European Medicines Agency
Evaluation of Medicines for Human Use

London, 16 July 2009
Doc. Ref.: EMEA/HMPC/461156/2008

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

ASSESSMENT REPORT ON

URTICA DIOICA L., *URTICA URENS* L., THEIR HYBRIDS OR THEIR MIXTURES, RADIX

DISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	September 2008 November 2008 January 2009 July 2009
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	16 July 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 December 2009

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Note: This Assessment Report is published to support the release for public consultation of the draft 'Public Statement on *Urtica dioica* L., *Urtica urens* L., their hybrids or their mixtures, radix.' It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the public statement. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed, on an exceptional basis, to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft public statement.

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I. REGULATORY STATUS OVERVIEW[1]

MA: Marketing Authorization;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments[2]
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	☒ 32 db MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	5 authorized combination product
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
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:	Only in combination
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.
[2] Not mandatory field

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 x daily 1 sachet of 2.3 g containing 2.068g Urticae radix n 150 ml of boiling water, let 10 min extract and drink	1992
liquid extract from Urticae radix (1:1), extraction solvent: ethanol 30% V/V oral liquid		3 x daily 40 drops or 4 x daily 30 drops oral liquid containing 100% liquid extract 1 x daily 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,		1 x daily 1 film-coated tablet containing 460 mg dry extract 2 x daily 1 coated tablet containing 250 mg dry extract 3 x daily 1 hard capsule containing 150 mg dry extract At the begin of treatment for the first 3 month and in stage II 2 x daily 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 x daily 1 coated tablet containing 161 mg dry extract 1 x daily 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		1 x daily 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		2 x daily 1 coated tablet containing 150.5 mg dry extract 2 x daily 1 hard capsule containing 189 mg dry extract	at least since 1976

Table 2 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 x daily 1 film-coated tablet containing 285 mg dry extract	2001
dry extract from Urticae radix (5.4-6.6:1), extraction solvent: ethanol 80% (V/V) hard capsules		3 x daily 1 hard capsule containing 240 mg dry extract At the begin of treatment 2 x daily 2 hard capsules 3 x 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 x 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		2 x daily 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		1 x daily 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 begin of treatment 3 x daily 1 hard capsule containing 115 mg dry extract After amelioration of discomfort and for long-term treatment 2 x daily 1 hard capsule	1991

II. ASSESSMENT REPORT ON *URTICA DIOICA* L., *URTICA URENS* L., THEIR HIBRIDS OR THEIR MIXTURES, RADIX

BASED ON ARTICLE 10A OF DIRECTIVE 2001/83/EC AS AMENDED

(WELL-ESTABLISHED USE)

BASED ON ARTICLE 16D (1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Whole, cut or powdered dried root and rhizomes *of Urtica dioica* L. *Urtica urens* L, their hybrids or mixtures of these.
Herbal preparation(s)	Liquid extract, extraction solvent water Liquid extract, extraction solvent ethanol Dry extract, extraction solvent methanol Dry extract, extraction solvent ethanol
Pharmaceutical forms	Herbal substance or herbal preparation in solid or liquid dosage forms or as an herbal tea for oral use.
Rapporteur	Dr. Susanna Biro-Sándor
Assessor(s)	Dr. Susanna Biro-Sándor Dr. Dezső Csupor

II.1 INTRODUCTION

This assessment report reviews the available scientific data for nettle root until the end of December 2008 (PubMed).

II.1.1.1 Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s) [3]:

Definition of the herbal substance:

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.
The material complies with the German Pharmacopoeia (DAB 10).

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

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

Phytotherapy 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 (Deutches Arzneibuch - DAB 10, 1993)

British Herbal Pharmacopoeia (BHP 1996)

Phytotherapy in der Urologie (Schilcher & Wülker 1992)

Hagers Handbuch (Blaschek et al. 1998)

WHO monographs (WHO 2002)

- Herbal preparation(s):

Herbal tea
Comminuted herbal substance (products on the market since 1992)

3 According to the 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMEA/HMPC/182320/2005 Rev.2) and the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use (EMEA/HMPC/182352/2005 Rev.2)

Extracts

A) Liquid extract from Urticae radix (1:1), extraction solvent: water (Blaschek et al. 1998)

B) Liquid extract from Urticae radix (1:1), extraction solvent 16% ethanol (ESCOP 2003, Engelmann et al. 1996)

C) Liquid extract from Urticae radix (1:1), extraction solvent: ethanol 30% V/V (product on the market at least since 1976)

D) Liquid extract from Urticae radix (1:5), extraction solvent: ethanol 40% (ESCOP 1996, 2003)

E) Liquid extract from Urticae radix (1:1), extraction solvent: ethanol 45% V/V, prepared according to PF X) (ESCOP 1996, 2003; Blaschek et al. 1998 and Goetz 1989)

F) Dry extract from Urticae radix (7-14:1), extraction solvent: methanol 20% V/V (Blaschek et al. 1998; ESCOP 2003) (products on the market since 1991/2000)

G) Dry extract from Urticae radix (7.1-14.3:1), extraction solvent: methanol 20% V/V (product on the market at least since 1976)

H) Dry extract from Urticae radix (6-11:1), extraction solvent: methanol 20% V/V (product on the market since 2001/2003)

I) Dry extract from Urticae radix (6.7-8.3:1), extraction solvent: ethanol 20% V/V (product on the market since at least 1976)

J) Dry extract from Urticae radix (7-9:1), extraction solvent: ethanol 60% V/V (product on the market since 1992)

K) Dry extract from Urticae radix (8-12:1), extraction solvent: ethanol 60% m/m (product on the market since 1998/1999)

L) Dry extract from Urticae radix (8.3-12.5:1), extraction solvent: ethanol 60% m/m (Blaschek et al. 1998)

M) Dry extract from Urticae radix (12-16:1), extraction solvent: ethanol 70% V/V (product on the market at least since 1976)

N) Dry extract from Urticae radix (15-20:1), extraction solvent: ethanol 80% (V/V) (product on the market since 2001)

O) Dry extract from Urticae radix (5.4-6.6:1), extraction solvent: ethanol 80% (V/V) (product on the market since 1993/1994)

P) Dry extract from Urticae radix (15.75-19.25:1), extraction solvent: ethanol 80% (V/V) (product on the market since 1991)

II.1.2 Information on period of medicinal use in the Community regarding the specified indication

Evidence regarding the indication/traditional use

Nettle roots were mentioned as herbal medicines first by Paracelsus and Matthiolus (Madaus 1938). In folk medicine, nettle herb and leaves were of higher importance than nettle roots. In the Russian folk medicine, the powder of the roots and seeds 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 blood purifier, styptic, stimulating tonic and diuretic to treat diarrhoea, dysentery, discharges, chronic diseases of the colon and chronic skin eruptions (Mills 2003).

A 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. Today it is used mainly in the symptomatic treatment of early stages of benign prostatic hyperplasia (BPH) (Bradley 2006). The Commission E approved the use of nettle root for difficulty in urination in BPH stages I and II (Blumenthal 1998). 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). 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 dysorders in the early stages of 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). 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:

Hagers Handbuch (Blaschek et al. 1998). In folk medicine as a component in 'blood-purifying' combination-preparations, against dropsy, for prostatitis, rheuma, gout similar to nettle herb.

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

Jaspersen-Schib R. (1989): mild diuretic

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

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.

Evidence regarding the specified posology

- Herbal substance:

Daily dose: 4-6 g of the drug as an infusion (ESCOP 1996, 2003; Schilcher & Wülker 1992; Bisset 1994; Blaschek et al. 1998)

- Herbal preparation(s):

Infusion: „Making tea: 1.5g of the coarsely powdered drug 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 extracts:

A) Liquid extract from Urticae radix (1:1), extraction solvent: water, daily dose: 6 ml (Blaschek et al. 1998)

B) Liquid extract from Urticae radix (1:1), extraction solvent: 16% ethanol, 2x3 ml daily (equivalent to 4.68 g of the fluid extract) (ESCOP 2003; Engelmann et al. 1996)

C) Liquid extract from Urticae radix (1:1), extraction solvent: ethanol 30% V/V,
3 x daily 40 drops or 4 x daily 30 drops (product on the market at least since 1976)
1 x daily 5 ml (product on the market at least since 1990)

D) Liquid extract from Urticae radix (1:5), extraction solvent: ethanol 40% (ESCOP 1996), 5 ml daily

E) Liquid extract from Urticae radix (1:1), extraction solvent: ethanol 45% V/V, prepared according to PF X (Blaschek et al. 1998) At the beginning 30 drops daily, later in most of the cases the dose increased to 150 drops daily (ESCOP 2003; Goetz 1989)

Dry extracts:

F) Dry extract from Urticae radix (7-14:1), extraction solvent: methanol 20% V/V
2 x 300 mg daily corresponding to 6300 mg drug daily (ESCOP 2003; Blaschek et al. 1998)

1 x daily 1 film-coated tablet containing 460 mg dry extract, corresponding to 4830mg drug (products on the market since 2000)

2 x daily 1 coated tablet containing 250 mg dry extract, corresponding to 5250 mg drug (products on the market since 2000).

3 x daily 1 hard capsule containing 150 mg dry extract, corresponding to 4725 mg drug daily, at the beginning of treatment for the first 3 months and in stage II, 2 x daily 2 hard capsules, corresponding to 6300 mg drug daily (products on the market since 1991).

G) Dry extract from Urticae radix (7.1-14.3:1), extraction solvent: methanol 20% V/V,
3 x daily 1 coated tablet containing 161 mg dry extract, corresponding to 5168 mg (products on the market at least since 1976)

1 x daily 1 film-coated tablet containing 459 mg dry extract, corresponding to 4911 mg (products on the market at least since 1976)

H) Dry extract from Urticae radix (6-11:1), extraction solvent: methanol 20% V/V,
1 x daily 1 film-coated tablet containing 600 mg dry extract, corresponding to 5100 mg drug daily (products on the market since 2001/2003)

I) Dry extract from Urticae radix (6.7-8.3:1), extraction solvent: ethanol 20% V/V,
3 x daily 1 soft capsule containing 240 mg dry extract corresponding to 5400 mg drug daily (products on the market at least since 1976/1996/1997)

J) Dry extract from Urticae radix (7-9:1), extraction solvent: ethanol 60% V/V,
2 x daily 2 film-coated tablets containing 125 mg dry extract corresponding to 4000 mg drug daily (products on the market since 1992)

K) Dry extract from Urticae radix (8-12:1), extraction solvent: ethanol 60% m/m,
1 x daily 1 coated tablet containing 475 mg dry extract, corresponding to 4750 mg drug daily (products on the market since 1998/1999)

L) Dry extract from Urticae radix (8.3-12.5:1), extraction solvent: ethanol 60% m/m, 2 x 120 mg daily corresponding to 2496 mg drug daily (Blaschek et al. 1998)

M) Dry extract from Urticae radix (12-16:1), extraction solvent: ethanol 70% V/V, 2 x daily 1 coated tablet containing 150.5 mg dry extract, corresponding to 4214 mg drug daily (products on the market at least since 1976)

2 x daily 1 hard capsule containing 189 mg dry extract, corresponding to 5292 mg drug daily (products on the market at least since 1976)

N) Dry extract from Urticae radix (15-20:1), extraction solvent: ethanol 80% (V/V), 1 x daily 1 film-coated tablet containing 285 mg dry extract, corresponding to 4988 mg drug daily (product on the market since 2001)

O) Dry extract from Urticae radix (5.4-6.6:1), extraction solvent: ethanol 80% (V/V), 3 x daily 1 hard capsule containing 240 mg dry extract, corresponding to 4320 mg drug daily. At the beginning of treatment 2 x daily 2 hard capsules corresponding 5760 mg drug daily (product on the market since 1993)

3 x daily 1 hard capsule containing 240 mg dry extract, corresponding to 4320 mg drug daily (product on the market since 1994)

P) Dry extract from Urticae radix (15.75-19.25:1), extraction solvent: ethanol 80% (V/V), at the beginning of treatment 3 x daily 1 hard capsule containing 115 mg dry extract, corresponding to 6038 mg drug daily. After amelioration of discomfort and for long-term treatment, 2 x daily 1 hard capsule, corresponding to 4025 mg drug daily (product on the market since 1991)

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

II.2.1.1.1 Constituents

Based on Blaschek 1998; ESCOP 2003; Mills 2003; Blumenthal 1998; 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.

Phenyl propanes: 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%.

II.2.1.1.2 Pharmacodynamics

Aromatase inhibition

A potential role of estrogens in the development of BPH has been emphasized by animal studies (Habenicht 1991). The biological action of estrogens may be blocked either by estrogen receptor antagonists or by suppressing estrogen 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 needs still 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 aromatized (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 5α-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 5α-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 5α-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 estrogens. 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: estrogen 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 (11*E*)-9,10,13-trihydroxy-11-octadecenoic acid and (10*E*)-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 recognized 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 catalyzes 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 recognized (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 900 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 an urogenital sinus (UGS) into the ventral prostate gland of an adult mouse) five differently prepared stinging nettle root extracts were. The 20% methanolic extract was the most effective with a 51.4% inhibition of 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 UDA, lectin and saccharyde content of the extract. (Lichius 1997; Blaschek 1998).

II.2.1.2 Assessor's overall conclusions on pharmacology

The reputed beneficial effect of nettle root on BPH is supported by *in vitro* and *in vivo* pharmacological studies, however, the active substances for the pharmacologic actions are unknown, which makes quality control and chemical standardization of extracts difficult (Blumenthal 1998).

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No studies.

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

No studies.

II.2.3.2 Assessor's overall conclusions on toxicology

No studies.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

II.3.1.1 Pharmacodynamics

II.3.1.1.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

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 prostate (Oberholzer et al. 1987.

II.3.1.1.2 Assessor's overall conclusions on pharmacodynamics

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

II.3.1.2 Pharmacokinetics

II.3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

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).

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

The therapeutically active components of nettle root are not known, therefore no conclusion can be drawn.

II.3.2 Clinical Efficacy[4]

II.3.2.1 Dose response studies

There are no studies.

II.3.2.2 Clinical studies (case studies and clinical trials)

II.3.2.2.1 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; Schneither & 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:

[4] In case of traditional use the long-standing use and experience should be assessed.

(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))

Fisher & Wilbert (1992): In a randomized, double blind, placebo controlled study 40 BPH II patients (1200mg extract preparation per day (2x2 caps) n= 20; placebo n=20), 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 considerably. 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. (See also Appendix I - tables of placebo controlled studies).

Dathe & Schmid (1987): In double blind, placebo controlled study patients in stadium I of BPH were randomized to 600 mg of nettle root extract (2 x 1 caps.) (n=35 or to matching placebo (n= 37). After 6-8 weeks of treatment in the verum group significant improvements of 14% in average urinary flow rate (ml/s), 13% in micturation duration (second), 12% in maximum urinary flow (ml/s) and 40% in residual urine volume (ml) were observed. There was no remarkable difference between the two groups in subjective symptoms. (See also Appendix I.)

Vontobel et al. (1985): 50 BPH I-II patients enrolled in a double-blind, controlled study were treated daily for 9 weeks with 600 mg of extract preparation (n=25) or placebo (n=25). A significant increase of 44% in micturition volume (ml) ($p<0.05$) and a highly significant decrease in serum levels of SHBG ($p=0.0005$) were observed. Maximum urinary flow (ml/s) improved with 8.6% in the treated group, but decreased in the same degree in the placebo group ($p=0.062$). There was no remarkable difference between the two groups in subjective symptoms. (See also Appendix I.)

Schneider & Rübben (2004): The authors performed a randomized, double-blind , placebo controlled multi-center study for 1 year wit Bazoton®-uno, 459 mg dry extract of stinging nettle roots, [(7.1-14.3:1), extraction solvent methanol 20% V/V, from Rote Liste] 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; $p=0.0233$). The median Qmax increased by 3.0±0.4 ml/s in comparison to 2.9±0.4 ml/s (placebo) thus not a statistically significantly different, as well as the median volume of residual urine, which changed from 35.5±3.4 ml before therapy to 20±2.8ml 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 also Appendix I.)

'Figure.from **Schneider & Rübben (2004)**

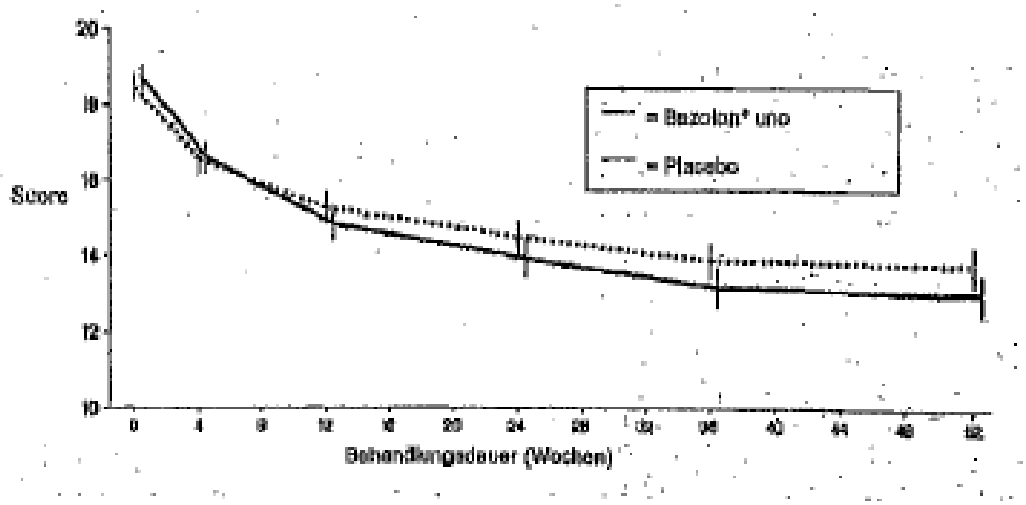


Abb. 1 ▲ Mittelwertverläufe des IPSS ± SEM über 52 Wochen (Itt: n=226)
(p=0,0233 im „repeated measures model")

Placebo controlled studies with other preparations:

Engelmann et al. (1996): In a double blind, multi-centric study, 41 BPH patients were treated for 3 months with either 2x3ml 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). A decrease in residual urinary volume of 19.2 ml in the verum group compared to 10.7 ml in the placebo group, and an increase in maximal urinary flow of 7.1 ml/s in the verum group compared to 4.4 ml/s in placebo group, were observed. A significantly greater improvement (p=0.002) in International Prostate Symptoms Score* in the verum group was also reported.

Safarinejad (2005): A 6 month, double blind, placebo controlled, randomized, partial crossover, comparative trial of *Urtica dioica* with placebo in 620 patients was conducted. Patients were evaluated using International Prostate Symptoms Score* (IPSS), the maximum urinary flow rate (Qmax), postvoid residual urine volume (PVR), Serum Prostatic-Specific Antigen (PSA), testosterone levels, and prostate size. At the end of the 6 month trial, unblinding revealed that patients who initially received the placebo were switched to *Urtica dioica*. Both groups continued the medication up to 18 months. 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). 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 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 Qmax 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 the prostate volume at the end of study with placebo. At 18-month follow-up, only patients who continued therapy had a favorable treatment variables value, with all values remaining stable from the end of the double-blind study to the 18-month follow-up. There was no additional effect from the longer treatment period. No side effects were identified in either group. CONCLUSION: In the present study, *Urtica dioica* has beneficial effects in the treatment of symptomatic BPH. Further clinical trials should be conducted to confirm these results before concluding that *Urtica dioica* is effective.

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

II.3.2.2.2 Open clinical studies

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

Other 7 open studies were conducted with the above preparation, Bazoton® whereof 4 were multi-centric, prospective observational studies with 14,408 patients altogether (Tosch & Müssiggang 1983; Stahl 1984; Friesen 1988; Vandierendounck & Burkhardt 1986; Maar 1987; Djulepa 1982; Bauer et al. 1988; Feiber 1988). Detailed data from three multi-centric studies can be seen in Appendix II. of the nettle root assessment report (Tables of open clinical studies: Tosch & Müssiggang 1983; Stahl 1984; Friesen 1988)

In most studies the indication was the benign prostatic hyperplasia (BPH), only in one study the preparation was also used for treatment of prostatitis (Djulepa 1982). The patients were mostly in stadium I-II of the disease.
The evaluation criteria were the change in the subjective symptoms (micturition frequency, nocturia frequency), and objective parameters were also measured (prostate volume, maximum urinary flow rate, residual urine volume).

The dosage was 600-1200 mg of extract preparation per day in the open studies and duration of treatment was 10 weeks - 24 moths. 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). Even in one study decrease in the prostate volume in 54% of cases were observed (Feiber 1988).

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 in an open study with 10 BPH patients. (See Appendix II.)

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

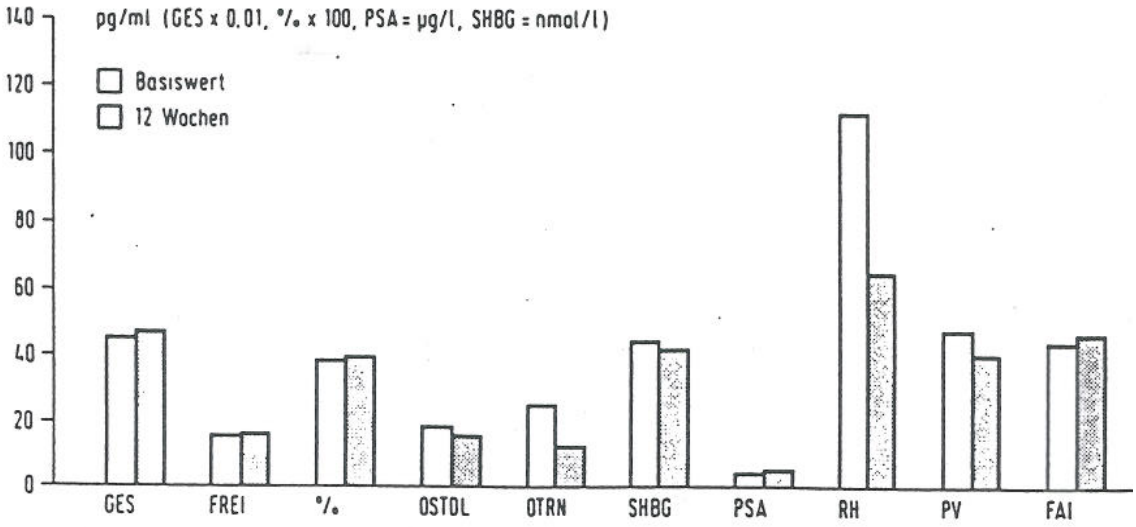
Kaldewey (1995): In an open multi-centre study involving 1319 patients with BPH and/or prostatitis, daily treatment for 6 months with 378-756 mg of a native extract of nettle root (12-16:1, 70% v/v ethanol) led to substantial improvements in dysuria, nycturia, pollakisuria, urinary flow and residual urine volume. 79.9% of the patients reported an improvement in their quality of life (See Appendix II.).

II.3.2.2.3 Changes in serum parameters in clinical studies

In 3 studies SHBG, testosterone, 5-alfa-DHT, estradiol and oestron serum levels were also measured (Fischer & Wilbert 1992; Vontobel et al. 1985; Bauer et al. 1988). In the study published by Safarinejad (2005), prostate volume, serum PSA and testosterone levels were documented.
SHBG levels decreased significantly in the three studies. Sexual hormone parameters did not change significantly (Fischer & Wilbert 1992; Vontobel et al. 1985). Serum PSA and testosterone levels were unchanged after 6-month therapy (Safarinejad 2005).

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 **(**2x2 Bazoton capsules**)** and after 12 weeks.

Figure from **Bauer et al. (1988)**



Results of the ERU study. (n=253) GES: Total-testosterone, FREI: free testosterone, %=percent 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: Since the recent study of Safarinejad (2005) is placebo-controlled and of longer duration than previous studies, the Committee appreciated the results of this study. The fact that the value of PSA did not change during a 6 month-long placebo-controlled study is mentioned in the monograph. Bauer et al. (1988) did not publish any numeric data (only a figure) and the article was part of a promotion work from one of the authors, therefore the significance of this publication is questionable.

II.3.2.3 Clinical studies in special populations (e.g. elderly and children)

Most of the patients were over 60 years. This disease generally appears in men over 50 years due to ageing.

II.3.2.4 Assessor's overall conclusions on clinical efficacy

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. In three of them the patients number was very low, and in two of them the treatment period is 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 under GCP circumstances as well.
Since in this disease the placebo effect is considerable, only long-term (at least 6-12 moths) studies can be accepted. Only three studies met this requirement.

Fisher & Wilbert (1992): It is a randomized, 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. Standard deviation values can not be found as well. They found statistically significant ($p<0.05$) but clinically not relevant decrease in micturition frequency (from 7.4 to 6.1, during 24 hours) in the verum group after 6 months, the data in the placebo group were not given. Significant decrease SHBG level was observed as well. The subjective symptoms

score, which consist of hesitancy, intermittency, terminal dribbling, desire to urinate, decrease in force and size of the urinary stream, dysuria, and sensations of incomplete emptying, improved considerably. 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. It can be concluded, that this article does not give relevant data for evaluation of the efficacy.

Schneider & Rübben (2004): Although 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 p=0.0233, the *„repeated measures model"* as used for statistical evaluation seems not to be persuasive.

'Figure from **Schneider & Rübben (2004)**

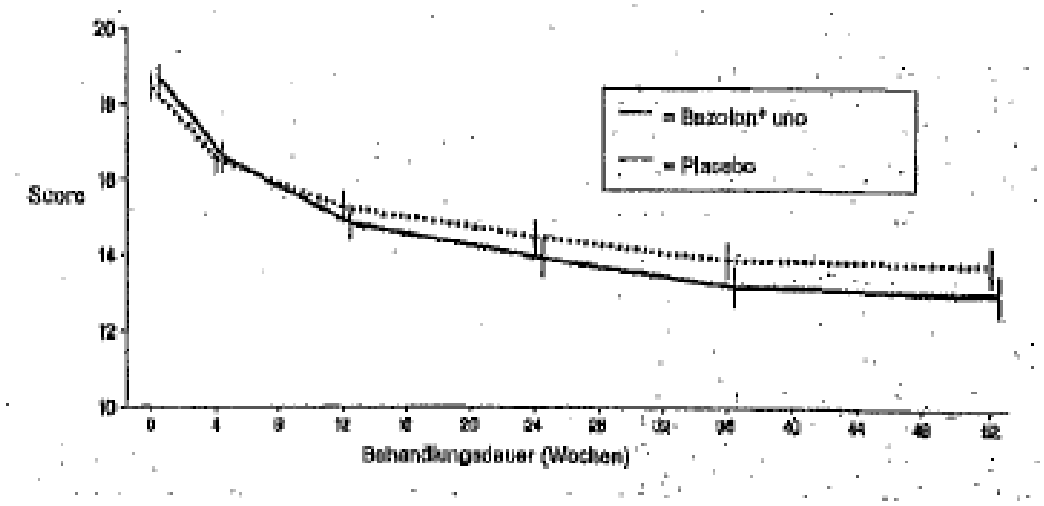


Abb. 1 ▲ Mittelwertverläufe des IPSS ± SEM über 52 Wochen (ITT: n=226)
(p=0,0233 im „repeated measures model")

The median Qmax increased by +3.0±0.4 ml/s in comparison to +2.9±.0.4 ml/s (placebo), the median volume of residual urine, which changed from 35.5±.3.4 ml before therapy to 20.0±.2.8 ml and from 40.0±.4.0 ml to 21.0±.2.9 ml under placebo application. They are not statistically significant different.
[The dosage was 459 mg of extract (7.1-14.3:1, extraction solvent: methanol 20% V/V).]

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

In summary, the effectiveness of nettle root is not proven sufficiently. One properly conducted placebo-controlled study was too short (with duration of only three months) (Engelmann et al/ 1996). The study published by Schneider & Rübben (2004) was long enough, but the result was not persuasive. In the article by Safarinejad (2005) it is impossible to identify the herbal preparation. None of these studies give answers for questions concerning the percentage of the responders, what they consider clinically relevant changes in the objective parameters before the treatment.

The large open multi-centre studies can serve only as positive signals.

II.3.3 Clinical Safety/Pharmacovigilance

II.3.3.1 Patient exposure

II.3.3.2 Adverse events

Over 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 under 5%. No serious adverse effects have been reported, the majority of complaints being mild gastrointestinal upsets. 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, not serious adverse effects occurred. Mainly gastro-intestinal complaints and in some cases allergic reactions occurred.
In the Schneider & Rübben (2004) study the number of adverse events (29/38) as well as urinary infection etc. (3/10 events) was smaller under Bazoton ®-uno therapy compared to placebo. Only very few gastro-intestinal and one allergic side-effects (urticaria) occurred.

Frequency data of adverse effects from the SPC of Bazoton preparations:

According to MedDRA system organ class and frequency convention:

Gastrointestinal disorders: Gastro-intestinal complaints (nausea, heartburn, feeling of repletion, flatulentia, diarrhoea) may occur commonly (>1/100, <1/10).

Immune system disorders: Allergic reactions i.e. pruritus, rash, urticaria may occur uncommonly (>1/1,000, <1/100).

II.3.3.3 Serious adverse events and deaths

There were no serious adverse events reported.

II.3.3.4 Laboratory findings

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

II.3.3.5 Safety in special populations and situations

II.3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

II.3.3.5.2 Contraindication

Hypersensitivity to the active substance(s).

II.3.3.5.3 Warnings

If urinary tract complaints worsen and symptoms such as fever, spasm, blood in the urine, retention of urine occur during the use of medicinal product, a doctor should be consulted.
In order to minimise cancer risk, regular medical checks of the prostate are recommended, because symptoms may improve without decrease of the size of the prostate.

II.3.3.5.4 Drug interactions

Not reported.

II.3.3.5.5 Use in pregnancy and lactation

Not relevant.

II.3.3.5.6 Overdose

No case of overdose has been reported.

II.3.3.5.7 Drug abuse

Not reported.

II.3.3.5.8 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.

II.3.3.5.9 Effects on ability to drive or operate machinery or impairment of mental ability

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

II.3.3.5.10 Assessor's overall conclusions on clinical safety

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

II.4 ASSESSOR'S OVERALL CONCLUSIONS

The effectiveness of the nettle root is not proven sufficiently in BPH. There are only three properly conducted placebo controlled studies. One of these studies was too short (only three months), the other two were long enough. However, one of those is not persuasive and in the other study the products can not be identified. The studies did not provide satisfactory answers to some important questions: the percentage of the responsive patients and what they considered clinically relevant changes in the objective parameters before the treatment.

The large open multi-centre studies can serve as positive signals only.

The Committee concluded that the effectiveness of nettle root in BPH is not proven properly. Since BPH is a disease which can not be treated without medical control, a traditional indication can not be accepted. Consequently, a positive monograph can not be prepared for nettle root, neither for well-established use nor for traditional use.

APPENDICES

1. TABLES OF PLACEBO CONTROLLED STUDIES

Name of author:	**Dathe G, Schmid H.**					
Reference /Year	Urologe [B] 1987; 27:223-6 [26]					
Name of the product:	Bazoton® 300mg					
Producer:	**KANOLDT Arzneimittel GmbH**					
Active substance	300mg Extractum Radicis Urticae (ERU)					
	DER: 7-14:1		**Extraction solvent:** 20% V/V methanol			
Type	Randomised, double blind, placebo controlled					
Patient number:	Verum: 35 Placebo: 37 Age: 54-83 years					
Indication:	BPH I					
Duration Dosage/day	Time: 6-8 weeks		Dosage/day: 2x1caps. (600mg)			
Evaluation criteria:	**Results**					
	Verum			Placebo		
	Before	After	**Difference**	Before	After	**Difference**
micturition volume (ml	282	292	**+10**	291	289	- 2
micturition duration (s)	31	27	**-4 (13%) significant**	31.6	31.3	- 0.3
average urinary flow rate (ml/s)	9.4	10.7	+1.3 (14%) **significant**	9.3	9.5	+ 0.2
maximum urinary flow (ml/s)	13.8	15.4	+ 1.6 (12°%) **significant**	13.9	13.2	- 0.7
flow rising time (s)	6.1	5.2	- 0.9 (15%) **significant**	6.2	6.1	- 0.1.
residual urine volume (ml) measured with catheter	94	56	38 (40%) **significant**	75	69	- 6

Name of author:	**Dathe G, Schmid H. (continued)**					
Evaluation criteria:	Results					
	Verum			Placebo		
	Before	After	**Difference**	Before	After	**Difference**
residual urine volume (ml) measured by Sonographie	95	72	- 15 (24%)	85	113	+ 28
Residual volume under 100ml	62	29	- 32 (53%)	35	30	-5
subjective symptoms: (micturition frequency, nocturia frequency, difficulty in initiating urination, quality of the urinary stream, terminal dribbling)	no remarkable difference between the two groups					
Adverse effect	No					

Name of author:	**Engelmann U. et al.**						
Reference /Year	Urologe [B] 1996; 36: 287-91 [40]						
Name of the product:	Bazoton® solution						
Producer:	***KANOLDT Arzneimittel GmbH***						
Active substance	Liquid extract from Urticae radix						
	DER: 1:1		**Extraction solvent:** 16 % (V/V) ethanol, 20% methanol ?				
Type	Randomised, double blind, placebo controlled, **GCP**						
Patient number:	Verum: 20 Age: 67 (49-84)			Placebo: 21 Age: 63(51-84)			
Indication:	BPH; Max. Urine. flow <15ml/s, Micturition volume >100ml residual urine volume > 30ml						
Duration Dosage/day	Time: 3 months			Dosage/day: 2x3ml= 4,68g fluid extr.			
Evaluation criteria:	**Results**						
	Verum			Placebo			Significance
	Before	After	Differ.	Before	After	Differ.	
International Prostate symptoms score**	18.2	8.7	9.5	17.7	12.9	4.7	**p=0.002** 95% CI: 1.995-7.541
micturition volume (ml)	225	247	+22	232	262	+ 30	
micturition duration (s)	36.6	27	- 9.6	32.5	26.4	- 6	
maximum urinary flow (ml/s)	10.9	18.1	+ 7.1	12.3	16.8	+4.4	**Significant (2.7 ml/s)**
residual urine volume (ml)	47.8	28.6	-19.2	40.8	30.1	-10.7	
Prostate volume (Sonograph) (cm)	34.4	33.3	1.1	38.3	35	3.3	
Quality of life	3.4	1.6	1.7	3.2	2.5	0.7	95% CI: 0.4-1.6
Adverse effects	1 dizziness			1 heartburn			

*This value is for Alfuzosin 1.5ml/s, for Tamsulosin 1.0ml/s, Finasterid 1.4ml/s in comparison with placebo.
** 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 point = slight-grade, 8-19 point = middle-grade, 20-35 = great-grade

Name of author:	**Fischer M & Wilbert D.**	
Reference /Year	Fischer M, Wilbert D. Wirkprüfung eines Phytopharmakons zur Behandlung der benignen Prostata hyperplasie (BPH). In Rutishauser G, Editor. Benigne Prostatahyperplasie III. Klinische und experimentelle Urologie 22. München-Bern-New York: Zuckschwert, 1992:79-84	
Name of the product:	1200mg Extractum Radicis Urticae (ERU) Bazoton®300mg	
Producer:	**KANOLDT Arzneimittel GmbH**	
Active substance	300mg Extractum Radicis Urticae (ERU)	
	DER: 7-14:1	**Extraction solvent:** 20% V/V methanol
Type	Randomised, double blind, placebo controlled	
Patient number:	Verum: 20 Placebo: 20 Age: 54-83 years	
Indication:	BPH II.	
Duration Dosage/day	Time: 1 month placebo therapy 6 months placebo or verum	Dosage/day: 2x2 caps.
	Results	
Evaluation criteria:	Verum	Placebo
Micturition frequency (during 24 hours)	from 7.4 to 6.1 decreased ($p<0.05$)	*No change*
nocturia frequency	considerable improvement	
Subjective symptoms-score: hesitancy, intermittency, terminal dribbling, desire to urinate, decrease in force and size of the urinary stream, dysuria, sensations of incomplete emptying	**from 4.8 to 3.63** decreased, significant improvement	from 3,29 to 3,3 no change
Objective parameters (prostate volume, urinary flow, residual urine volume)	did not change	worsening

Name of author:	**Fischer M &Wilbert D. (continued)**	
Evaluation criteria:	**Results**	
	Verum	Placebo
Endocrine parameters: **SHBG levels** 5α-DHT concentration difference free and bounded testosterons conc. free and bounded oestradiol conc.	 decreased significantly +3,7 ng/100ml, slight increasing tendency slight rose slight rose	 + 0.4 decrease decrease
Adverse effect		

Name of author:	**Schneider T & Rübben H.**						
Reference /Year	Urologe [B] 1996; 36: 287-91 [40]						
Name of the product:	Bazoton® -uno filmtablets						
Producer:							
Active substance	459 mg dry extract from Urticae radix						
	DER: 7.1-14.3:1			**Extraction solvent:** methanol 20% (V/V)			
Type	Randomised, double blind, multi-centric (27), placebo controlled, Phase 4,						
Patient number:	Verum: ITT 124 , 114 Age: 64±0..6			Placebo: ITT 122, 112 Age: 63±0..6			
Indication:	BPH I-II; Exclusion criteria: IPPS ≥ 13 Max. Urine. flow ≤15ml/s, Micturition volume ≥ 150ml, residual urine volume <200 ml						
Duration Dosage/day	Time: 1 week placebo-run-in Phase 52 weeks			Dosage/day: 1 film tablet			
Evaluation criteria:	**Results**						
	Verum			Placebo			
	Before	After	Differ.	Before	After	Differ.	Significance
International Prostate symptoms score** (±SEM)	18.7 ±.0.3	13.0 ±0.5	- 5.7 ±0.5 (31%)	18.5 ±0.3	13.8 ±0.5	- 4.7 ±0.5 (25%)	p= 0.0233 „repeated measures model"
maximum urinary flow (ml/s±SEMD)	11.0 ±.0.2	13.8 ±0.5	+ 3.0 ±0.4	10.7 ±0.3	12.3 ±0.5	+2.9 ±.0.4	p=0.49 Wilcoxon-Test
residual urine volume (ml±SEMD)	35.5 ±.3.4	20.0 ±.2.8	- 0.5 ±.2.1	40.0 ±.4.0	21.0 ±.2.9	- 4 ±.1.6	p=0.67 Wilcoxon-Test
Quality of life	Better 63%, Worse 8% No change: 27%			Better 62%, Worse 7% No change: 31%			p=0.69 Wilcoxon-Test
Adverse effects	29 (3 infections of the urinary tract, haematuria, dysuria, Gastro-intestinal, allergic			38 (10 infections of the urinary tract, haematuria, dysuria)			

** 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 point = slight-grade, 8-19 point = middle-grade, 20-35 = great-grade

Figure from **Schneider T &Rübben H. 1996 (continued)**

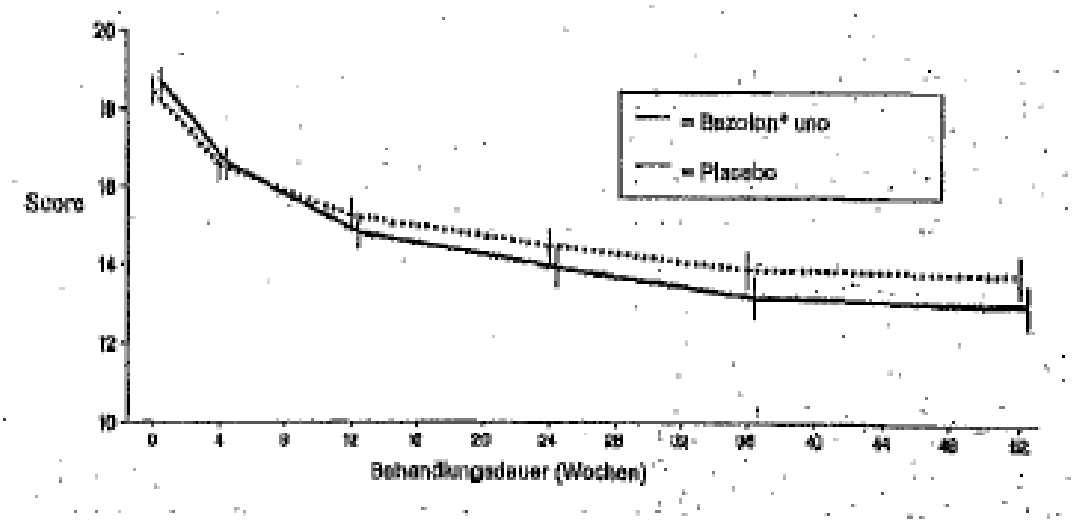


Abb. 1 ▲ Mittelwertverläufe des IPSS ± SEM über 52 Wochen (Itt: n=226)
(p=0,0233 im „repeated measures model")

Name of author:	**Vontobel HP *et al***		
Reference /Year	Urologe [A] 1985; 24: 49-51 [27]		
Name of the product:	Bazoton® 300mg		
Producer:	**KANOLDT Arzneimittel GmbH**		
Active substance	300mg Extractum Radicis Urticae (ERU)		
	DER: 7-14.1	**Extraction solvent:** 20% V/V methanol	
Type	Randomised, double blind, placebo controlled		
Patient number:	Verum:19 Placebo: 22 Age: 67.9 Age: 66		
Indication:	BPH I-II (Patients over 150 ml residual volume were excluded)		
Duration Dosage/day	Time: 9 weeks	Dosage/day: 2x1caps. (600mg)	
Evaluation criteria:	**Results**		
	Verum	Placebo	**Difference**
micturition volume (ml)	Increased 43.7%	decreased 9%	**p=0.027**
average urinary flow rate (ml/s)	slight increase		no significant
maximum urinary flow (ml/s)	improved 8.6%	similar decrease	p=0.062
residual urine volume (ml) measured by Sonograph			no significant.
SHBG serum levels	with average 2.43 nmol/litre decreased	increased	**p=0.0005**
testosterons serum levels			no signif.
5α-DHTserum levels			no signif.
Subjective symptoms: (micturition frequency, nocturia frequency, difficulty in initiating urination, quality of the urinary stream, terminal dribbling)	significant improvement	significant improvement	no remarkable
Adverse effects	Obstipation Diarrhoea, gastro-intestinal complaints	Feeling of perineales pressure	

Name of author:	**Safarinejad M, Z**				
Reference /Year	Journal of Herbal Pharmacotherapy 2005				
Name of the product:					
Producer:					
Active substance	Fluid extract 100 mg of *Urtica dioica* root extract in 1 ml				
	DER:		**Extraction solvent:**		
Type	6 months placebo controlled study + 18 months follow-up period with active treatment				
Patient number:	Verum: 305 Age: 64 (57-71)		Placebo: 315 Age: 62(53-73)		
Indication:	Lower urinary tract symptoms due to BPH;				
Duration Dosage/day	Time: 6 months placebo controlled study 340 patients + 18 months with active treatment		Dosage/day: 3x120mg		
Evaluation criteria:	**Results after 6 months**				
	Verum		Placebo		Significance
	Before	After	Before	After	
International Prostate symptoms score**	19.8±4.9	11.8±4 (-40%)	19.2±4.6	17.7±3.1 (-9%)	**p=0.002**
maximum urinary flow (ml/s)	10.7±2.4	18.9 ±4.7 (+ 8.2)	10.8±2.8	14.2 ±3.7 (+3.4)	p<0.05
Postvoid residual urine volume (ml)	73±32.6	36 ± 25.5	74±29.6	71 ± 24.4	p<0.05
Prostate size (transrectal ultrasonograph) (cc)	40.1±6.8	36.3 ± 4.2	40.8±6.2	40.6 ± 5.1	
Adverse effects	No		No		

2. TABLES OF SOME OPEN STUDIES

Belaiche P & Lievoux O. 1991

<table>
<tr><td>Year
Type</td><td>Indication
Patient number</td><td>Duration
Dosage/day</td><td>Evaluation criteria</td><td colspan="4">Results</td><td>Adverse effect</td></tr>
<tr><td rowspan="6">open</td><td rowspan="6">BHP

67</td><td rowspan="6">6 month

3 x 5 ml
fluid extract
(DER1:5, 40%
Ethanol)</td><td>Patient’ number</td><td rowspan="2">Before treatment</td><td colspan="3">After treatment</td><td rowspan="6"></td></tr>
<tr><td></td><td>no need to get up</td><td>≤ 2</td><td>no improvement</td></tr>
<tr><td>Micturition frequency /night</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Group A ≤ 2</td><td>12</td><td>10</td><td>2</td><td></td></tr>
<tr><td>Group B ≤ 3</td><td>27</td><td>13</td><td>10</td><td>4</td></tr>
<tr><td>Group C > 3</td><td>28</td><td>7</td><td>17</td><td>4</td></tr>
<tr><td></td><td>Prostate volume</td><td colspan="4">unaffected</td></tr>
<tr><td></td><td>Residual bladder volume
post micturition</td><td colspan="4">decreased</td></tr>
</table>

Friesen A. 1988

Type	indication patient number	Duration Dosage /day	Evaluation criteria	Results					Adverse effects
Open Multi-centric	BHP 4480	Six months 600-1200mg ERU (Bazoton®) (DER: 7-14:1, 20% V/V methanol) At the begining. 2x2 caps. 1 month later 2x1 cap.	Percent of patients who thought their status improved	1. month 31 %		3. month 77 %		6. month 89.8%	0.7% gastro-intestinal complaints
			The grade of the improvement Percent of patients	No complain 19.6%	improvement 23.8%	Consider. improv. 47.5%		no improvement 8.8%	
			Nocturia frequency/ percent of patients without nocturia > 3 **Pollakisuria** /percent of patients	At the beginning 4.2% 48.1% 73%		At the end of the study 37.8% 6.3% 12.6%		Difference **Significant** **Significant** **high signif.**	
			Average urinary flow ml/s	0. month 13.26		3. month 15.94		6. month 17.69	**Difference** **P<0.01**
			Residual urine volume Percent of the patients % At the beginning At the end	0 ml 7.4 25.5	>0-50 22.7 53.9	>50-100 45.7 17.2	>100-200 16.9 3.1	>200 2.2 0.4	

Goetz P. 1989

<table>
<tr><th>Type</th><th>Indication
patient
number</th><th>Duration
dosage /day</th><th>Evaluation criteria</th><th colspan="3">Results</th><th>Adverse
effects</th></tr>
<tr><td rowspan="6">open</td><td rowspan="6">BHP

10</td><td rowspan="6">2 months

90-150 drops
4.5-7.5ml fluid extract
(DER: 1:1, 45%
ethanol</td><td>Subjective symptoms (problems in emptying of the bladder, decreased urinary stream)</td><td colspan="3">Satisfying improvement an all cases</td><td rowspan="6">no
complain</td></tr>
<tr><td>nocturia frequency/night
Patient’s number before treatment

after treatment</td><td>0-2
1

10</td><td>3-4
4</td><td>> 5
5</td></tr>
<tr><td>Residual urine volumen decreased with 66%
Patient’s number before treatment
after treatment</td><td>0-50 ml
3
9</td><td>50-100 ml

1</td><td>>100ml
7</td></tr>
<tr><td>prostate size</td><td colspan="3">in 5 cases decreased, in 4 cases not changed, in 1case increased
decreasing is 14.8 cm on average</td></tr>
</table>

Kaldewey W. 1995

Type	Indication patient number	Duration dosage /day	Evaluation criteria	Results			Adverse effects
open multi centr.	BHP 1074 **(**81.4%) StadiumI : 233 (16.9%) Stadium II: 766 (58.1%) Stadium III: 226 (17.1%) Stadium IV: 6 (0.5%) Prostatitis 70 (5.3%) Prost.+BHP 172 (13%)	6 months 540-1080 mg ERU (Urtica Plus N® 270mg) at the beginning 73.3% of patients 2x2 caps. 12.4% 2x1 5.4% 3x1 8 weeks later 60% of patients 2x1 caps.	Overall evaluation of effectiveness by physicians by patients as change in life quality average urinary flow rate micturition volume duration of micturition	72,2 % very good or good 79.9 % improved, 14.6% not changed, 2.7% worsened improved in 71.6% of the patients increase 4 ml/s on average increased with 26 ml on average decreased with 5 seconds on average			13 cases (1%) minor gastro-intestinal complain 3 patients (0.2%) stopped the treatment because of adverse effects
			symptoms	percent of patients			
				improved	at the beginning	at the end	
			nocturia frequency by nights	60.3%			
			0-1		15.5%	61.1%	
			>4		22.7%	2%	
			policusuria /day >8		27.5%	2.7%	
			dysurie	76.9%	56%	11.4%	
			difficulty in initiating urination	70.3%			
			no hesitancy		6.7%	22.4%	
			residual urine volumen	56.9%			
			0		11.7%	29%	
			>100ml		8.6%	1.1%	

Stahl HP. 1984

Type	Indication and patient number	Duration Dosage / day	Evaluation criteria	Results				Adverse effects
				1st week (mean value)	10th week (mean value)	improvement %	No effect %	
Open Multi-centric	BHP 4051	10 weeks 2X2 caps. 1200mg ERU **(**DER: 7-14:1, 20% V/V methanol**)** (Simic®)	NOCTURIA FREQUENCY 1. group weekly 0-7 (n = 384) 2. group weekly **8-21** (n = 2464) 3. group weekly **22-35** (n = 961) 3. group weekly **>36** (n = 136) can not be evaluated (n=106)	 5.5 14.7 26.3 42.9	 3.8 7.3 11.9 18.6	 31 50 **p<0.0001** 55 **p<0.0001** 57 **p<0.0001**	 32 9.7 4.4 5.9	

Tosch U. Müssiggang H. 1983

<table>
<tr><th>Type</th><th>Indication and patient's number</th><th>Duration
Dosage /day</th><th>Evaluation criteria</th><th colspan="3">Results</th><th>Adverse effects</th></tr>
<tr><td rowspan="2">open multi-centric</td><td rowspan="2">Stadium I: 2194
Stadium II: 2928
Stadium III: 370

All: 5492</td><td rowspan="2">3-4 months

600-1200mg ERU (DER: 7-14:1,
20% v/v methanol)
(simic®)

at the beginning 2x2,
1 month later 2x1 caps.</td><td rowspan="2">Evaluation by the doctor

Subjective symptoms

improvement score 1-3
micturition frequency
nocturia frequency

Objective parameters:
average urinary flow rate improvement in ml/sec.

residual urine volume (measured with catheter or x-ray or Sonograph) improvement score 1-4</td><td>Stadium I

83,2% of the patients improved</td><td>Stadium II

80,4% of the patients improved</td><td>Stadium III

61% of the patients improved</td><td rowspan="2">84 patients stopped the treatment because of adverse eff.: gastric comp. nausea, heartburn, diarrhoea
86 further adverse effects: 54 gastric comp.
12 diarrhoea
others: allergy, itching, palpitation, impotence, dizziness, lower leg oedema, urge to urination</td></tr>
<tr><td colspan="3">High significant improvement
Age < 50 51-60 61-70

2.5 1.7 1.5
2.5 1.0 1.5

3.2 2.5 2.4

improvement: 1 score in general</td></tr>
</table>

The effectiveness of the therapy in the age of 50-69 and in the stadium I-II was very significant, but it decreased in advanced age and advanced stadium.

III. ANNEXES

III.1 LITERATURE REFERENCES