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SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Urtica dioica* L.; *Urtica urens* L., radix

Final - Revision 1

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)		*Urtica dioica* L. and *Urtica urens* L., radix (nettle root)
Herbal preparation(s)		Comminuted herbal substance Dry extract (DER 7-14:1), extraction solvent methanol 20% V/V Dry extract (DER 5.4-8.3:1), extraction solvent ethanol 20% V/V Dry extract (DER 12-16:1), extraction solvent ethanol 70% V/V Liquid extract (DER 1:1), extraction solvent ethanol 30% V/V Dry extract (7-9:1), extraction solvent ethanol 60% V/V Dry extract (5.4-6.6:1), extraction solvent ethanol 80% V/V
Pharmaceutical form(s)		Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid dosage forms 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)

  The European Pharmacopoeia monograph (01/2022:2538) defines the herbal substance as the dried, whole or fragmented underground parts of *Urtica dioica* L. or *Urtica urens* L., their hybrids or their mixtures.

- Herbal preparation(s)

  No pharmacopoeia monographs are available for preparations.

  Constituents:

  Based on Blaschek et al. 1998; ESCOP, 2003; Mills and Bone, 2003; Blumenthal et al., 2000; Bruneton, 1999; Wichtl, 2002; Bradley, 2006, apart from the common constituents glucosides, amino acids and minerals, the main constituents of nettle root are the following:

  - Lectins: 0.05-0.6% *Urtica dioica* agglutinin (UDA), a small monomeric protein
  - Lignans: Urtica dioica roots contain lignans in higher amount than Urtica urens roots
  - Sterols
  - Phenylpropanes
  - Ceramides
  - Hydroxy fatty acids
  - Fatty alcohol
  - Monoterpenes
  - Triterpenes
  - Phenols
  - Tannins
  - Coumarins

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

  Not applicable.

1.2. Search and assessment methodology

This Assessment Report resulted from the systematic review of that previously issued (EMA/HMPC/461156/2008) considering the new information from data published in the literature (Books, Book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations) between 2008 and 2022. Scientific/Medical/Toxicological databases (Web of Knowledge, PubMed, SciFinder) were used. The complete and updated List of references is included as an Annex.

Pharmacovigilance data were retrieved from EudraVigilance database on 16.11.2021 using the key words: URTICA, URTICA DIOICA, URTICA DIOICA ROOT, URTICA EXTRACT, URTICA ROOT DRY EXTRACT, URTICA URENS, URTICA URENS L., URTICA URENS ROOT, CRYOGROUND, URTICAE RADICIS EXTRACTUM FLUIDUM (1:1; ETANOL 70º), URTICAE RADIX, URTICAE RADICIS EXTRACTUM METHANOLICUM SICCUM, URTICA URENS Ø, URTICA DIOICA/URENS L. EXTRACT (UR 102), URTICA DIOICA Ø, URTICA DIOICA ROOT, CRYOGROUND, URTICA DIOICA L., SUCCUS URTICAE PHYTOPHARM,

DRY EXTRACT FROM NETTLE ROOT (12-16:-1), EXTRACTION SOLVENT: ETHANOL 70% V/V, DRY EXTRACT OF NETTLE ROOT (5.5-8.5:1), EXTRACTION SOLVENT: ETHANOL 20% V/V, DRY EXTRACT OF NETTLE ROOT (7-14:1), EXTRACTION SOLVENT: METHANOL 20% V/V, DRY EXTRACT OF NETTLE ROOT (DER 8-12:1), EXTRACTION SOLVENT: ETHANOL 60% (M/M), DRY EXTRACT OF NETTLE ROOTS, EXTRACT FROM NETTLE ROOT (1:1), EXTRACTION SOLVENT: ETHANOL 30 % (V/V), NETTLE ROOT DRY EXTRACT (7.6-12.5:1), EXTRACTION SOLVENT: ETHANOL 60% W/W, NETTLE ROOT, CRYOGROUND, STINGING NETTLE ROOT DRY EXTRACT (7-9:1), EXTRACTION SOLVENT: ETHANOL 60% (V/V), URTICA DIOICA (NETTLE) EXTRACT.

Scientific databases: Web of Knowledge, PubMed, SciFinder

2. Data on medicinal use

2.1. Information about products on the market

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

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Posology and method of administration**	**Regulatory status**
Urticae radix	Difficulties with urination	2.5 g - pour with 1 glass of boiling water, infuse under cover about 15 min. cool and strain 2 times daily	National registration, PL, 2004
Urticae radix	Symptomatic treatment of benign prostatic hyperplasia at stages I and II as defined by Alken or stages II and III as defined by Vahlensieck	2.068g Urticae radix in 150 ml of boiling water, let 10 min extract and drink Adults and adolescents over 16 years: 2-3 times daily Herbal tea	WEU, DE, 1992
Liquid extract from Urticae radix (1:1), extraction solvent: ethanol 30% V/V		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	WEU, DE, 1976 - 2011 and 1990 - 2019
Fluid extract of the nettle root (Urticae radices extractum fluidum) DER (1:1), extraction solvent ethanol 70% (V/V		1 teaspoon (about 5 g) 3 time a day	National registration, PL, 1998

Dry extract from Urticae radix (7-14:1), extraction solvent: methanol 20% V/V		film-coated tablet, coated tablet, hard capsule 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	WEU, DE, 1991 2000 1991
Dry extract from Urticae radix (7.1-14.3:1), extraction solvent: methanol 20% V/V		3 times daily 1 coated tablet containing 160 mg dry extract Once a day 1 film-coated tablet containing 460 mg dry extract	WEU, DE, 1976-2016 and 1976-2019 WEU, DE, 2000
Dry extract from Urticae radix (6-11:1), extraction solvent: methanol 20% V/V		Once a day 1 film-coated tablet containing 600.1 mg dry extract	WEU, DE, 2001
Dry extract from Urticae radix (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	WEU, DE, 1976-2013 1976-2010
Dry extract from Urticae radix (15-20:1), extraction solvent: ethanol 80% V/V	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	WEU, DE, 2001
Dry extract from Urticae radix (5.4-6.6:1), extraction solvent: ethanol 80% V/V		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	WEU, DE, 1993, 1994
Dry extract from Urticae radix (6.7-8.3:1), extraction solvent: ethanol 20% V/V		3 times daily 1 soft capsule containing 240 mg dry extract	WEU, DE, 1976, 1996, 1997
Dry extract from Urticae radix (7-9:1), extraction solvent: ethanol 60% V/V		twice a day 2 film-coated tablets containing 125 mg dry extract each	WEU, DE, 1992-2022
Dry extract from Urticae radix (8-12:1), extraction solvent: ethanol 60% m/m		once a day 1 coated tablet containing 475 mg dry extract	WEU, DE, 1999
Dry extract from Urticae radix (15.75-19.25:1), extraction solvent: ethanol 80% V/V		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	WEU, DE, 1991-2015
Dry extract from Urticae radix (5.4-6.6:1), extraction solvent ethanol 20% (V/V)		Male adults Single dose: 240mg Daily dose: 720mg Can be taken over a long time.	WEU, DE, 1993

Urticae radix, powdered herbal substance	Functional disturbances of urinary system with urination difficulties in patients with BPH, after exclusion of more serious changes by the doctor	One tablet contain 330 mg of powdered nettle root. 4 tablets 3 to 4 times a day. Adult patients should take 4 to 6 tablets 3 times a day after meals, with plenty of water. One capsule contains 290 mg of powdered nettle root. 2-3 capsules, twice a day	National registration, PL, 2001 TU, Lithuania, 2007 TU, Spain, 2012

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

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

Table 2: Overview of data obtained from combination medicinal products marketed in the EU

Active substance	**Indication**	**Pharmaceutical form / Strength / Posology / Duration of use**	**Regulatory status (date, Member State, Type of Marketing authorisation/registration where possible)**
Soft extract from *Serenoae repentis fructus* (10-14.3:1); extraction solvent: ethanol 90% (V/V) and Dry extract from *Urticae radix* (7.6-12.5:1); extraction solvent: ethanol 60% (m/m)	Symptomatic treatment of benign prostatic hyperplasia at stages I and II as defined by Alken or stages II and III as defined by Vahlensieck	solid and liquid dosage forms for oral use (oral liquid, capsule, soft) *Male adults:* SD: 106.6-160 mg / 80-120 mg DD: 320 / 240 mg Duration of use is principally not limited in time	1976, DE, WEU
Urticae folium, powder and Dry extract from *Urticae radix* (5.5-8.5:1); extraction solvent: ethanol 20% (V/V)	Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract	Film-coated tablet *Adults:* SD 150 / 140 mg DD 450 / 420 mg No longer than 4 weeks. If the symptoms remain longer than 1 week or adverse reactions not mentioned in the SPC occur, a doctor or a qualified health care practitioner should be consulted.	1976, DE, TU 11/2011, DE, TU

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

Not applicable.

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

Not applicable.

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

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 and Bone, 2003). Syrup made from the juice of root or leaves was said to relieve bronchial and asthmatic troubles (Mills and Bone, 2003). In African medicine, nettle root is used to treat diarrhoea and as an anthelmintic to expel intestinal worms (Blumenthal *et al.,* 2000).

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, 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 *et al.,* 2000).

Other uses reflected in folk medicine are its oral use against enteritis (diarhoeae) and external use as shampoo against loss of hair and dandruff formation (Rápóti and Romvári, 1974); against renal calculus (Lutomsky and Speichert, 1983), as mild diuretic (Jaspersen-Schib, 1989), diuretic and astringent in the form of gargles because of its tannin content (Bisset and Wichtl, 1994); 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 (Berger, 1960; Kern, 1979; Blaschek *et al*., 1998).

Table 3: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	***Pharmaceutical form / Strength / Posology / Duration of use***	**Reference**
Comminuted herbal substance	Relief of lower urinary tract symptoms related to benign prostatic hyperplasia	Single dose: 1.5 g Daily dose: 4-6 g of the herbal substance as a decoction	Bisset and Wichtl, 1994 Blumenthal et al., 1998
Liquid extract (1:1), extraction solvent: water		6 ml daily	Blaschek et al., 1998

Herbal preparation	Documented use / Traditional use	*Pharmaceutical form / Strength / Posology / Duration of use*	Reference
Dry extract (DER: 5.4-6.6:1), extraction solvent ethanol 20% V/V		240 mg, twice daily.	Veit et al., 1998
Dry extract (DER: 8.3-12.5:1), extraction solvent ethanol 60% m/m		120 mg twice daily	Blaschek et al., 1998

2.3. Overall conclusions on medicinal use

Table 4: Overview of evidence on period of medicinal use

Herbal preparation / Pharmaceutical form	Indication	Posology / Strength	Period of medicinal use
Comminuted herbal substance	THMP for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a medical doctor	2.068 g Urticae radix in 150 ml of boiling water 2-3 times daily	On the market since 1992
Dry extract (DER 7-14:1), extraction solvent methanol 20% V/V		150 mg 3 times per day At the beginning of treatment for the first 3 months: twice a day 300 mg 160 mg 3 times per day 460 mg once a day	On the market since 1991, 1992
Dry extract (DER 5.4-8.3:1), extraction solvent ethanol 20% V/V		240 mg dry extract 3 times daily	On the market since 1976, 1993
Dry extract (DER 12-16:1), extraction solvent ethanol 70% V/V		150.5-189 mg dry extract twice a day	On the market 1976-2013 and 1976-2010
Liquid extract (1:1), extraction solvent ethanol 30% V/V		3 times daily 40 drops or 4 x daily 30 drops oral liquid containing 100% liquid extract	On the market 1976-2011
Dry extract (7-9:1), extraction solvent ethanol 60% V/V		250 mg, twice daily	On the market 1992-2022

Herbal preparation / Pharmaceutical form	Indication	Posology / Strength	Period of medicinal use
Dry extract (5.4-6.6:1), extraction solvent: ethanol 80% V/V		3 times daily 240 mg At the beginning of treatment 2 times daily 480 mg	On the market since 1993

Assessor's comment:
The preparations Dry extract (DER 6.7-8.3:1), extraction solvent ethanol 20% V/V and Dry extract (5.4-6.6:1), extraction solvent ethanol 20% V/V (see table 1) were be merged; they have exactly the same posology.

3. Non-Clinical Data

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

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 (Phua, 2021).

3.1.1. Primary pharmacodynamics

In a review article, Chrubasik *et al*. (2007) summarized in vitro and in vivo studies. It was pointed out that only a few components of the active principle have been identified, and the mechanism of action is still unclear. It was claimed likely that sex hormone binding globulin (SHBG), aromatase, epidermal growth factor and prostate steroid membrane receptors could be involved in the anti-prostatic effect, but less likely that 5a-reductase or androgen receptors are involved. Furthermore, it was pointed out, that an extract and a polysaccharide fraction were shown to exert anti-inflammatory activity and a proprietary methanolic nettle root extract and particular fractions inhibited cell proliferation.

3.1.2. Secondary pharmacodynamics

Only studies not mentioned in Chrubasik *et al*. (2007) will discussed below.

Anti-angiogenic activity

The effect of a purified extract of *U. dioica* on the angiogenesis of chicken embryos was evaluated by Samadian *et al*. (2022). *Urtica dioica* roots were extracted with water and after purification, a specific agglutinin (UDA) crude extract was obtained which was later purified to be tested on the extra-embryonic layer of the chick egg, at different concentrations, for its anti-angiogenicl activity. Authors found that UDA at 100 μg/kg was able to prevent vascularization events in the animal model tested.

Previous studies had shown some effect of UDA on BPH cells (Kayser *et al*., 1995).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Results from relevant experimental studies are limited and not required. The effect of different nettle root preparations on BPH was evaluated in older 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 have been discussed in literature to be among the active principles, however, data were not seen to be sufficient for a conclusive evaluation. Phytosterol components are thought to be the least important since their content in nettle products is very low (0.01%).

In literature, it was discussed that sex hormone binding globulin (SHBG), aromatase, epidermal growth factor and prostate steroid membrane receptors seem to be involved in the anti-prostatic effect, but it is less likely that 5-α-reductase or androgen receptors are involved.

It is to conclude that it is unclear whether the in vitro or in vivo data are a surrogate for usage in humans.

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

No data available regarding Urticae radix.

Pusztai (1986) described experiments in which additional [125I]-labeled lectins were given to animals via stomach tubes. These findings showed that lectins can penetrate the intestinal barrier and bind to different bodily regions and reach blood serum concentrations from 0.01%/ml to 0.7%/ml. The amount of radioactive label found in various organs was 1-5% of the total radioactivity administered.

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

3.3.1. Single dose toxicity

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

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

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).

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other studies

No data available.

3.3.8. Conclusions

Non-clinical data regarding Urticae radix are scarce. No tests on carcinogenicity and reproductive and developmental toxicity have been performed. Adequate tests on Genotoxicity have not been performed.

No constituents with potential safety concerns are known.

Non-clinical information on the safety of preparations of Urticae radix is scarce. With the limited data available it is difficult to draw any firm conclusions especially regarding genotoxicity, carcinogenicity and reproductive and developmental toxicity. The published Ames test is in no way (e.g. number of tested strains) Guideline-conform and therefore not sufficient for evaluating genotoxicity.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation could not be recommended.

The following text is included in the monograph section 5.3:
Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on Urticae radix to support the proposed indications are very limited and not required. The reported pharmacological effects are not considered contradictory to the traditional uses.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of Urticae radix is scarce.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Tests on carcinogenicity have not been performed. Adequate tests on genotoxicity have not been performed.

4. Clinical Data

4.1. Clinical pharmacology

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

Changes in serum parameters

Three studies were conducted 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, oestradiol and oestrone serum levels were measured (Fischer and 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 and 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, oestrone and SHBG at the beginning of the therapy and after 12 weeks.

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

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 months 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

Apart from the EMA Guideline on the Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005 – Rev. 1), other publications such as the European Association of Urology Guidelines on the Management of Non-neurogenic Male Lower Urinary Tract Symptoms, have been taken in account for the evaluation of the clinical trials. According to the European Association of urology (Gravas *et al*., 2023), the assessment of men with lower urinary tract symptoms (LUTS) should include validated symptom scores, urine test, uroflowmetry, and postvoid urine residual, as well as frequency-volume charts for patients with nocturia or predominately storage symptoms should be used. Urodynamics should be performed for selected patients.

Other published guidelines have also been consulted as described below:

American Urological Association: Guideline on the Management of Benign Prostatic Hyperplasia (BPH) (Sandhu et al., 2023)

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

There are several clinical studies performed with preparations from nettle root. In accordance with the guideline 'Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005 – Rev. 1), the assessment of well-establish use should also include if the products reported in the market overview can be considered as similar to the product studied in relevant clinical studies found in the literature (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Coherent and conclusive clinical recommendations cannot be obtained if major methodological deficiencies are identified in the pivotal clinical data. Demonstration that the clinical data are covering a sufficient number of patients and that they are conclusive and coherent with respect to the indication, safety and efficacy.

Therefore, the scope of the assessment in this section is BPH. Only studies related to this indication are included below.

Beside these investigations, *Urtica dioica* (not further defined) has been tested for clinical efficacy for instance in allergic rhinitis. There is no information available that an Urtica preparation has been in medicinal use for more than 10 years in EU in these indications (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Thus, these studies will not be considered for a well-establish use monograph.

Placebo controlled studies

Preparations similar to the ones in the monograph

Several randomised, double blind, placebo controlled clinical studies with dried methanolic extracts of nettle root have been published between 1985 and 2020.

Dathe and 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 with 300 mg each) (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 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).

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, no clinical relevance was shown due to the lack of standard deviation values and confidential limits in the article, with 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.

Schneider and Rübben (2004) performed a randomised, double-blind, placebo controlled multi-centre study for a 1-year treatment with 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 significant difference compared to placebo (18.5±0.3 to 13.8±0.5; p=0.0233 repeated measures model). The median Qmax 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 verum therapy compared to placebo.

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". 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.

In the study by Vontobel *et al.* (1985), 50 BPH I-II patients were 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 the finding that the starting values of residual urine volume of the patients in the two groups were not homogenous.

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. Moreover, the number of patients was very low. Therefore, the results of this study are of limited value.

Other preparations

Engelmann et al. (1996) conducted a double blind, multi-centre study with 41 BPH patients who were treated for 3 months with either 2 times 3 ml of an aqueous extract preparation equivalent to 4.68 g of fluid extract (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. Some improvement was obtained in comparison to placebo.

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. Also the number of patients was very low and the duration of the study very short.

Fischer and Wilbert (1992) conducted a randomised, double blind, placebo-controlled study with 40 BPH II patients (n=20; placebo n=20) who were investigated according to the Guidelines of Food and Drug Administration on Investigations of benign prostatic hypertrophy (Boyarsky *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, for 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. 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).

Assessor's comment:
The number of patients was very low, 40 in the study. The baseline parameters in the two groups were not mentioned in the article, and the standard deviation values couldn't 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 Table 5). 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 publication gives a negative outcome for the evaluation of the efficacy of the tested preparation.

Safarinejad (2005) conducted a 6-month, double blind, placebo controlled, randomised, partial crossover, comparative trial of *Urtica dioica* with placebo in 620 patients in a non-European country. Each patient was given 120 mg of fluid extract of *Urtica dioica* root (100 mg of *Urtica dioica* root extract in 1 ml) (n=305) three times daily or placebo (n=315). 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. No side effects were identified.

Assessor's comment:
This study was a double blind, placebo controlled, randomised, partial crossover, comparative trial of Urtica dioica with placebo. The duration of the treatment was adequate, 6 months followed by an 18-month follow-up and the number of the patients involved (620) was sufficient. Nevertheless, the authors did not mention what they considered clinically relevant changes in the different efficacy parameters before the treatment, and 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. Moreover, the study was performed in a non-EU country (Iran). Since this could lead to different outcomes, the requirements of ICH E5 (R1) should have been addressed to allow an assessment for the EU.

Two other studies were also conducted in non-EU countries: Ghorbanibirgani *et al*. (2013) conducted a randomized, double-blind clinical trial for 8 weeks with 100 participants having BPH and no specific complications to assess the effect of *U. dioica* in BPH. Severity of BPH symptoms was assessed using the International Prostate Symptom Score (IPSS). As explained for the study by Safarinejad (2005), the results of this trial cannot be used for assessment since the study drug is not described properly ("one group was given nettle and other group placebo (two capsules of 300 mg each, 2 times a day").

The study by Karami *et al.* (2020) was a randomized, double-blind, placebo-controlled study with 12-weeks follow up period involving 60 patients with BPH. Participants were treated either with 450 mg of *U. dioica* root or placebo. Once more, the results of this study cannot be used for further assessment since the administered extract is not properly defined.

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 and 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 is the following:

Tosch and 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, the authors 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.

In another open, multi-centre study, 4480 BHP patients received 600-1200 mg of extract preparation per day for 20 weeks (Friesen, 1988). 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).

Open studies with other preparations

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 (Goetz, 1989). All patients experienced satisfying improvement in subjective symptoms (problems in emptying of the bladder, decreased urinary flow).

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 (Belaiche *et al*., 1991).

Kaldewey (1995) published an open multi-centre study with 1319 patients with BPH and/or prostatitis who 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.

In the study by 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.

Table 5: Clinical studies on humans, in Urinary tract and genital disorders

Type	Study	Test product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Efficacy on BPH Fischer and Wilbert, 1992	Randomized, double blind, controlled study 6 months	1200 mg dried native extract of nettle root (DER: 7-14:1; extraction solvent methanol 20% V/V) or placebo	40	BPH I-II	Subjective symptoms, micturition volume	Signed-ranked test	No clinically relevant: low number of patients, non homo-geneous groups, no change in the objective parameters
Effect in long-term treatment of BPH Schneider and Rübben, 2004	Randomized, double blind, placebo-controlled study 1 year	459mg dry extract (7-14:1, 20% MeOH)	246	BPH	IPSS, volume of residual urine	Statistical analysis performed	No clinically relevant: not statistically significant differences
Effect in BPH symptoms Engelmann *et al*., 1996	Double blind study 3 months	2 x 3ml of aqueous extract equivalent to 4.68g fluid extract (78g aqueous extract from 84g crude drug, 16% ethanol)	41	BPH	IPSS, volume of residual urine Quality of life, maximum urinary flow	Statistical analysis performed	No clinically relevant: evaluation criteria no properly defined, low number of patients

4.3. 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.

4.4. Overall conclusions on clinical pharmacology and efficacy

Only the studies for which all information is available are taken in account to assess efficacy.

Results from pharmacodynamic studies conducted with nettle root extract show some morphological changes to prostatic cells (Chrubasik *et al*., 2007).

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 larger number of patients with randomised, placebo-controlled, matched group design in BHP treatment (Jardin et al., 1991).

In spite of this suggestion only eight randomised, double-blind, placebo-controlled clinical studies can be found in the literature. Three of them were conducted with preparations similar to the ones included in the Urticae radix monograph: the studies by Dathe and Schmid (1987) and Schneider and Rübben (2004), despite other design deficiencies (low number of patients, short treatment period), did not show any clinical relevance; in fact, no remarkable or significant difference could be found between placebo and treated groups. The study by Vontobel *et al*. (1985) can't be assessed because no complete data are available.

Five clinical trials have been published with other Urticae radix preparations. The studies by Fisher and Wilbert (1992) and Engelmann et al. (1996) did not prove clinical relevance due to the lack of evaluation criteria, low number of patients or short duration. Finally, the three other studies (Safarinejad, 2005; Ghorbanibirgani *et al.,* 2013; Karami *et al*., 2020) were performed in non-EU countries with no properly defined preparations. Since this could lead to different outcomes, the requirements of ICH E5 (R1) should have been addressed to allow an assessment for the EU.

In summary, the effectiveness of nettle root has not yet been proven sufficiently to state the well-established use for the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia

A meta-analysis assessed the efficacy of *Urtica dioica* in BPH (Men *et al*., 2016). The search strategy and the study selection process is not properly described. Altogether 5 studies were included in the meta-analysis, 2 of them studied combination products. Two of the other 3 studies were already included in the current version of the Assessment report on *Urtica dioica* L., *Urtica urens* L., their hybrids or their mixtures, radix (EMA/HMPC/461156/2008)). Although the meta-analysis that *Urtica dioica* is superior to controls in improving the IPSS, Qmax and decreasing prostate volume, the involvement of combination product affects the results of this analysis.

5. Clinical Safety/Pharmacovigilance

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

The following safety information are included in the SmPC of products on the market:

Table 6: Safety information from products marketed in the EU/EEA.

Herbal preparation	**SmPC section**	**Safety information**
Dry methanolic extracts	4.8 Undesirable effects	Frequency not known: - Gastrointestinal complaints (nausea, heartburn, diarrhoea) - Allergic skin reactions (pruritus, rash)

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

Table 7: Clinical safety data from clinical trials

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Effectiveness in conservative treatment of BPH Vontobel *et al*., 1985	Double blind, controlled study 9 weeks	600 mg extract Urtica radix or placebo	50	BPH	Constipation, diarrhoea, gastrointestinal complaints (n=4)	Undesirable effects reported in the monograph
Effect in BPH symptoms Engelmann *et al*., 1996	Double blind study 3 months	2 x 3ml of aqueous extract equivalent to 4.68g fluid extract	41	BPH	Dizziness (n=1)	Maybe related to the presence of ethanol
Tosch and Müßiggang, 1983	Open study 3-4 months	50% native extract of nettle root (DER: 5:1, extraction solvent methanol 20% V/V)	5492	BPH	54 gastric complaints (nausea, heartburn, eructation), 12 diarrhoea and 22 other complaints: allergy itching, palpitation, impotence, dizziness, lower leg oedema, and urge to urination	Undesirable effects reported in the monograph
Kaldewey, 1995	Multicentric open study 6 months	Extract DER 12-16, extraction solvent 70% ethanol	1074	BPH	Minor gastrointestinal complaints (n=13)	Undesirable effects reported in the monograph

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Efficacy of *U. dioica* in BPH Ghorbani-birgani *et al*., 2013	Randomized, double-blind clinical trial, 8 weeks	300 mg *U. dioica* root (capsules), 2 times daily or placebo	100 male: 50 intervention, 50 control 40-80 years Average age: 62.4± 1.2 y	BPH	No side effects	-
Effect of *U. dioica* root extract on clinical and biochemical parameters of BPH Karami *et al*., 2020	Randomized, double-blind, placebo-controlled 12 weeks	150 mg of *U. dioica* root extract (tablets), 3 times daily or placebo	60 male: 30 intervention, 30 control 50-80 years Average age: 62.6 y (intervention group)	BPH	No side effects	-

5.2. Patient exposure

So far, more than 17,000 men have been treated with various nettle root preparations in 34 clinical studies. Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

Data obtained from more than 17,000 patients, tested for safety during clinical trials, showed the following results: gastrointestinal complaints, constipation, diarrhoea, heartburn, nausea.

The nettle root monograph contains the undesirable effects mentioned in the Summary of Product characteristics of the most often used preparations (dry methanolic extracts).

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.

No safety concerns were derived from the Euravigilance data, as no cases were reported.

5.4. Laboratory findings

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

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

Not relevant.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special warnings and precautions for use

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

5.5.4. Drug interactions and other forms of interaction

None reported.

5.5.5. Fertility, pregnancy and lactation

Pregnancy and lactation: not relevant.

No fertility data available.

5.5.6. Overdose

No case of overdose has been reported.

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

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

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

On the basis of the information on its traditional use, Urticae radix proves not to be harmful in the specified conditions of use (recommended indications/recommended preparations).

6. Overall conclusions

Some clinical studies have been conducted with Urticae radix for the treatment or relief of lower urinary tract symptoms related to BHP.

Eight randomised, double-blind, placebo-controlled clinical studies can be found in the literature. However, the HMPC was of the opinion that the placebo-controlled studies with Urticae radix were not adequate to prove the efficacy of the preparations included in the EU monograph: the duration was not long enough, the number of patients included was low, the preparations assayed were not properly defined or did not correspond to any preparation in the monograph and finally some studies were performed in non-EU countries.

In 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.

According to the market overview, several preparations of Urticae radix have been on the market for more than 30 years with therapeutic indications related to lower urinary tract symptoms in men. Therefore, these preparations meet the requirement of traditional use in the meaning of Directive 2004/24/EC.

And thus, the indication
- "Traditional herbal medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a medical doctor" can be accepted for the following preparations:
  - Comminuted herbal substance
  - Dry extract (DER 7-14:1), extraction solvent methanol 20% V/V
  - Dry extract (DER 5.4-8.3:1), extraction solvent ethanol 20% V/V
  - Dry extract (DER 12-16:1), extraction solvent ethanol 70% V/V
  - Liquid extract (DER 1:1), extraction solvent ethanol 30% V/V
  - Dry extract (7-9:1), extraction solvent ethanol 60% V/V
  - Dry extract (5.4-6.6:1), extraction solvent: ethanol 80% V/V

A European Union list entry for Urticae radix is not supported due to lack of adequate published data on genotoxicity.

Annex

List of references