patients, indicating that biological activity in these cells had decreased (Ziegler 1983).

The presence of nettle root constituents or their metabolites in prostate tissue obtained (through prostatectomy) from BPH patients treated with nettle root extracts was demonstrated by fluorescence microscopy. The granular fluorescence was not observed in prostate tissue from patients not treated with nettle root extract, but could be stimulated to some extent by *in vitro* incubation of this tissue with nettle root extract (Dunzendorfer 1984).

Morphological examination of prostate tissue obtained by needle biopsy from BPH patients before and 6 month after therapy with nettle root extract confirmed ultrastructural changes in the smooth muscle cells and epithelial cells of the prostate (Oberholzer et al. 1987).

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

After oral administration of 20 mg of purified *Urtica dioica* agglutinin (UDA) to patients and healthy volunteers, 30-50% was excreted unchanged in the faeces. The concentration in urine was less than 1% of the administered dose. These data confirmed the extreme stability of UDA in the digestive tract and its partial uptake and renal clearance (Samtleben et al. 1996).

4.2. Clinical Efficacy

4.2.1. Dose response studies

No studies.

4.2.2. Clinical studies (case studies and clinical trials)

Placebo controlled studies

In spite of the fact that in BPH the placebo effect is considerable, only six randomised, double blind, placebo controlled clinical studies can be found in the literature: Dathe & Schmid 1987; Engelmann et al. 1996; Fischer & Wilbert 1992; Safarinejad 2005; Schneider & Rübben 1996; Vontobel et al. 1985.

Placebo controlled studies with dried native extract of nettle root (DER: 7-14:1; extraction solvent methanol 20% V/V) in a preparation containing an equal amount of diluent:

[Similarly to the published references the following dosages (in mg) relate to the extract preparation, of which only 50% was native extract (7-14:1)].

Short-term studies

Dathe & Schmid (1987): In a double blind, placebo controlled study patients in stadium I of BPH were randomized to 600 mg of nettle root extract (2 times 1 capsules) (n=35) or to matching placebo (n=37). Patients were excluded if they had residual urine of more than 150 ml, average urinary flow higher than 10 ml/s, maximum urinary flow higher than 15 ml/s. The study was based on the Guidelines of Food and Drug Administration on Investigations of benign prostatic hypertrophy (Boyarsky S et al. 1977). After 6-8 weeks of treatment in the verum group significant improvements of 14% in average urinary flow rate (ml/s), 13% in micturition duration (second), 12% in maximum urinary flow (ml/s) and 40% in residual urine volume (ml) were observed. Comparing the verum group with the placebo group statistically significant differences were found the in the change of the average urinary flow rate (1.3 ml/s versus 0.2 ml/s) and in the decrease of the residual urine volume (40% versus 8%). There was no remarkable difference between the two groups in subjective symptoms (micturition frequency, nocturia frequency, difficulty in initiating urination, quality of the urinary stream, terminal dribbling).

Table 3. Summary of the results of the Dathe & Schmid (1987) study

Evaluation criteria:	**Results**					
	Verum			Placebo		
micturition volume (ml	Before	After	Difference	Before	After	Difference
	282	292	+10	291	289	-2
micturition duration (s)	31	27	-4 (13%)	31.6	31.3	-0.3
average urinary flow rate (ml/s)	9.4	10.7	**+1.3 (14%)***	9.3	9.5	+0.2
maximum urinary flow (ml/s)	13.8	15.4	+1.6 (12%)	13.9	13.2	-0.7
flow rising time (s)	6.1	5.2	-0.9 (15%)	6.2	6.1	-0.1.
residual urine volume (ml) measured with catheter	94	56	**-38 (40%)***	75	69	-6
residual urine volume (ml) measured by Sonographie	95	72	-15 (24%)	85	113	+28
residual urine volume under 100ml	61	29	-32 (53%)	35	30	-5
subjective symptoms**	There was no remarkable difference between the two groups.					

*statistically significant difference between verum and placebo group

**subjective symptoms: micturition frequency, nocturia frequency, difficulty in initiating urination, quality of the urinary stream, terminal dribbling

Assessor's comment: In this clinical study some of the objective parameters (the average urinary flow rate and the residual urine volume) showed statistically significant improvement in the verum group compared with the placebo group. However the lack of standard deviation values and confidential limits in the article restrict the evidence of conclusions which may be derived from these results. The most important fact, however, is that there was no remarkable difference between the two groups in the improvement of the subjective symptoms. If the study were long enough it could have been possible to evaluate a difference between the two groups in this aspect as well.

Vontobel et al. (1985): 50 BPH I-II patients enrolled in a double-blind, controlled study were treated daily with 600 mg of extract preparation (n=25) or placebo (n=25) **for 9 weeks**. Patients were excluded if their residual urine exceeded more than 150 ml. A significant increase of 44% in micturition volume (ml) ($p<0.027$) and a highly significant decrease in serum levels of SHBG ($p=0.0005$) were

observed. Maximum urinary flow (ml/s) improved by 8.6% in the treated group, but decreased with the same degree in the placebo group (p=0.062). The improvement of the average flow in the ERU group was not significant. There was no remarkable difference between the two groups in subjective symptoms (micturition frequency, nocturia frequency, difficulty in initiating urination, weakened urinary stream, terminal dribbling). Contrary to other studies an increase of residual urine volume was observed in both groups. The authors stated this did not seem to be significant according to the covariance-analysis and they explained this finding that the starting values of residual urine volume of the patients in the two groups were not homogenous.

Table 4. Summary of the results of the Vontobel et al. (1985) study

Evaluation criteria	**Results**		
	Verum	Placebo	Difference (*T*-test)
micturition volume (ml)	Increased by 43.7%	decreased by 9%	**p=0.027**
average urinary flow rate (ml/s)	slight increase		not significant
maximum urinary flow (ml/s)	improved by 8.6%	decreased by 8.6%	p=0.062
residual urine volume (ml) measured by Sonograph	no significant change	no significant change	not significant
subjective symptoms*	significant improvement	significant improvement	not significant

*subjective symptoms: dysuria, difficulty in initiating urination, weakened urinary stream

Assessor's comment: There were no numerical data given in the article. The results were shown only graphically. Moreover, the authors mentioned that the starting values of residual urine volume of the patients in the two groups were not homogeneous. Therefore, the results of this study are of limited value.

Long-term studies

Fisher & Wilbert (1992): In a randomised, double blind, placebo controlled study 40 BPH II patients (n=20; placebo n=20) were investigated according to the Guidelines of Food and Drug Administration on Investigations of benign prostatic hypertrophy (Boyarsky S et al. 1977). First all the patients received placebo for four weeks, then they were treated with 1200 mg extract preparation per day (2 times 2 capsules) or placebo **for 6 months**. Wilcoxon-Test was used for the statistical analysis at the different time points in both groups. Changes within the groups were analysed with the help of Signed –ranked –tests. Statistically significant (p<0.05) decreases in micturition frequency (from 7.4 to 6.1, during 24 hours) and SHBG level was observed in the verum group after 6 months. The subjective symptoms score, which consists of hesitancy, intermittency, terminal dribbling, desire to urinate, decrease in force and size of the urinary stream, dysuria and sensations of incomplete emptying improved significantly in the verum group (decreased from 4.8 to 3.63) and there was no change in the placebo group (from 3.29 to 3.3). The objective parameters (prostate volume, urinary flow, residual urine volume) did not change in the nettle root extract group but worsened in the placebo group.

Table 5. Fisher & Wilbert (1992): Average point of the subjective symptoms score with difference compared to the first month

Group	Time	Patients' number	Average score	Difference compared to the first month
placebo	1. month	17	3.29	
	4. month	14	3.29	0.00
	7. month	12	3.33	+0.04
verum	1. month	20	4.80	
	4. month	20	4.00	-0.80
	7. month	19	3.63	-1.17

The subjective symptoms score consists of hesitancy, intermittency, terminal dribbling, desire to urinate, decrease in force and size of the urinary stream, dysuria, and sensations of incomplete emptying. This score was the sum of the scores for each symptom; scores ranged from 0 (absent) to 3 (maximum severity).

Table 6. Average micturition volume with difference compared to the first month (Fisher & Wilbert (1992)

Group	Time	Patients' number	Average score	Difference compared to the first month
placebo	1. month	12	203.8	
	4. month	11	173.6	-30.2
	7. month	7	174.3	-29.5
verum	1. month	13	215.4	
	4. month	14	235.7	+20.3
	7. month	15	217.7	+2.3

Assessor's comment: The patients' number is very low, 40 in the study. The baseline parameters in the two groups are not mentioned in the article, and the standard deviation values cannot be found. A statistically significant decrease was found in the symptom score in the verum group compared to placebo. Nevertheless this statement cannot be taken into account because the two groups were not homogeneous after the first month placebo running period, the average symptoms score was 4.8 in the verum group and 3.29 in the placebo group, the average micturition volume was 215.4 in the verum group versus 203.8 in the placebo group (See Tables 5. and Table 6. above). After 6 months a statistically significant ($p<0.05$), but clinically not relevant decrease was found in micturition frequency (from 7.4 to 6.1, during 24 hours) in the verum group, but the data in the placebo group were not given. The objective parameters (prostate volume, urinary flow, residual urine volume) did not change. It can be concluded, that this article does not give relevant data for the evaluation of the efficacy.

Schneider & Rübben (2004): The authors performed a randomised, double-blind , placebo controlled multi-centre study **for a 1 year treatment** with Bazoton®-uno, 459 mg dry extract of stinging nettle roots, with 246 patients. The IPSS decreased on average from 18.7±0.3 to 13.0±0.5 with a statistically significant difference compared to placebo (18.5±0.3 to 13.8±0.5; p=0.0233 repeated measures model). The median Q_{max} increased by 3.0±0.4 ml/s in comparison to 2.9±0.4 ml/s (placebo). This difference was not statistically significant, neither was the median volume of residual urine, which changed from 35.5±3.4 ml before therapy to 20±2.8 ml and from 40.0±4.0 ml to 21.0±2.9ml under placebo application. The number of adverse events (29/38) as well as urinary

infections etc. (3/10 events) was smaller under Bazoton®-uno therapy compared to placebo. (See Table 7.).

Table 7. Summary of the results of the Schneider & Rübben (2004) study

Evaluation criteria	**Results**						
	Verum			Placebo			p-value
	Before	After	Difference	Before	After	Difference	
IPSS (±SEM) **	18.7± 0.3	13.0±0.5	-5.7 ±0.5	18.5± 0.3	13.8±0.5	-4.7±0.5	0.0233[a]
maximum urinary flow (ml/s±SEMD)	11.1±0.2	13.8±0.5	3.0±0.4	10.7±0.3	12.3±0.5	2.9±0.4	0.49[b]
residual urine volume (ml±SEMD)	35.5 ±3.4	20.0±2.8	-5.0±2.1	40.0±0.4	21.0±2.9	-4.0±1.6	0.67 [b]
quality of life After 52 weeks	Better 65%	Worse 8%	No change 27%	Better 62%	Worse 7%	No change 31%	0.69 [b]

[a] Repeated Measures Model

[b] Wilcoxon Test

** International Prostate Symptoms Score (1-5, micturition frequency, nocturia frequency, hesitancy, decreased urinary stream, residual urine, urge to urine) according to the suggestion of the American Urological Association. 0-7 points=slight-grade, 8-19 points=middle-grade, 20-35 points=great-grade.

Assessor's comment: In this study only the IPSS decreased on average from 18.7±.0.3 to 13.0±0.5 with a statistically significant difference compared to placebo (from 18.5±.0.3 to 13.8±0.5 p=0.0233) according to the „repeated measures model" (see Figure 2.). However this method is not the generally accepted Wilcoxon test. The authors did not explain why this special method was applied. If 31% decrease of IPSS score (- 5.7±0.5) in the verum group are compared to 25% decrease (-4.7±0.5) in the placebo group the difference of 6% between the two groups cannot be considered clinically significant. Consequently, the result cannot be considered persuasive.

Figure 2.: Changes in the average IPSS during the 52-week-long treatment (Schneider & Rübben 2004):

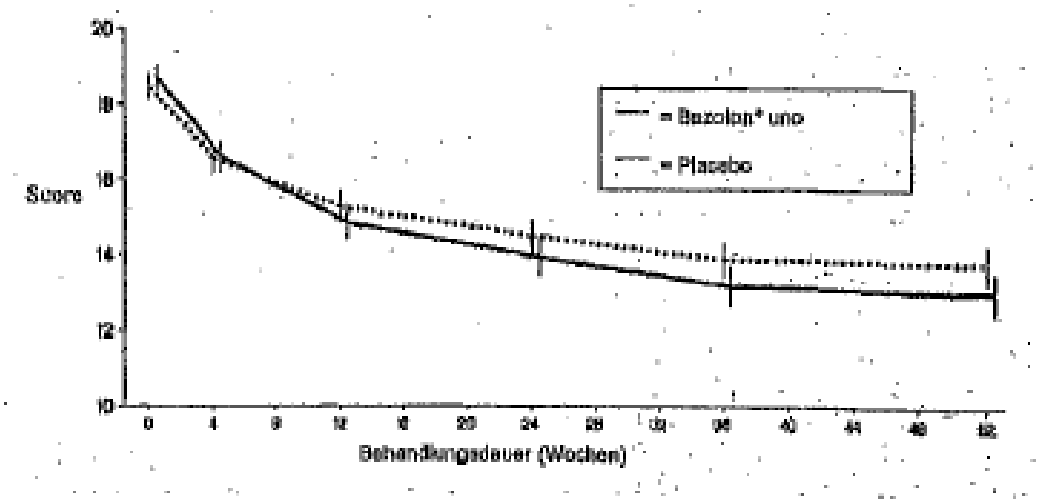


Abb. 1 ▲ Mittelwertverläufe des IPSS ± SEM über 52 Wochen (Itt: n=226) (p=0,0233 im „repeated measures model")

Placebo controlled studies with other preparations:

Short-term study

Engelmann et al. (1996): In a double blind, multi-centre study, 41 BPH patients were treated **for 3 months** with either 2 times 3 ml of an aqueous extract preparation equivalent to 4.68 g of fluid extract (Bazoton Liquidum 1:1, 16% ethanol (n=20) or placebo (n=21). The study was performed according to the GCP standard. Patients had to have a maximum urinary flow higher than 1 ml/s, a micturition volume exceeding 100 ml, and a residual urine volume exceeding 30 ml. The primary study end point was the change of the International Prostate Symptoms Score** for which a statistically and clinically significant (p=0.002 95% CI=1.955-7.541) improvement was reported comparing the verum group (9.5 ±1.04, 52%) with the placebo group (4.7±0.91, 27%). The secondary end points which included changes in quality of life, maximum urinary flow, residual urine volume, prostate volume also improved markedly. The Quality of life index decreased with 1.7 point in the verum group and with 0.7 point in the placebo group (no data for p value, 95% CI=0.4-1.6). A decrease of 19.2 ml in residual urinary volume in the verum group compared to 10.7 ml in the placebo group, and an increase of 7.1 ml/s in the maximal urinary flow in the verum group compared to 4.4 ml/s in the placebo group were observed. The difference of 2.7 ml/s in the maximum urinary flow between the verum group and the placebo group seems to be significant since this value was 1.6 ml/s at 13 week for Alfuzosin (Jardin A et al. 1991) 1.4 ml/s at 12 week for Tamsulosin (Abrams P 1995) and 1.4ml/s at 12 months for Finasterid (Gormley 1992) in comparison with placebo.

Table 8. Summary of the results of the Engelmann et al. (1996) study

Evaluation criteria	**Results**					
	Verum			Placebo		
	Before	After	Difference ±SEM	Before	After	Difference
IPSS	18.2 (12-26)	8.7 (4-14)	**9.5 ±1.04****	17.7 (12-29)	12.9 (6-24)	**4.7±0.91****
quality of life	3.4 (3-5)	1.6 (1-3)	1.7±0.16	3.2(3-5)	2.5 (1-5)	0.7±0.24
micturition volume (ml)	224.5 (113-317)	246.9 (119-560)	+22±22.9	232 (125-303)	262 (149-163)	+30±22.6
micturition duration (s)	36.6 (19.5-73)	27 (14-53)	-9.6±3	32.5 (19-65.5)	26.4 (18-49)	-6±1.6
maximum urinary flow (ml/s)	10.9 (3.7-16.7)	18.1 (11.5-25.2)	+7.1±1.2	12.3 (7.2-26.5)	16.8 (7.2-40.6)	+4.4±1.7
residual urine volume (ml)	47.8 (17.5-77.5)	28.6 (0-66.5)	-19.2±4.3	40.8 (21-102.5)	30.1 (9.0-5.5)	-10.7±5.6
prostate volume (sonograph) (cm)	34.4 (20.9-60)	33.3 (15.7-75)	1.1±1.7	38.3 (16.5-98)	35 (13-110)	3.3±1.3
Adverse effects:	1 dizziness			1 heartburn		

*International Prostate Symptoms Score (1-5, micturition frequency, nocturia frequency, hesitancy, decreased urinary stream, residual urine, urge to urine) according to the suggestion of the American Urological Association. 0-7 points=slight-grade, 8-19 points=middle-grade, 20-35 points=great-grade.

** A statistically significant improvement was reported (p=0.002 95% CI=1.955, 7.541) in International Prostate Symptoms Score comparing the verum group with the placebo group.

Assessor's comment: The results of the statistical analysis were given only for IPSS. SEM (Standard error of the mean) was used instead of SD (standard deviation). The article did not mention whether there was homogeneity evaluation between the two groups at the beginning and how many percentages of the patients responded to the treatment. The authors did not mention what they considered clinically relevant changes in the different efficacy parameters before the treatment. The product was removed from the market because of its unacceptable taste.

Long-term study

Safarinejad (2005): A **6 month**, double blind, placebo controlled, randomised, partial crossover, comparative trial of *Urtica dioica* with placebo in 620 patients was conducted. Each patient was given 120 mg of fluid extract of *Urtica dioica* root (n=305) three times daily or placebo (n=315). The herbal blend contained a standard preparation of 100 mg of *Urtica dioica* root extract in 1 ml. The placebo was indistinguishable from the *Urtica dioica*. Patients were evaluated using the International Prostate Symptoms Score* (IPSS), the maximum urinary flow rate (Q_{max}), postvoid residual urine volume (PVR), Serum Prostatic-Specific Antigen (PSA), testosterone levels, and prostate size. The unpaired t-test was used to assess differences between all the variables in the original double-blind trial protocol. By intention-to-treat analysis, at the end of the 6-month trial, 232 (81%) of 287 patients in the *Urtica dioica* group reported improved lower urinary tract symptoms (LUTS) compared with 43 (16%) of 271 patients in the placebo group (p<0.001). Both IPSS and Q_{max} showed greater improvement with drugs than with placebo. The IPSS went for 19.8 down to 11.8 with *Urtica dioica* and from 19.2 to 17.7 with

placebo (p=0.002). Peak flow rates improved by 3.4 ml/s for placebo recipients and by 8.2 ml/s for treated patients (p<0.05.) In *Urtica dioica* group, PVR decreased from an initial value of 73 to 36 ml (P < 0.05). No appreciable change was seen in the placebo group. Serum PSA and testosterone levels were unchanged in both groups. A modest decrease in prostate size as measured by transrectal ultrasonography (TRUS) was seen in *Urtica dioica* group (from 40.1 cc initially to 36.3 cc; P < 0.001). There was no change in prostate volume at the end of study with placebo.

At the end of the 6-month trial, unblinding revealed that patients who initially received placebo were switched to *Urtica dioica*. Both groups continued the medication up to 18 months. From 305 eligible patients taking *Urtica dioica* during the randomised trial, only 52 (17%) chose to discontinue after unblinding while most remained on *Urtica dioica* treatment. The reason for discontinuation included lack of efficacy (n=22), bothered by participation in the study (n=16) and achieved enough improvement (n=14). At the **18-month follow-up**, only patients who continued therapy had a favourable treatment variables value, with all values remaining stable from the end of the double-blind study to the 18-month follow-up. Of the 315 placebo patients, 236 (75%) subjects chose phytotherapy over the 18-month follow-up period. When they started *Urtica dioica* therapy, they had the same extent of symptom relief as had those who took *Urtica dioica* during the randomised study.

Five-hundred fifty-eight patients (90%) completed the study (287/305, 91% in the *Urtica dioica* group, and 271/315, 86% in the placebo group). Overall, patients had a substantial and lasting favourable effect compared with symptoms severity at randomisation. There was no additional effect from the longer treatment period. No side effects were identified in either group. The author concluded that in the present study, *Urtica dioica* has beneficial effects in the treatment of symptomatic BPH. Active treatment was generally better than watchful waiting. Further clinical trials should be conducted to confirm these results before concluding that *Urtica dioica* is effective.

Table 9. Summary of the results of the Safarinejad 2005 study

Evaluation criteria	**Baseline mean±SD**	**6. month mean±SD**	**At 18-month follow-up**	
			Urtica treatment continued mean ± SD	Urtica treatment discontinued mean ± SD
IPSS				
Urtica dioica (305)	19.8±4.9	**11.8±4***	11.1±4.8 (n=253)	19.1±4.2 (n=52)
Placebo (n=315)	19.2±4.6	17.7±3.1	12.1±3.8 (n=236)	19.4±3.9 (n=79)
Q_{max} (ml/s)				
Urtica dioica	10.7±2.4	**18.9±4.7****	16.2±3.2	11±3
Placebo	10.8±2.8	14.2±3.7	18.2±3.4	10.2±3.3
PVR (ml)				
Urtica dioica	73±32.6	**36±25.5*****	37±28.2	70±28
Placebo	74±29.6	71±24.4	38±25.5	77±22
Prostate volume (cc)				
Urtica dioica	40.1±6.8	36.3±4.2	36.1±7.2	39.5±6
Placebo	40.8±6.2	40.6±5.1	40.6±4.1	42.4±5.2

IPSS=International Prostate Symptoms score, Q_{max}= Maximum urinary flow rate, PVR= Postvoid residual urine volume SD= standard deviation

*P= <0.002 vs. placebo, **P= <0.05 vs. placebo, *** P=< 0.001 v placebo

Assessor's comment: This study was well designed. The duration of the treatment was also adequate, 6 months followed by an 18-month follow-up and the number of the patients involved (620) was sufficient. The authors did not mention what they considered clinically relevant changes in the different efficacy parameters before the treatment. However, it is impossible to identify the herbal preparation from the article. In case of a herbal preparation the exact composition (DER, extraction solvent) must be known.

The review article written by Chrubasik et al. 2007 mentioned in a table on nettle root products used in clinical and preclinical trials that the preparation investigated in the above study was Urtidin which had a drug-extract-ratio of 20:1 and was prepared using diethyl ether (100 mg/ml were standardised on 35 ppm scopoletin). However, this product has not been on the European market according to the market overview supplied by the Member States.

Open clinical studies

Open studies with dried 50% native extract of nettle root (DER: 7-14:1; extraction solvent methanol 20% V/V):

Eight open studies were mentioned in the ESCOP monograph (2003) with the above mentioned preparation whereof 4 were multi-centre, prospective observational studies with 14,408 patients altogether (Tosch and Müssiggang 1983; Stahl 1984; Friesen 1988; Vandierendounck & Burkhardt 1986; Maar 1987; Djulepa 1982; Bauer et al. 1988; Feiber 1988).

In most studies the indication was the benign prostatic hyperplasia (BPH), only in one study the preparation was also used for the treatment of prostatitis (Djulepa 1982). The patients were mostly in stadium I-II of the disease.

The dosage was 600-1200 mg of extract preparation per day in the open studies and duration of treatment ranged from 10 weeks to 24 months. In every open study the subjective symptoms improved significantly. Objective parameters as urinary flow and residual urine volume also decreased

(Friesen 1988; Maar 1987; Djulepa 1982; Feiber 1988). **In one study even a decrease in the prostate volume in 54% of cases were observed** (Feiber 1988).

The summary of the three large-scale multi-centre studies are the following:

Tosch und Müßiggang (1983): In an open, multi-centre study 5492 patients with BPH (Stadium I: n=2194, Stadium II: n=2928, Stadium III: n=370 as defined by Vahlensieck) were treated with 1200 mg of the above mentioned extract for one month and 600 mg for 2-3 months. According to the evaluation of the physicians the therapy was successful in 88.2% of total patients, 83.2%, 80.4% and 60.4% of patients with BPH stages I, II and III, respectively. Subjective and objective symptoms were evaluated according to the age groups with the help of a 3-point scale. Three points could be given for the maximum effect. Significant improvements were seen in the age group of below fifty with the value of 2.5 point in nocturia and daytime micturition frequency. The improvement was average of 1.7 point on average in the age group of 50-59 and 1.5 points in the age group of 60-69 in the daytime micturition frequency and 1 and 1.5 points respectively in nocturia. The mean urinary flow rate markedly increased as well. The increase was 3.2 ml/s in patients below 50 years, 2.5 ml/s in patients aged 50-59, 2.4 ml/s in patients aged 60-69 and 2.6 ml/s in patients older than 70 years. **From the results it can be concluded that the effectiveness of the therapy in the age group of 50-69 and in the stadium I-II was very significant, but it decreased with advanced age and advanced stadium.**

Eighty-four patients gave up treatment because of adverse effects which were the following: gastric complaints, nausea, heartburn, diarrhoea. Forty-four people stopped taking the preparation because of for example surgery, permanent catheter or wishing other medication. Eighty-six further adverse effects occurred: 54 gastric complaints (nausea, heartburn, eructation) 12 diarrhoea and 22 other complaints: allergy itching, palpitation, impotence, dizziness, lower leg oedema, and urge to urination.

Table 10. Summary of the results of the Tosch & Müssiggang 1983 study

Evaluation criteria	**Results**		
	Stadium I.	Stadium II.	Stadium III.
Opinion of physician about on the percentage of patients who improved	83.2	80.4	61
Evaluation criteria	Age <50	Age: 50-59	Age:60-69
Subjective symptoms (improvement score 1-3)			
daytime micturition frequency	2.5	1.7	1.5
nocturia	2.5	1.0	1.5
Objective parameters:			
average urinary flow rate improvement in ml/sec	3.2	2.5	2.4
residual urine volume (measured with catheter, X-ray or Sonograph, improvement score 1-4)	1	1	1

Stahl HP (1984): In a multicentric study 4051 patients with prostate adenoma in all stadiums were treated by 580 physicians with 1200 mg extract daily for 10 weeks for nocturnal pollakisuria.

Patients were categorised into four groups according to the seriousness of their nocturnal micturition frequency (see Table 11.)

Table 11. Categorisation of the patients according to their nocturnal micturition frequency (Stahl 1984)

Group	**Average micturition frequency**		**Number of patients**
	By night	By week	
1. group	up to 1	from 0 up to 7	384
2. group	from 1 up to 3	from 8 up to 21	2464
3. group	from 3 up to 5	from 22 up to 35	961
4.group	more than 5	36 and more	136
Cannot be evaluated			106
Total			4051

In the second, third and fourth group the average micturition frequency decreased by at least 50 percentage ($p<0.0001$).

Table 12. Summary of the results of the Stahl 1984 study

Evaluation criteria **Nocturia frequency (n= patients' number)**	**Results**				
	First week mean value (standard deviation)	Fifth week mean value	Tenth week mean value	Improvement comparing the mean value of the first week to the mean value of the tenth week	No effect
1. group weekly 0-7 (n=384)	5.5 (0.09-0.17)	4.6	3.8	31%	32%
2. group weekly 8-21 (n=2464)	14.7 (0.08-0.10)	10.3	7.3	50% P<0.0001	9.7%
3. group weekly 22-35 (n=961)	26.3 (0.11-0.25)	17.7	11.9	55% P<0.0001	4.4%
4. group weekly >36 (n=136)	42.9 (0.60-1.05)	27.8	18.6	57% P<0.0001	5.9%

Friesen A (1988): In another open, multi-centre study 4480 BHP patients received 600-1200 mg of extract preparation per day for 20 weeks. After 6 months 19.6% of the patients had no complaints, 47.5% of them felt significant improvement, 23.8% of them only small improvement and 8.8 % of them had no therapeutic effect. At the beginning of the treatment 4.2% of the patients were without nocturia and after 6-month treatment this value increased to 37.8%. At baseline, most of the patients (48.1%) had to urinate more than 3 times during the night but due to the therapy the percentage of these patients decreased to 6.3%. At start of the study pollakisuria characterised 73% of the patients, but after treatment only 12.6 % of them had this problem. All these changes were considered highly statistically significant by the authors.

The mean urinary flow increased significantly from 13.26 ml/s at baseline to 15.94 ml/s and 17.69 ml/s after 3 months and 6 months of therapy, respectively ($p < 0.01$).

During the treatment period the residual volume decreased significantly ($p < 0.01$) as well. Only 11.8 percentages of patients were without a residual volume (0 ml) before therapy and this rate increased after 3 months and 6 months of therapy to one quarter and to one third of the patients, respectively. Percentage of patients with a residual volume between 50 ml and 100 ml decreased from an initial 39.5% after 3 months to 23.7% and after 6 months to 14%. Percentage of patients with a residual volume between 100 ml and 200 ml decreased from initial 12.9% to 2.6% after 6 months. Only 0.7% of the patients experienced adverse effects (gastro-intestinal complaints).

Table 13. Summary of the result of the Friesen A study (1988)

Evaluation criteria	**Results**		
	At the beginning	At the end	difference
Nocturia frequency by night Percent of the patients without nocturia >3	 4.2% 48.1%	 37.8% 6.3 %	 Highly significant Highly significant
Pollakisuria Percent of the patients	 73%	 12.6%	 Highly significant
Average urinary flow rate (ml/s)	13.26	17.69	Highly significant P<0.01
Residual urine volume Percent of the patients with 0 ml 50-100 ml 100-200 ml	 11.8% 39.5% 12.9 %	 33% 14% 2.6%	 Highly significant P<0.01 for all groups

Open studies with other preparations:

Goetz (1989): Daily treatment for 60 days with 90-50 drops of a fluid extract (1:1, 45% ethanol; Ph. Fr.) led to 66% decrease in residual urine and **a decrease of the volume of the prostate** in an open study with 10 BPH patients. All patients experienced satisfying improvement in subjective symptoms (problems in emptying of the bladder, decreased urinary flow).

Table 14. Summary of the results of the Goetz 1989 study

Evaluation criteria	**Patients number before treatment**	**Patients number after treatment**
Nocturia frequency by night 0-2 3-4 >5	 1 4 5	 10
Residual urine volume 0-50 ml 50-100 ml >100ml	 3 0 7	 9 1 0
Prostate size	decreased in 5 cases unchanged in 4 cases increased in 1 case increased	

Belaiche et al. (1991): 67 BPH patients were treated with 3 times 5 ml of a fluid extract (1:5, 40% ethanol). After 6 months a reduction in nocturnal micturition frequency was observed (see Table 15. below)

Table 15. Summary of the results of the Belaiche at al study 1991

Evaluation criteria **Micturitition frequency / night**	**Results** **Patient' s number**			
	Before treatment	After treatment		
		No need to get up	≤2	No improvement
Group A ≤2	12	10	2	
Group B ≤3	27	13	10	4
Group C <3	28	7	17	4

Kaldewey (1995): In an open multi-centre study 1319 patients with BPH and/or prostatitis were treated daily with 378-756 mg of a native extract of nettle root (12-16:1, 70% V/V ethanol) for 6 months. 79.9% of the patients reported an improvement in their quality of life, 14.6 % of them felt that their conditions did not change and 2.7% of them thought that it worsened. 72.2% of the physicians evaluated the treatment as very good or good. Sixty point three percent of the patients experienced a substantial improvement in nocturia, 76.9% of them in dysuria and 70.3% of them in difficulty to initiate urination, respectively. Residual urine volume decreased in 56.9% of the cases and did not change in 38.6% (see details below in table 16). The average urinary flow rate improved in 71.6% of the patients with an increase of average 4 ml/s (from 13±8 ml/s to 17±8 ml/s). The micturition volume increased with an average of 26 ml (from 188±107 ml to 214±104 ml). The average of micturition duration shortened with 5 seconds (from 33±19 s to 28±15 s). **Prostate volume measured by ultra-sound decreased in average from 45±18 cm^3 to 41±18 cm^3**. Only 1% of the patients reported adverse effects in the form of mild gastro-intestinal disturbances.

Table 16. Summary of the result of the Kaldwey 1995 study

Evaluation criteria	**Number of the patients**	
	before treatment	after treatment
Nocturia frequency by night 0-3 >4	 204 (15.5%) 300 (22.7%)	 806 (61.1%) 26 (2%)
Pollakusuria (micturition ≥8 /day)	363 (27.5%)	35 (2.7%)
Dysuria	739 (56%)	150 (11.4%)
No hesitancy to initiate urination	88 (6.7%)	296 (22.4%)
Residual urine volume 0 >100ml	 154 (11.7%) 113 (8.6%)	 383 (29%) 15 (1.1%)

Klein-Bischoff et al. (2007): One hundred patients suffering from complaints of the lower urinary tract were investigated in a 24-week multi-centre study. The patients received 2 times 2 capsules of a preparation containing 240 mg of the dry extract from nettle root (PU240)(5.4-6.6:1, ethanol 20% V/V). After 24 weeks, the mean IPSS decreased significantly from 19.5±4.8 points to 13.0±5.0 points ($p<0.0001$). Maximum and average flow rate increased significantly from day 0 to day 168 ($p<0.0001$), with a simultaneous decrease of the mean voiding time and the mean time to maximum flow. For all subjective and objective parameters an improvement was demonstrated. The tolerability of PU 240 was assessed as 'very good' or 'good'. It was concluded that this preparation is an effective, safe and well-tolerated therapy for the treatment of patients with LUTS.

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

Most of the patients included in clinical studies were over 60 years old. BPH generally appears in men over 50 years due to ageing.

4.3. Overall conclusions on clinical pharmacology and efficacy

It can be concluded from the pharmacodynamic studies that nettle root extract can cause some morphological changes to prostatic cells.

Because of the variability of symptoms with time and inter-individual variability, a substantial placebo effect, and expected high dropout rate, there is a need for clinical trials with large number of patients with randomised, placebo-controlled, matched group design in BHP treatment (Jardin et al. 1991).

In spite of this suggestion only six randomised, double-blind, placebo-controlled clinical studies can be found in the literature. In three of them the patients number was very low, and in two of them the treatment period was very short (Dathe & Schmid 1987: 72 patients, 6-8 weeks; Engelmann et al. 1996: 41 patients, 3 months; Fisher & Wilbert 1992: 40 patients, 6 months).

Three studies used the International Prostate Symptoms Score (IPSS) for the evaluation (Engelmann et al. 1996; Schneider & Rübben 2004; Safarinejad 2005). Only Engelmann et al. (1996) mentioned they followed the rules of GCP, but from the date of the issue of the two other articles it can be presumed that they were conducted in a GCP environment as well.

As BPH is a chronic disease it is important to know whether a preparation is effective after long-term treatment.

There were only three studies reported with duration of 6-12 moths.

Fisher & Wilbert (1992): It is a randomised, double blind, placebo controlled study but only with 40 BPH II patients. The preparation is a dry extract (DER: 7-14:1, extraction solvent: 20% V/V methanol). The dosage is 1200 mg extract preparation per day. Duration of treatment is 6 months. The baseline parameters in the two groups are not mentioned in the articles. The standard deviation values can neither be found. A statistically significant decrease was found in the symptom score in the verum group (decreased from 4.8 to 3.63) compared to placebo (no change). Nevertheless this statement cannot be taken into count because the two groups were not homogenous after the first month placebo running period, the average symptoms score was 4.8 in the verum group and 3.29 in the placebo group, the average micturition volume was 215.4 in the verum group versus 203.8 in the placebo group (see Tables 5. and 6. above). After 6 months a statistically significant ($p<0.05$), but clinically not relevant decrease was found in micturition frequency (from 7.4 to 6.1, during 24 hours) in the verum group, but the data in the placebo group were not given. **The objective parameters (prostate volume, urinary flow, residual urine volume) did not change**. It can be concluded, that this article does not give relevant data for the evaluation of the efficacy.

Schneider & Rübben (2004): In this a randomised, double-blind, placebo controlled multi-centre study the same type of extract was used (DER: 7-14:1, extraction solvent: 20% V/V methanol), but the 246 patients took it only in a once-a-day formulation (459 mg dry extract) **for 1 year.** In this study the IPSS decreased on average from 18.7±.0.3 to 13.0±0.5 with a statistically significant difference compared to placebo (from 18.5±.0.3 to 13.8±0.5) $p=0.0233$, according to the „repeated measures model" (see Figure 1). However this method is not the generally accepted Wilcoxon test. The authors did not explain why this special method was applied. If the 31% the decrease of the IPSS score (-5.7± 0.5) in the verum group is compared with the 25% decrease (-4.7±0.5) in the placebo

group, the 6% difference cannot be considered as clinically significant. Conclusively, the result cannot be considered as persuasive.

The median Q_{max} increased by +3.0±0.4 ml/s (verum) in comparison to +2.9±0.4 ml/s (placebo), the median volume of residual urine changed from 35.5±3.4 ml to 20.0±2.8 ml (verum) and from 40.0±4.0 ml to 21.0±2.9 ml under placebo application. But these differences were not statistically significant.

Safarinejad (2005): In this study a significant improvement of subjective symptoms and objective parameters was reported. The study was well designed, with duration of 6 months (followed by an 18-month follow-up) and 620 patients were involved. However, it is impossible to identify the herbal preparation from the article.

Chrubasik et al. 2007 in their review article mentioned in a table on nettle root products used in clinical trials that the preparation investigated in the above study was Urtidin, which had a drug-to-extract ratio of 20:1 and which was prepared using diethyl ether. It is stated that this information came from the author, namely from Safarinejad.

Nevertheless, the well-established use concept of CD 2001/83/EC cannot be applied for this product. This product was not reported to be on the European market. It is a special extract where the extraction solvent is not a usual one: diethyl ether. The pharmacological and toxicological profile of this special extract is not mentioned in the article. It is not known how long this product has been on the market and how many people have been using it. The quantitative aspects of the use of the product cannot be estimated.

In summary, the effectiveness of nettle root has not yet been proven sufficiently to state the well-established use.

Short–term studies (Dathe & Schmid 1987 and Engelman et al. 1996) showed some favourable results, the large open multi-centre studies can also serve as positive signals as well, thus it would be worth to continue the work and to prove the efficacy of nettle root in the for symptomatic treatment of micturition disorders related to benign prostatic hyperplasia.

Furthermore, it should be taken into consideration that other treatment possibilities can guarantee better effectiveness.

Controlled studies have shown that α-blockers typically reduce the International Prostate Symptom Score (IPSS), after a run-in period, by approximately 35-40% and increase the maximum urinary flow rate Q_{max} by approximately 20-25%. Although these improvements take a few weeks to develop fully, statistically significant efficacy over placebo was demonstrated within hours to days. α-blockers seem to have a similar efficacy, expressed as a percent improvement in IPSS, in patients with mild, moderate and severe symptoms. Efficacy of α-blockers does not depend on prostate size and is similar in all age groups. However, α-blockers do not reduce prostate size and do not prevent acute urinary retention in long-term studies), so that eventually some patients will have to be surgically treated. Nevertheless, the efficacy of α-blockers appears to be maintained over at least 4 years (Oelke M et al. EAU Guideline 2010).

5. Clinical Safety/Pharmacovigilance

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

More than 16,000 patients have been treated with nettle root extracts in clinical studies and have taken daily doses of up to 756 mg of hydro-alcoholic dry native extract for periods of up to 6 months

or, in a few cases, 300 mg of dry native extract for 24 months. The incidence of adverse events was generally below 5%. No serious adverse effects have been reported, the majority of complaints being mild gastrointestinal upsets (ESCOP 2003). In the most recent large open study, involving 1319 patients, the incidence of adverse events probably related to treatment with nettle root extract was 1.0% (Kaldewey 1995).

The tolerability of the preparations was excellent. Only few, but not serious adverse effects occurred. Mainly gastro-intestinal complaints and in some cases allergic reactions occurred.

5.2. Patient exposure

So far, a total of about 40,000 men suffering from BPH have been treated with various nettle root preparations in 34 clinical studies (Chrubasik et al. 2007).

5.3. Adverse events and serious adverse events and deaths

Vontobel et al. (1985): Fifty BPH I-II patients enrolled in a double-blind, controlled study were treated daily with 600 mg of extract preparation (n=25) (DER: 5:1, extraction solvent: 20% V/V methanol) or placebo (n=25) for 9 weeks. Four patients in the Urticae radix group experienced adverse effects, obstipation, diarrhoea, gastro-intestinal complaints and one patient in the placebo group felt perineales pressure.

In the **Dathe G and Schmid (1987)** placebo controlled study the same preparation was used by 37 patients and nobody mentioned adverse effect during the 6-8 weeks treatment period.

Schneider & Rübben (2004): In the randomised, double-blind, placebo controlled multi-centre study, 459 mg of the nettle root extract (DER: 5:1, extraction solvent: 20% V/V methanol) was used daily by 246 patients for 1 year. The number of adverse events (29/38) as well as urinary infections etc. (3/10 events) was smaller in the treated group compared to placebo.

With the liquid preparation (1:1, extraction solvent: 16 % V/V ethanol) in the **Engelmann U et al. (1996)** study one patient in the treated group felt dizziness and one patient in the placebo group heartburn.

In the **Tosch und Müßiggang (1983)** open study with dried 50% native extract of nettle root (DER: 5:1; extraction solvent methanol 20% V/V) from 5492 treated patients 84 gave up treatment because of the following adverse effects: gastric complaints, nausea, heartburn, diarrhoea. Forty-four people stopped taking the preparation because of for example operation, permanent catheter or wishing other medication. 86 further adverse effects occurred: 54 gastric complaints (nausea, heartburn, eructation) 12 diarrhoea and 22 other complaints: allergy itching, palpitation, impotence, dizziness, lower leg oedema, and urge to urination. The study was 3-4 months long.

In the other big open multi-centric 6-month-study with the same preparation only 0.7 % of the 4480 patients complained about gastro-intestinal complaints **(Friesen A. 1988).**

Kaldewey W. (1995): In the multi-centric open studies where 1074 patients were treated with other extract of nettle root (DER 12-16 extraction solvent 70% ethanol) for six months only in 13 cases (1%) minor gastro-intestinal complaints were reported. 3 patients (0.2%) stopped the treatment because of adverse effects.

Chrubasik et al. (2007) in their review article gave the following summary: the number of adverse events has not been stated in all studies. Thus, the real number of adverse events may be higher than 699 adverse events which have been reported (estimated 2%). Most common complaints were urogenital, specifically impotence and decreased libido. Since the majority of patients were treated

with an extract prepared with 20% methanol, treatment with this particular proprietary extract seems to be safe in short term. Only few data are available for longer treatment periods and more long-term studies are needed to confirm the safety of nettle root products.

The nettle root monograph contains the undesirable effects mentioned in the Summary of Product characteristics of the most often used preparation (7.1-14.3:1, extraction solvent: 20% V/V methanol).

The frequency of the below mentioned adverse effects is not known.

Gastro-intestinal complaints such as nausea, heartburn, feeling of fullness, flatulentia, diarrhoea may occur.

Allergic reactions i.e. pruritus, rash, urticaria may occur.

Laboratory findings:

The value of PSA did not change during an 18-month long study (Safarinejad 2005).

5.4. Safety in special populations and situations

Contraindication

Hypersensitivity to the active substance.

Warnings

To draw the attention of the patients that if the complaints worsen or if the symptoms of other serious diseases occur they should look for a consultation with a physician the following warning can be found in the monograph:

If the urinary tract complaints worsen or if symptoms such as fever, spasm, blood in the urine, painful urination or retention of urine occur during the use of the medicinal product, a doctor should be consulted.

Drug interactions

Not reported.

Use in pregnancy and lactation, fertility

Not relevant.

Effects on ability to drive and use machines

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

Overdose

No case of overdose has been reported.

Withdrawal and rebound

In the Safararinejad (2005) study, patients, who discontinued the treatment after 6 months, had a relapse at the 18-month follow-up.

5.5. Overall conclusions on clinical safety

The tolerability of the preparations was excellent during the clinical studies. Only a few, not serious adverse effects occurred.

The safe use of nettle root preparations can be ensured with the help of the above mentioned contraindication and warnings in the suggested indication.

6. Overall conclusions

6.1. Assessor's Overall Conclusions

The guideline on the assessment of clinical safety and efficacy (EMA/HMPC/104613/05) states "In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy" for well-established use.

In the case of BPH, there is a need for long-term, randomised, placebo-controlled therapeutic trials with large number of patients, with a matched group design because of the variability of symptoms with time, inter-individual variability, a substantial placebo effect and an expected high dropout rate (Jardin et al. 1991).

Six randomised, double-blind, placebo-controlled clinical studies can be found in the literature.

Based on the discussion of the Committee on Medicinal Herbal Products these studies are not suitable to support well-established use of nettle root in BPH.

According to the earlier decision at the HMPC, a traditional indication was not regarded to be suitable for registration which led to a public statement that no monograph could be established.

Taken into account the comments by interested parties and considering the communication with the European Commission about options for indications for traditional use, the HMPC revised its position and concluded that an indication may be acceptable if it is including the phrase "…after serious conditions have been excluded by a medical doctor." (See Public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in Community herbal monographs (EMA/HMPC/473587/2011).)

The reputed beneficial effect of nettle root on BPH seems to be supported by *in vitro* and *in vivo* pharmacological studies. It seems likely that sex hormone binding globulin (SHBG), aromatase, epidermal growth factor and prostate steroid membrane receptors are involved in the prostatic effect of nettle root; however, it is less likely that 5-α-reductase or androgen receptors are involved.

So far more than 40 000 men have been treated with various nettle root preparations in 34 clinical studies. Only a few adverse effects have been reported. Nettle root preparations have been on the market for more than 30 years. From this period of use there are no substantial safety concerns.

Based on the above mentioned arguments, the indication of "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" is accepted for defined nettle root preparations.

Due to inadequate data on genotoxicity the inclusion of Urticae radix in the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

Annex

List of references