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Committee on Herbal Medicinal Products (HMPC)

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

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., herba (nettle herb)
Herbal preparation(s)		Comminuted herbal substance Powdered herbal substance Expressed juice (1:0.5-1.1) from fresh herb Expressed juice (1:1) from fresh herb, stabilized and adjusted with ethanol 96% (V/V) Expressed juice (1.36-1.96:1) from fresh herb Liquid extract (1:1), extraction solvent ethanol 25% (V/V) Liquid extract (1:1.8-2.2), extraction solvent ethanol 30% (V/V) Tincture (1:5), extraction solvent ethanol 45% (V/V) Dry extract (5-10:1), extraction solvent water
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)

Nettle herb is described in the Deutscher Arzneimittel-Codex as "dried, whole or cut aerial parts with parts of the stems and inflorescences of *Urtica dioica* L., *Urtica urens* L. (Urticaceae), their hybrids or mixtures thereof (DAC, 2020).

Nettle herb has been also mentioned in the Pharmacopoeia Helvetica VII (Ph. Helv., 1995) and the British Herbal Pharmacopoeia (BHP, 1983).

Constituents

Minerals
In 100 g fresh herb: 85 g water, 3.55 g mineral substance: 1050 mg calcium, 613 mg potassium, 340 mg silicon, 50-265 mg phosphorus, 2-200 mg iron, 180 mg chloride, 175 mg magnesium, 58 mg sodium, 8 mg manganese, 4 mg boron, 2.7 mg titanium, 1.3 mg cuprum, 0.03 mg nickel *(*Blaschek *et al.,* 1998).
In the dried herb: Content of the mineral substances can be 20%. Trace element contents: 0.4% mg Cu, ~ 6 mg % Mn, ~ 1 6mg % Al and not determined quantity of cobalt and zinc. The ash consists of 24-33% CaO, 14-20% K_2O, 3-10% MgO, 3-6% Fe_2O_3, 1-2% Na_2O, 4-9% P_2O_5, 6-10% SiO_2 and 4-6% chloride (Schilcher, 1988).

Flavonoids: Principally kaempferol, isorhamnetin, quercetin and their 3-rutinosides and 3-glucosides in the herb and similar flavonol glycosides in the flowers (ESCOP, 2003).

Amines: Small amounts of histamine, choline, acetylcholine and serotonin (5-hydroxytryptamine), particularly in the stinging hairs (Bradley, 1992).

Triterpenes and sterols including β-sitosterol (Bisset, 1994)

Cumarins: Scopoletin ca. 1-10 mg/kg herbal substance (Blaschek *et al.,* 1998)

Leukotrienes in hair and extracts (Czarnetzki *et al.,* 1990).

- Herbal preparation(s)

No pharmacopoeia monographs are available for preparations.

- 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.

Nettle herb can be found in combinations with other herbal substances with diuretic effects in several countries.

1.2. Search and assessment methodology

This assessment report is based on the data search for "*Urtica dioica* L., *Urtica urens* L., their hybrids or their mixtures, herba". Call for data started on 01.02.2020 and ended on 31.04.2020. A literature search in medical and scientific databases was performed as follows:

- PubMed (Using the search terms: "nettle OR urtica OR Urtica dioica OR Urtica urens OR urticae herba" from 2008 to present, Search date: 17 August 2020, 983 hits),

- Embase (Using the search terms "nettle OR urtica OR Urtica dioica OR Urtica urens OR urticae herba" from 2008 to present, Search date: 18 August 2020, 1597 hits),
- Cochrane Database of Systematic Reviews (Using the search terms "nettle OR urtica OR Urtica dioica OR Urtica urens OR urticae herba" from 2008 to present, Search date: 17 August 2020, 86 hits)

During the review, 1870 new references not yet available during the first/previous assessment were identified. No references were provided by Interested Parties during the Call for data.

EudraVigilance was searched for pharmacovigilance data by the Pharmacovigilance Department of OGYÉI for adverse reactions on 11 September 2020, and no reports were found for the reference period.

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
Fragmented Urticae herba	Mild diuretic, adjuvant in the treatment of rheumatic complaints and urinary tract inflammation. Adjuvant for enhance of diuresis, for the prevention of nephrolithiasis, and urinary sand, and for the treatment of irritable bladder in women.	Adults: 1 teaspoon or 1 tea bag (1.5 g) infused with 0.25 l of boiling water (extracted for 15 minutes) three times daily	1999; CZ
Fragmented Urticae herba consissa			1997-2010; CZ
Powder of Urticae herba	Traditional herbal medicinal product to support the elimination function of the kidney.	Adolescents and adults 3-4 times daily 380-570 mg	THMP; 1976-2017; DE
Expressed juice from fresh Urticae herba (1.36-1.96:1)	Traditional herbal medicinal product to support the elimination function of the kidney.	Adolescents and adults 4 times daily 3.5 ml oral liquid containing 100% expressed juice	THMP; 1979-2019; DE

Active substance	Indication	Posology and method of administration	Regulatory status
Expressed juice from fresh Urticae herba (1:0.5-1.1)	As a purging in inflammatory diseases of the urinary tract collection system. As a purging to prevent renal gravel. For symptomatic treatment of osteoarthritis.	Adolescents and adults 3 times daily 10-15 ml oral liquid containing 100% expressed juice	WEU; 1976-2008; DE
Expressed juice from fresh Urticae herba (1:0.55-0.82)	Traditional herbal medicinal product for relief of minor articular pain. Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.	Adults Single dose: 10 ml Daily dose: 30 ml	THMP; 2011; DE
Liquid extract from Urticae herba (1:1.8-2.2); extraction solvent: ethanol 30% (V/V)	As a purging in inflammatory diseases of the urinary tract collection system. As a purging to prevent and support treatment of renal gravel.	Adolescents and adults 4 times daily 100 drops containing 100% liquid extract	WEU; 1976-2019; DE
Dry extract from Urticae herba (5-10:1); extraction solvent: water	As a purging in inflammatory diseases of the urinary tract collection system. As a purging to prevent and support treatment of renal gravel. For symptomatic treatment of osteoarthritis.	Adolescents and adults 4 times daily 300 mg dry extract 3 times daily 450 mg dry extract each	WEU; 1976-2018; DE
Powdered dried aerial parts	Traditionally used in seborrhoeic skin conditions	Adolescents from 12 years of age 3 times daily 275 mg	1992-2024; FR
Urticae herb. extr. alc. (60% V/V) (1:5)	For relive the complaints of rheumatic and joint	3 times 30-35 drops	"Healing product"; 1999; HU

Active substance	Indication	Posology and method of administration	Regulatory status
	diseases, urinary sand, and cystitis		
Urticae herba	Adjuvant in treating mild arthritic complaints.	2.5 g boil in 200 ml of water for 5 min. Drink 3-4 times daily a glass of decoction.	1976-1997; PL
Urticae herba	Diuretic in inflammatory of lower urinary tract and adjuvant in treating mild arthritic complaints	Like above decoction made of 2 g of herbal substance.	1991-1997; PL
Juice of fresh nettle herb, stabilized with ethanol 96% (V/V), DER (1:1).	To stimulate quantity of urine in mild inflammatory states of urinary ways. To promote urinary flow in mild rheumatic complaints	Adolescents and adults 2.5 – 5.0 ml, diluted with a small amount of water, 3 times daily	National registration R/1988; 1990; PL

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

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

Nettle herb can be found in combination preparation with other herbal substances with diuretic effects in several countries.

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 was already known in the ancient times. The ancient Greeks were familiar with its effects. Dioscorides wrote about it in his work. He regarded it as tonic, diuretic, digestive, blood-purifier, antitussive, styptic, aid in wound- and carbuncle-healing. Scrobinius Largo claimed that nettle herb cures poisoning and epilepsy. Plinius, Lusitanius and Sartorius described nettle herb as a very good styptic. In the 16th century Dioscorides's book was the main source of information on the healing characteristics of nettle herb. Lehnhardt used *Urtica dioica* and *Urtica urens* for dropsy. Quarin, Deider (1746) and Rosner used nettle for cough, cutaneous eruption and as a styptic. In the Czech folk medicine nettle was used as a substance against lung diseases (tuberculosis), sleeplessness, and as

compress for swelling. In France, nettle herb was considered as a metabolic enhancer especially in renal- and liver diseases (Lutomski *et al.,* 1983).
According to Hagers Handbuch (Blaschek *et al.,* 1998) nettle herb is used in folk medicine Internally in renal and liver diseases, as a blood-forming agent, blood-purifier (Reile, 1928) and metabolic enhancer (Kneipp, 1891);in cardiac disorders, arthritis, goutiness, podagra, rheumatism of the joints and muscles, weak or insufficient lactation, congestive conditions, fluid accumulation, as styptic (bloody cough, haematuria, profuse period) (Eckstein and Flamms, 1932). In the French publication Les Cahiers de l'Agence No.3. Agence du Médicament (1998), nettle herb is accepted for traditional use in the treatment of seborrhoeic conditions of the skin.

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form / Strength (where relevant) Posology / Duration of use**	**Reference**
Comminuted herbal substance	Adjuvant treatment of rheumatic conditions. Irrigation in inflammatory conditions of the lower urinary tract/ As a diuretic, for example to enhance renal elimination of water in inflammatory complaints of the lower urinary tract.	Adults 3-5 g of the drug as an infusion up to 3 times daily	ESCOP 1997, 2003
Comminuted herbal substance	Supportive therapy for rheumatic ailments. For irrigation in inflammation of the urinary tract and in the prevention and treatment of kidney gravel.	Daily dose: 8-12 g of drug or equivalent preparations. In irrigation therapy, intake of copious amounts of fluids must be observed	Blumental et al., 1998
Comminuted herbal substance	Rheumatic condition	3-6 g or by infusion, 3 times daily	Bradley, 1992
Comminuted herbal substance	To increase the amount of urine, Supportive treatment of complaints associated with urination	1.5 g as infusion for 10 min or decoction for a short time, several times a day	Wichtl, 1994

Herbal preparation	Documented use / Traditional use	Pharmaceutical form / Strength (where relevant) Posology / Duration of use	Reference
	Contraindication: water oedema as a result of cardiac and renal function.		
Liquid extract (1:1), extraction solvent: ethanol 25% (V/V)	rheumatic conditions	2-4 ml as single dose up to 3 times daily	Bradley, 1992
Tincture (1:5), extraction solvent: ethanol 45% (V/V)	rheumatic conditions	2-6 ml as single dose up to 3 times daily.	Bradley, 1992
Fresh juice	internally or topically: rheumatic conditions	5-10 ml 3 times daily	Bradley, 1992

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology / Strength	Period of medicinal use
Comminuted herbal substance	Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as in minor urinary complaints	1.5 g as infusion several times daily	Wichtl, 1994
	rheumatic condition	Adults, elderly 3-6 g of the comminuted herbal substance as a herbal infusion, 3 times daily	Bradley, 1992
Powdered herbal substance	Traditional herbal medicinal product to support the elimination function of the kidney	Adolescents, adults, elderly SD= 380-570 mg DD=1.14-2.28 g	Products on the market since 1976

Herbal preparation Pharmaceutical form	Indication	Posology / Strength	Period of medicinal use
	Traditional herbal medicinal product used in seborrheic skin conditions	Adolescents, adults 275 mg powdered herbal substance as single dose 3 times daily	Products on the market 1992-2024
Expressed juice from fresh Urticae herba (1:0.5-1.1)	As a purging in inflammatory diseases of the urinary tract collection system. As a purging to prevent renal gravel. For symptomatic treatment of osteoarthritis	Adolescents, adults, elderly 3 times daily 10-15 ml	Products on the market 1976-2008
Juice of fresh nettle herb, stabilized with ethanol 96% (V/V), pressed and adjusted with the ethanol, DER (1:1)	Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as in minor urinary complaints. Traditional herbal medicinal product for relief of minor articular pain	Adolescents, adults, elderly 2.5 – 5.0ml of product, diluted with small amount of water 3 times daily	Products on the market since 1988
Expressed juice from fresh Urticae herba (1.36-1.96:1)	Traditional herbal medicinal product to support the elimination function of the kidney	Adolescents, adults, elderly 4 times daily 3.5 ml	Products on the market 1979-2019
Liquid extract (1:1), extraction solvent: ethanol 25% (V/V)	Traditional herbal medicinal product for relief of minor articular pain	adults, elderly 2-4 ml as single dose, up to 3 times daily	Bradley, 1992
Liquid extract (1:1.8-2.2) extraction solvent: ethanol 30 (V/V)	As a purging in inflammatory diseases of the urinary tract collection system. As a purging to	Adolescents, adults, elderly 4 times daily 100 drops containing 100% liquid extract	Products on the market 1976-2019

Herbal preparation Pharmaceutical form	Indication	Posology / Strength	Period of medicinal use
	prevent and support treatment of renal gravel.		
Tincture (1:5), extraction solvent: ethanol 45% (V/V)	Traditional herbal medicinal product for relief of minor articular pain	Adults, elderly 2-6 ml as single dose, up to 3 times daily.	Bradley, 1992
Dry extract (5-10:1), extraction solvent: water	As a purging in inflammatory diseases of the urinary tract collection system. As a purging to prevent and support treatment of renal gravel. For symptomatic treatment of osteoarthritis	Adolescents, adults, elderly 4 times daily - 300 mg dry extract 3 times daily – 450 mg dry extract	Products on the market 1976-2018

The information about therapeutic indications of preparations from *Urticae herba* is available from literature and from the market overview, which shows the internal use of nettle herb preparations to increase the amount of urine to achieve flushing of the urinary tract in minor urinary complaints, for the relief of minor articular pain and for seborrhoeic skin conditions.

Thus, historical data and documented period of use in the EU support the evidences of traditional use of *Urticae herba* preparations a) Comminuted herbal substance, b) Powdered herbal substance, c) Expressed juice (1:0.5-1.1) from fresh herb, d) Expressed juice (1:1) from fresh herb, stabilized and adjusted with ethanol 96% (V/V), 20-25% ethanol content in final product, e) Expressed juice (1.36-1.96:1) from fresh herb, 3.5 ml as a single dose up to 3-4 times daily, f) Liquid extract (1:1), extraction solvent ethanol 25% (V/V), g) Liquid extract (1:1.8-2.2), extraction solvent ethanol 30% (V/V), h) Tincture (1:5), extraction solvent ethanol 45% (V/V), i) Dry extract (5-10:1), extraction solvent water, for different therapeutic indications:

- Indication 1): Preparations a), b), c), d), e), g) and i): Traditional herbal medicinal product used for the relief of symptoms associated with minor urinary complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine.
- Indication 2): Preparations a), c), d), f), h), and i) Traditional herbal medicinal product for relief of minor articular pain.
- Indication 3): Preparation b): Traditional herbal medicinal product used in seborrhoeic skin conditions.

Assessor's comments:
In the former version of the monograph 'adjuvant' is added in the therapeutic indication 1). However, 'adjuvant' supposes a defined treatment to which the herbal treatment can be added. As there is no clear instruction in that way, the therapeutic indication is reduced, not any longer mentioning the use as adjuvant.

For indication 1) relief of symptoms associated with minor urinary complaints, the only preparation not suitable for adolescents is preparation a) comminuted herbal substance. For the rest of preparations, the Posology in the monograph is for adolescents, adults and elderly. For indication 2) minor articular pain, it is considered that this indication is not suitable for adolescents. Articular pain must have medical supervision in adolescents as it can be related to different health problems. This limit is consistent with the one adopted for other monographs in the same therapeutic area. Thus, the Posology in the monograph is for Adults and elderly.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

***In vivo* experiments**

***Urticae herba* preparations**

- Diuretic effect

Early studies demonstrated the diuretic effect of nettle herb in animals, accompanied by increased excretion of chlorides and urea. Flavonoids and the high potassium content may contribute to the diuretic action, which is not, however, fully clarified (Bradley, 1992).

A study was performed on anaesthetized male Wistar rats that received a continuous i.v. perfusion for 1.25 h of an aqueous extract (no further information) of aerial parts of *Urtica dioica* at a low dose of 4 mg/kg/h or at a high dose of 24 mg/kg/h, or furosemide (control diuretic) at a dose of 2 mg/kg/h. As compared with a control period in each rat, an increase of diuresis (11 and 84% $p<0.001$, respectively) and natriuresis (28 and 143%, $p< 0.001$, respectively was observed, related to the dose of plant extract used, together with a reduction in blood pressure. In the rats perfused by furosemide, the arterial blood pressure was reduced by 28% ($p<0.001$). The diuresis and natriuresis were also increased proportionally (85 and 155%, $p<0.001$, respectively). Nevertheless, the hypotensive action of *U. dioica* was reversible during the recovery periods in about 1 h in the case of the lowest dose of the plant extract and furosemide, while the effect of the highest dose was persistent, indicating a possible toxic effect. The results demonstrate an acute hypotensive action of the *U. dioica*, which indicates a direct effect on the cardiovascular system. Moreover, diuretic and natriuretic effects were also observed, suggesting an action on the renal function. The plant extract seems to have a toxic effect at the highest dose of 24 mg/kg/h (Tahri *et al*., 2000).

No effect on diuresis or ion excretion could be demonstrated in rats after oral administration of an aqueous extract (no further information) of nettle herb at a dose of 1 g/kg body weight (Lasheras *et al.,* 1986).

No significant diuretic effect was observed during the 2 hours following the oral administration to rats of an unspecified ethanolic extract of nettle at 1 g/kg body weight, whereas urinary excretion increased significantly after intraperitoneal administration of 500 mg/kg. Na^+ excretion was unaffected, while both K^+ concentration in urine and K^+ total extraction were significantly enhanced (Tita *et al.,* 1993).

Administration of freshly squeezed nettle juice diluted in water 1:10 via a gastric tube to rats increased urine output (exact posology not reported). Sodium, potassium and chloride concentrations increased, whereas urea content remained unaffected. In other experiments in rats, a 10% suspension containing 185 mg nettle herb or 35 mg of a nettle macerate 7:1, urine volume increased associated with an

increase of sodium, potassium and chloride concentrations. Both nettle preparations had only a weak effect in dogs. Due to lack of statistical analysis and great variation of data, further studies are necessary to clarify the diuretic effect of nettle herb (Lutomski, 1981).

- Analgesic activity

After oral administration of nettle herb aqueous extract (no further information) at a dose of 1200 mg/kg to mice, animals showed much greater resistance to thermal stimulation in the hot plate test at 55°C, taking 190% longer time to react than the control animals (Lasheras *et al.,* 1986). Nevertheless, this dosage represents at least 3.5 times more than the maximum posology in the monograph.

In the acetic acid-induced writhing test in mice, aqueous nettle extract (20 g dried aerial parts of nettle, powdered and mixed with 400 ml boiling water during 15 min; 20 mg of the lyophilized extract was dissolved in 20 ml water) in a dose of 50, 100 and 200 mg/kg; after i.p. administration, it produced a dose-dependent inhibition in writhing (decrease 62.1, 70.4 and 89.2%, respectively), which was more pronounced than that of metamizole 200 mg/kg (decrease compare to control: 39.4%) (Gülcin *et al*., 2004).

- Local anaesthetic activity

Local application to the rat tail of 0.05 ml of nettle herb aqueous extract (100 mg lyophilised extract per ml), in the same region as subsequent application of exposure to heat in the tail flick test, produced a local anaesthetic effect comparable to that of lignocaine (Lasheras *et al*., 1986).

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main outcome(s) according to the authors**
Comparable/similar preparations to preparations of the monograph				
Aqueous extract of aerial parts of *Urtica dioica*	4 mg/kg/h 24 mg/kg/h control: furosemide 2 mg/kg/h	Continuous *i.v*., male Wistar rats	Tahri *et al*., 2000	Diuretic and natriuretic effects observed; also acute hypotensive action
Aqueous extract of nettle herb	1 g/kg body weight	Rats, oral	Lasheras *et al*., 1986	No diuretic effect
Aqueous extract of nettle herb	100 mg lyophilised extract per ml	Rats, cutaneous route, hot plate test	Lasheras *et al*., 1986)	Local anaesthetic effect comparable to that of lignocaine
Aqueous nettle extract	25, 50, 100 mg/kg body weight	male and female mice, *i.p.* route, acetic acid-induced writhing	Gülcin *et al*., 2004	pretreatment produced a dose-dependent inhibition
Other preparations				
Ethanolic extract of nettle	100 mg//kg body weight 500 mg/kg body weight	Rats, *i.p.*	Tita *et al*., 1993	with 500 mg/kg urinary excretion increased, Na^+ excretion was unaffected, while both K^+ concentration in urine and K^+ total extraction were significantly enhanced; no activity in hot plate test, but reduced

Herbal preparation tested	Posology	Experimental model	Reference	Main outcome(s) according to the authors
				writing response to phenylquinone
Ethanolic extract of nettle	1 g/kg body weight 2 g/kg body weight (diuretic only)	rats, oral , hot plate test	Tita *et al*., 1993	no significant diuretic effect, o analgesic activity in hot plate test; reduction in writhing response to phenylquinone

3.1.2. Secondary pharmacodynamics

***In vivo* experiments**

- CNS –depressant activity

A nettle herb infusion (*i.p.;* 1.66 g/kg and 3.33 g/kg) and an aqueous extract (drug extract ratio 3:1, *i.p.*; 303 mg/kg and 606 mg/kg) produced inhibition of drug-induced convulsion (by i.v. caffeine 0.25 mg/kg, cardiazol 60 mg/kg and strychnine 18.6 mg/kg) and a lowering of body temperature in rats (Broncano *et al.,* 1987).

- Spontaneous motility

The above-mentioned nettle herb infusion and the aqueous extract produced dose-dependent reduction in spontaneous motility in rats and mice when administered *i.p*. at a dose of 1.739 and 3.748 g/kg bodyweight for the infusion and 303 and 606 mg/kg for the extract (Broncano *et al.,* 1987).

An aqueous extract of nettle herb administered to mice by oral route at a dose 750 mg/kg led to a significant reduction in spontaneous activity during the first 16 hours after administration (Lasheras *et al.,* 1986).

- Hypotensive effects

Nettle herb produced a rapid but only transient decrease of 31.7% in the blood pressure of anaesthetized rats after intravenous administration of an aqueous extract at a dose 25 mg/kg/body weight (Lasheras *et al*., 1986).

In cats, an aqueous extract (3.3:1) administered by cannula at a dose of 26.6 mg/kg body weight (88 mg/kg crude herbal substance) produced a marked hypotensive effect and bradycardia, which was not compensated by subsequent administration of adrenalin (0.066 mg/kg). In rats, the hypotensive effect of the same extract in doses of 166 or 333 mg/kg could not be inhibited by atropin (0.05 mg/kg). The effect was similar to the effect of dihydroergotamin so a mode of action via α–adrenoceptors was suggested by the authors. I.v. doses of 33.3 mg/kg and 333 mg/kg of this extract caused significant bradycardia in rats (Broncano *et al.,* 1983).

- Blood lipids lowering effects

Aqueous (150 mg/kg/day) and to a lesser extent ether (20 mg/kg/day) extract of *Urtica dioica* given for 30 days to rats (n=10) fed with normal or high-fat diet, improved the blood lipid profile. Significant decreases in total cholesterol, LDL (low-density lipoproteins), cholesterol, LDL/HDL (high-density lipoproteins) cholesterol ratio and plasma total apo B (apolipoprotein B) were observed. Assessment of

liver enzymes (GOT, GPT and LDH) activities showed that no liver damage has occurred during the study period (Daher *et al*., 2006).

- Effects on blood glucose

In oral glucose tolerance test (OGTT) animals (male Wistar rats) were fasted for 16 hours, before glucose (1 g/kg) was administered by gavage 30 min after oral administration of 250 mg/kg water extract. [drug extract ratio calculated from yield given in publication: ~5:1]. The decrease of glycaemia reached to 33 ± 3.4% of the control value (glibenclamide at dose 2 mg/kg) 1 hour after glucose loading. This effect was persistent during 3 hours. In contrast, nettle (500 mg/kg) did not show hypoglycaemic effect in alloxan-induced diabetic rats (*i.p.* with 120 mg/kg/day of alloxan for 3 consecutive days). The amount of glucose absorbed in segment jejunum in situ was 8.05 ± 0.68 mg in presence of nettle extract (250 mg/kg) vs. 11.11 ± 0.75 mg in control rats (perfusing solution) during 2 hours ($p<0.05$). The authors concluded the effect seen may be caused in part by the reduction of intestinal glucose absorption (Bnouham *et al.,* 2003).

On the contrary, both an 80%-ethanolic extract and an aqueous decoction of nettle herb, evaporated to dryness, resolubilized and administered to mice at the equivalent of 25 g dry crude material/kg body weight 2 h prior to glucose load, produced hyperglycaemic effects in an oral glucose tolerance test (Neef *et al.,* 1995). This contradictory effect may be due to the much higher tested dose when compared with the above cited studies.

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 on preparations from Urticae herba are limited and not required.

A diuretic effect was demonstrated only by intra-venous administration and only in rats, these results having limited relevance for humans. Related to oral use, there are some studies, which did not reveal any effect, although nettle herb has high mineral content, which may play a role in its supposed diuretic effect.

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

No data available.

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

3.3.1. Single dose toxicity

The intraperitoneal (48 h) LD_{50} of an aqueous extract of nettle herb in mice has been determined as 3.625 g/kg body weight (Lasheras *et al.,* 1986).

The LD_{50} (*i.v.* 72 h) of an infusion (100 mg/ml) of nettle herb in rats was 1928 mg herbal substance/kg body weight. LD_{50} (*i.v*. 72 h) of an aqueous extract of nettle herb in rats has been found 1721 mg. The hydro soluble product responsible for toxicological effects, which can be eliminated by boiling, is suspected to have a pyran-coumarin structure (Baraibar *et al.,* 1983).

An ethanolic extract (not further specified) of *Urtica dioica* showed low toxicity (no further information) in both rats and mice after oral and intraperitoneal administration of 2 g /kg body weight (Tita *et al.,* 1993).

3.3.2. Repeat dose toxicity

The subacute LD_{50} of an infusion (100 mg/ml) of nettle herb in rats (*p.o*.) was 1310 mg/kg body weight (Baraibar *et al.,* 1983).

3.3.3. Genotoxicity

ICH-conform test on preparations of Urticae herba have not been published.

An herbal tea from *Urtica dioica* proved to be weakly genotoxic in the wing Somatic Mutation and Recombination Test (SMART). Furthermore, it was shown that quercetin and rutin, two flavonols present in beverages of plant origin, also exhibited weak genotoxic activity in somatic cells of *Drosophila*. The standard herbal teas (infusions) were prepared by adding 20 g dry tea to 100 ml boiling tap water and allowing it to draw for 10 min (Graf *et al.,* 1994).

In the study by Basaran *et al.* (1996) the aerial parts of *Urtica dioica* were investigated for their genotoxic potential in the *Salmonella typhimurium* microsomal activation assay and the alkaline single cell gel electrophoresis (COMET) assay. The plant extract was prepared by weight 1 g of plant sample either in 100 ml saline or in 100 ml deionised water and extracted twice at 50°C lyophilised and stored as desiccated sample. Furthermore, flavonoid and apolar compound-rich fractions of water extracted herbs of *Urtica dioica* were isolated from the extracts by chromatographic methods generally used in phytochemistry. No positive response in was produced in S*. typhimurium* strains TA98 and TA100 with or without metabolic activation with a concentration of 80 µg/plate, but an increase above negative control values was produced in the COMET assay (400 µg). The extract was further investigated and produced dose-related increase. Not only the *Urtica* extract produced such responses, but so did its fractions. The flavonoid fraction over the same dose range was less positive than the chloroform fraction possibly due to less DNA damaging agents in the fraction or because the glycoside flavonoid may exert an antigenotoxic effect.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

A nettle extract (whole plant without root, prepared with 90% ethanol, no further information) was reported to have no antifertility activity following oral administration at 250 mg/kg dose to albino rats in days 1-7 of pregnancy (Sharma *et al.,* 1983).

3.3.6. Local tolerance

No data available.

3.3.7. Other studies

No data available.

3.3.8. Conclusions

Non-clinical information on the safety of preparations of Urticae herba 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 and COMET-Assay are in no way (e.g. design, concentrations) 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 cannot be recommended.

The following text is included in the monograph section 4.6:
Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data are available.

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 nettle herb preparations to support the proposed indications are very limited and not required.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of nettle herb preparations is scarce. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

4. Clinical Data

4.1. Clinical pharmacology

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

No data available.

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

No data available.

4.2. Clinical efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

There are some clinical studies performed with nettle herb preparations.
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').
Therefore, the scope of the assessment in this section is relief of symptoms associated with minor urinary complaints, relief of minor articular pain and usage in seborrhoeic skin conditions.
Only studies related to these indications are included below.

Beside these investigations, nettle leaf preparations have been tested for clinical efficacy for instance in allergic rhinitis and diabetes. There is no information available that nettle herb preparations have 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.

The study by Kirchhoff (1983), was on open study including 32 adults with myocardial or chronic venous insufficiency. Patients received 15 ml of nettle herb juice, orally, 3 times daily (afterwards the dosage changed for once a day in the morning). After 2 weeks of treatment, a significant increase in the daily volume of urine throughout the treatment was observed: the volume in day 2 was 9.2% higher ($p<0.0005$) than the baseline in patients with myocardial insufficiency and 23.9% higher ($p<0.05$) in the case of patients with chronic venous insufficiency. Nevertheless, it was an open study including low number of patients and long-term effects were not known, and thus, it cannot be taken in account to prove the efficacy of Urticae herba.

The study by Wegener *et al.* (2009) was an open study to assess the effect of an expressed juice (DER 0.55–0.82) of fresh nettle herb (*Urtica dioica* L. and/or *Urtica urens* L.) in urinary or rheumatic symptoms. 114 patients were included and treated for 12 weeks. In case of urinary symptoms (cystitis, irritable bladder, predisposition to urinary stone or sand formation), the efficacy was assessed based on the subjective self-assessment of the volume of excreted urine, pain and burning sensation associated with urination, frequent urination, and dysuria. In case of rheumatic symptoms (arthrosis, polyarthritis, gout), stiffness of the joints in the morning and during the day, intensity of joint pain, pain at rest, pain at walking and the measure of influence on overall health status was assessed.
Within 6 weeks of the therapy, the physicians rated the improvement in both indications by 56.5% (urinary) and 24.7% (rheumatic) and after 12 weeks by 69.1% (urinary) and 41.2% (rheumatic). Efficacy was confirmed by the patients rating: 53.5% of patients found the efficacy of therapy to be very good and 32.5% good. No relevance due to the study design (open), low number of subjects, non-validated scale was applied.

Table 6: Clinical studies on humans, in patients with urinary or rheumatic symptoms

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Diuretic effect Kirchhoff, 1983	Open	15 ml of nettle herb juice, 3 times daily (afterwards the dosage changed for once a day in the morning) 2 weeks	32	Adults, myocardial or chronic venous insufficiency	Statistically significant increase in the daily volume of urine throughout the treatment; volume in day 2 was 9.2% higher ($p<0.0005$) than the baseline in patients with myocardial insufficiency and 23.9% higher ($p<0.05$) in the case of patients with chronic venous insufficiency	Please add statistical model .	None: open study, low number of patients, long-term effects not known
Urinary or rheumatic symptoms Wegener *et al*., 2009	Open	Expressed juice (DER 0.55–0.82) of fresh nettle herb (*Urtica dioica* L. and/or *Urtica urens* L.) 12 weeks	114: 81 women, 33 men 16–83 years	Urinary symptoms (cystitis, irritable bladder, predisposition to urinary stone or sand formation), and/or rheumatic symptoms (arthrosis,	urinary symptoms: efficacy was assessed based on the subjective self-assessment of the volume of excreted urine, pain and burning sensation associated with urination, frequent urination, and dysuria rheumatic symptoms: stiffness of the joints in the morning and during the day, intensity of joint pain, pain at rest, pain at	No	No relevance due to the study design (open), low number of subjects, non-validated scale

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
				polyarthritis, gout).	walking and the measure of influence on overall health status Within 6 weeks of the therapy, the physicians rated the improvement in both indications by 56.5% (urinary) and 24.7% (rheumatic) and after 12 weeks by 69.1% (urinary) and 41.2% (rheumatic). Efficacy was confirmed by the patients rating: 53.5% of patients found the efficacy of therapy to be very good and 32.5% good		

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

Clinical studies aimed to assess the efficacy of nettle herb preparations in the therapeutic areas of Urinary tract and Pain and inflammation and seborrheic skin conditions are scarce and have several weaknesses. The study by Kirchhoff (1983) was an open study with a low number of patients and long-term effects were not known. The trial by Wegener *et at.* (2009) was an open, non-controlled study; moreover, non-validated scales were used, and statistical significance was not assessed.

5. Clinical Safety/Pharmacovigilance

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

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

Table 7. Safety information from products marketed in the EU/EEA.

Herbal preparation	**SmPC section**	**Safety information**
Urticae herba, expressed juice (1:0.55-0.82)	4.8 Undesirable effects	Frequency not known: mild gastro-intestinal complaints like nausea, diarrhoea and vomiting; hypersensitivity reactions like pruritus, exanthema, urticaria

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

Table 10: Clinical safety data from clinical trials

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Diuretic effect Kirchhoff, 1983	Open	15 ml of nettle herb juice, 3 times daily (afterwards the dosage changed for once a day in the morning). 2 weeks	32	Adults, myocardial or chronic venous insufficiency	Serum parameters were unaffected, and the treatment was well tolerated apart from some cases of diarrhoea	No safety concern. GI complaints reflected in the monograph.
Urinary or rheumatic symptoms Wegener et al., 2009	Open	Expressed juice (DER 0.55–0.82) of fresh nettle herb (*Urtica dioica* L. and/or *Urtica urens* L.) 12 weeks	114: 81 women, 33 men 16–83 years	Adults, urinary symptoms (cystitis, irritable bladder, predisposition to urinary stone or sand formation) or rheumatic symptoms (arthrosis, polyarthritis, gout).	treatment was well tolerated apart from 1 case nausea, which was not correlated to the medication	No safety concern; furthermore, GI complaints such as nausea are reflected in the monograph.

5.2 Patient exposure

Aside from market presence and data from studies including a low number of patients (around 150 patients), there are no concrete data concerning patient exposure.

5.3 Adverse events, serious adverse events and deaths

Some references report allergic reactions (cutaneous affections, oedema, oliguria, gastric irritation) which occurred occasionally after taking nettle tea (Bisset, 1994; Bradley, 1992).

Also the consumption of nettle tea may cause gastric irritation, a burning sensation of the skin, oedema and oliguria (Barnes *et al.,* 2002).

The accepted wording in the Monograph is: Gastrointestinal disorders: Nausea, vomiting and diarrhoea. The frequency is not known. Skin and subcutaneous tissue disorders: allergic pruritus, rash and urticaria. The frequency is not known.

5.4 Laboratory findings

No data available.

5.5 Safety in special populations and situations

5.5.1. Use in children and adolescents

No data available.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special warnings and precautions for use

For indication 1)

The use is not recommended in children under 12 years of age because of the lack of available experience, except for the comminuted herbal substance, which is only for adults and elderly.

Because adequate fluid intake is required during treatment *Urticae herba* is not recommended for patients with conditions where reduced fluid intake is advised.

If urinary tract complaints worsen and symptoms such as fever, dysuria, spasm, or blood in the urine occur during the use of medicinal product, a doctor or a qualified health care practitioner should be consulted.

For indication 2)

The use is not recommended under 18 years of age because of the lack of adequate data.

Articular pain accompanied by swelling of joints, redness and fever should be examined by a doctor.

5.5.4. Drug interactions and other forms of interaction

Most references report no or not known interactions for *Urticae herba* (Blumenthal *et al*., 1998;

Blaschek *et al.,* 1998; Bisset 1994, ESCOP 1997, 2003).

According to Barnes *et al*. (2002), - derived from preclinical pharmacodynamic studies - excessive use of nettle preparation may interact with concurrent therapy for diabetes or high blood pressure, and may potentiate drugs with CNS depressant action.

Assessor's comment:

As concluded already in the first version of the assessment report, there is no information needed in the monograph section 4.5 from the non-clinical pharmacodynamic studies cited by Barnes et al. (2002).

Related to the vitamin K content of nettle herb, it is very low, 0.16-0.64 mg/100 g (Bertok, 1956). The maximum daily dose of a nettle herb preparation, equivalent to about 15 g of dried herb, contains 24-96 microgram of vitamin K. These values are less than 1% of the therapeutic dosage range of vitamin K (10-20 mg/day) and thus, no interaction related to this vitamin is expected.

The accepted wording in the monograph is: None reported.

5.5.5. Fertility, pregnancy and lactation

Nettle is reputed to be an abortifacient and to affect the menstrual cycle. Utero-activity has been documented in animal studies.

Mills & Bones, 2005 point out: Nettle leaf and root: Use on pregnancy=category B2 (no increase in frequency of malformation or other harmful effects on foetus from limited use in woman. Animal studies are lacking), use in lactation=category C (Both leaf and root are compatible with breastfeeding). In this publication, there is no differentiation between leaf and root, and nettle is reputed to be an abortifacient and to affect the menstrual cycle (Barnes, 2002). In view of this, the use of nettle during pregnancy should be avoided. Due to the lack of data, nettle herb is not recommended during lactation (Barnes *et al.*, 2002; ESCOP 1997, 2003).

The wording in the Monograph is:
Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data are available.

5.5.6. Overdose

No data available.

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

No data available.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

According to the available data nettle herb is well-tolerated in the usual dosage and in the traditional usage form.

However, nettle herb cannot be recommended during pregnancy or breast-feeding.

For indication 1), except for the comminuted herbal substance, it is recommended for adolescents, adults and elderly. Because adequate fluid intake is required during treatment, Urticae herba is not recommended for patients with conditions where reduced fluid intake is advised by a medical doctor. If urinary tract complaints worsen and symptoms such as fever, dysuria, spasm, or blood in the urine occur during the use of medicinal product, a doctor or a qualified health care practitioner should be consulted.

For indication 2) it is not recommended under 18 years of age because of the lack of adequate data.

The use of nettle herb is contraindicated in patients with hypersensitivity to nettle herb.

6. Overall conclusions

The dried aerial parts of *Urtica dioica* L.*, Urtica urens* L., their hybrids or their mixtures have been used since ancient times in folk medicine for a broad variety of applications. Several preparations have been marketed in the European Union for more than 30 years and are used to increase the amount of urine to achieve flushing of the urinary tract in minor urinary complaints, for the relief of minor articular pain and for seborrhoeic skin conditions.

Several clinical studies have been published to investigate the pharmacological properties and efficacy of Urticae herba in different therapeutic areas, such as Urinary tract and genital disorders or Pain and inflammation. Nevertheless, the clinical trials are not well designed, include small sample sizes, the tested products are not fully characterised, or the clinical efficacy evidence is missing. Thus, available data are still inconclusive and evidence for clinical efficacy cannot be deduced, so the requirements for well-established use of Urticae herba preparations are not met.

According to the market overview and documented medicinal use, the following preparations of Urticae herba fulfil all the requirements for TU (documented medicinal use for at least 30 years, self-medication character, specified strength/posology, appropriate route of administration, plausibility and safety):

a) Comminuted herbal substance

b) Powdered herbal substance

c) Expressed juice (1:0.5-1.1) from fresh herb

d) Expressed juice (1:1) from fresh herb, stabilized and adjusted with ethanol 96% (V/V)

e) Expressed juice (1.36-1.96:1) from fresh herb

f) Liquid extract (1:1), extraction solvent ethanol 25% (V/V)

g) Liquid extract (1:1.8-2.2), extraction solvent ethanol 30% (V/V)

h) Tincture (1:5), extraction solvent ethanol 45% (V/V)

i) Dry extract (5-10:1), extraction solvent water

Preparations a), b), c), d), e), g) and i), for:

- *Traditional herbal medicinal product used for the relief of symptoms associated with minor urinary complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine.*

Preparations a), c), d), f), h), and i), for:

- *Traditional herbal medicinal product for relief of minor articular pain*.

Preparation b) Powdered herbal substance, for:

- *Traditional herbal medicinal product used in seborrhoeic skin conditions.*

A European Union list entry is not supported due to lack of data on genotoxicity.

Annex

List of references