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ASSESSMENT REPORT ON
URTICA DIOICA L., AND *URTICA URENS* L., HERBA

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ASSESSMENT REPORT

FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH TRADITIONAL USE

***Urtica dioica* L., *Urtica urens* L., herba**

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Urtica dioica* L., *Urtica urens* L., their hybrids or their mixtures, herba Dried cut or fragmented aerial parts of the plant collected or harvested during the flowering period
Herbal preparation(s)	Comminuted herbal substance Powdered herbal substance Expressed juice (1:0.5-1.1) from the fresh herb 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 forms	Herbal substance or herbal preparation in solid or liquid dosage forms or as herbal tea for oral use.
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I. REGULATORY STATUS OVERVIEW[1]

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

Member State	Regulatory Status				Comments[2]
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	In combination
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	+ In combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	+ In combinations
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	No medicinal products, only food supplements
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products, only food supplements
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

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

Table 1: Products on the market in some Member States

Name of the Product (country)	Active substance	Indication	Posology	Legal status
Kopřivový čaj (Czech)	Fragmented Urticae herba in tea bags	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.	1 tea spoon or 1 tea bag (1.5 g) infused with 0.25 l of boiling water (extracted for 15 minutes) three times daily	1999
Kopřivová nať (Czech)	Fragmented Urticae herba consissa			1997
Nettle tincture (Hungary)	Urticae herb. extr. alc. (60% V/V) (1:5)	For relive the complaints of rheumatic and joint diseases, urinary sand, and cystitis	3 times 30-35 drops	"Healing product" registered in 1999
Body Spring Ortica (Italy)	Dry extract of Urticae herba	It may have a bland draining action on excessive body fluids	2 capsules daily (2 times 250 mg)	as food-supplement 2004
(Poland)	Urticae herba as tea (two products)	Adjuvant in treating mild arthritic complaints.	2.5g (spoon) boil in 200ml (a glass) of water for 5 min. Drink 3-4 times daily a glass of decoction.	More than 30 years
(Poland)	Urticae herba as tea, infusion bags, 2 g	Diuretic in inflammatory of lower urinary tract and adjuvant in treating mild arthritic complaints	Like above decoction made of 1 sachet containing 2g of herbal substance.	More than 1 5 years
(Poland)	Urticae herbae succus (1:1) from fresh material as a „stabilized juice" oral liquid	Adjuvant in treating mild arthritic complaints and diuretic in urolithiasis	2.5- 5ml of product, 3 times daily.	More than 15 years (1989)
(France)	275 mg of powdered dried aerial parts/hard capsule	Traditionally used in seborrhoeic skin conditions	1 hard capsule 3 times daily	1992

Table 2: Products on the German market

Active substance	Indication	Posology	Legal status
powder of Urticae herba	Traditional herbal medicinal product to support the elimination function of the kidney.	3-4 times daily 2-3 capsules containing 190 mg powder each 4 x daily 3 coated tablets containing 190 mg powder each	THM at least since 1976
expressed juice from fresh Urticae herba (1.36-1.96:1)	Traditional herbal medicinal product to support the elimination function of the kidney.	4 times daily 3.5 ml oral liquid containing 100% expressed juice	THM at least since 1979 (DDR-AM)
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.	3 times daily 10 ml oral liquid containing 100% expressed juice 3 times daily 10-15 ml oral liquid containing 100% expressed juice	WEU at least since 1976
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.	4 times daily 100 drops containing 100% liquid extract	WEU At least since 1976
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.	4 times daily 1 coated tablet containing 300 mg dry extract 3 times daily 3 coated tablets containing 150 mg dry extract each	WEU At least since 1976

I.1 INTRODUCTION

This assessment report reviews the available scientific data for nettle herb. Evaulation of the literature on nettle was very difficult because in most of the cases data on nettle herb and nettle leaf were confused.

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

I.1.1.1. Herbal substance(s) [3]:

- **Definition of the herbal substance:**

ESCOP:
First Edition from 1997: "Nettle leaf consist of the dried leaves , and nettle herb consists of the dried aerial parts collected during the flowering season, of *Urtica dioica* L., *Urtica urens* L., their hybrids or mixtures of these."

Second Edition from 2003: "Nettle leaf consist of the dried leaves, and nettle herb consists of the dried flowering aerial parts of *Urtica dioica* L.,*Urtica urens* L., their hybrids or mixtures of these."

In both of the two Editions:
The material complies with the Deutsches Arzneibuch (nettle leaf) or the Pharmacopoeia Helvetica (nettle herb).
Fresh material may be used provided that when dried it complies with one of the above pharmacopoeias."

British Herbal Pharmacopoeia 1983:
"Urtica consists of the dried aerial parts of *Urtica dioica* L. (Fam. Urticaceae) gathered during the flowering period."

British Herbal Compendium (*Bradley 1992*):
"Nettle Herb consists of the dried leaves or aerial parts of *Urtica dioica* L. (Urticaceae) collected during the flowering period. *Urtica urens* L. (Small or Annual Nettle) is also used medically and included with *U. dioica* in the Ph. Helv. VII. and the DAC 1986."

Phytotherapie in der Urologie *(Schilcher 1992):*
Referring to nettle herb monograph (Urticae herba) in DAC [*Deutsches Arzneimittel Codex*] "The used plant part: dried and/or fresh (for preparation of fresh plant juice) herb, the aerial parts of the both *Urtica genus (U. dioica* L., or *U. urens* L.) or of their hybrids collected during the flowering season."

Definition of the herbal substance in the Monograph: Dried cut or fragmented aerial parts of the plant collected or harvested during the flowering period.

- **Description of the herbal substance:**
Pharmacopoeia Helvetica VII
British Herbal Pharmacopoeia 1983,
Hagers Handbuch *(Blaschek et al. 1998)*

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

Principal components of the herbal substance:

- 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%. The trace element content: 0.4% mg Cu, ~ 6 mg % Mn, ~ 1 6mg % Al and not determined quantity of cobalt and zinc. The ash consist of : 24-33% CaO, 14-20% K2O, 3-10% MgO, 3-6% Fe2O3, 1-2% Na2O, 4-9% P2O5, 6-10% SiO2 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, acethylcholine and serotonin (5-hydroxytryptamine), particularly in the stinging hairs (Bradley 1992)
- Acids: Carbonic acid, formic acid, silicic acid, citric acid, fumaric acid, glyceric acid, malic acid, oxalic acid, phosphoric acid, quinic acid, succinic acid, threnoic acid and threono-1,4-lactone (Barnes *et al.* 2002).

  Caffeic acid esters, principally caffeoylmalic acid in Urtica dioica (up to 1.6%) but none in Urtica urens; chlorogenic acid (up to 0.5%) small amounts of neochlorogenic acid and free caffeic acid in both species. Free amino acids (30 mg/kg) (ESCOP 2003).
- Chlorophylls a and b, chlorophyll degradation products and carotenoids (including β-carotene and xanthophylls) (Bisset 1994).
- Vitamins (among them C, B group, K1) (Bisset 1994).
- Vitamin K content is 0.16-0.64 mg/100 g (Bertok 1956).
- Triterpenes and sterols including β-sitosterol (Bisset 1994).
- Cumarins: Scopoletin ca. 1-10 mg/kg herbal substance (Blaschek *et al.* 1998)
- Leukotrienes in hair (Czarnetzki *et al.* 1990).

I.1.1.2. Herbal preparation(s)[3]

- **Comminuted herbal substance as infusion (**Tea): *ESCOP 1997, ESCOP 2003, British Herbal Pharmacopoeia 1983, Blumenthal 1998, Wren 1988, Bradley 1992, Bisset 1994, Barnes et al. 2002, Blaschek et al. 1998, Schilcher 1992)*
- **Powdered herbal substance** (*Products on the market in Germany and in France*)
- **Expressed juice from fresh herb**:
  (*Bradley 1992, ESCOP 1997, ESCOP 2003, Schilcher 1992, Kirchhoff 1983.)*

  The ratio of the fresh herb and expressed juice is: 1: 0.5-1.1.
  Method of the preparation of this juice according to the Urticae herba monograph of Hagers Handbuch (*Blaschek et al. 1998)*. Fresh nettle herb is pressed cold or for example with hot steam after plasmolysis and it than is autoclaved for the purpose of preservation.

The ratio of fresh herb and the expressed juice is: (1.36-1.96:1) *(Product on the German market)*

- **Extracts:**

  Liquid extracts with ethanol:

  Liquid extract (1:1), extraction solvent: ethanol 25% (V/V): (*BHP 1983, Wren 1988; Bradley 1992, Barnes et al. 2002)*

  Liquid extract (1:1.8-2.2), extraction solvent: ethanol 30% (V/V) (*Product on the German market)*

  Tincture (1:5), extraction solvent: ethanol 45% (V/V) *(BHP 1983, Barnes et al. 2002*)

  Dry extracts:

  DER: (5-10:1), extraction solvent: water (*Product on the German market)*

I.1.1.3. Combinations of herbal substance(s) and/or herbal preparation(s)[4]

In lots of countries nettle herb can be found in combination preparation with other herbal substances with diuretic effects.

- Vitamin(s)[5]
- Mineral(s)[5]

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

- **Evidence regarding the indication/traditional use**

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 promising metabolic enhancer especially in renal- and liver diseases. (Lutomsky *et al.* 1983)

In Hagers Handbuch (Blaschek *et al.*1998): In folk medicine: Internally: in renal and liver disease, as an blood-forming agent, blood-purifier, (Reile 1928) a 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 & Flamms 1932).

[4] According to the 'Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations' (EMEA/HMPC/166326/2005)

[5] Only applicable to traditional use

Indication 1:

"Irrigation in inflammatory conditions of the lower urinary tract." (*ESCOP 1997)*

"As a diuretic, for example to enhance renal elimination of water in inflammatory complaints of the lower urinary tract. " (*ESCOP 2003*)

"For irrigation in inflammation of the urinary tract and in the prevention and treatment of kidney gravel." *(Blumental et al. 1998, Bisset 1994)*

"Mild diuretic." (*Wren 1988, Bradley 1992)*

Indication 2:

"Adjuvant treatment of rheumatic conditions." (*ESCOP 1997*)

"Adjuvant in the symptomatic treatment of arthritis, arthroses and /or rheumatic condition. *(ESCOP 2003)*

"When taken internally and used externally: only supportive treatment for rheumatic complaints" *(Blumenthal et al. 1998, Bisset 1994)*

"Helpful in rheumatic and arthritic condition." *(Bradley 1992*)

Indication 3:
"Anti-haemorrhagic" [*Hagers Handbuch (Blaschek et al. 1998*)]

"Uterine haemorrhage, Epistaxis. Melaena" (*BHP 1983, Barnes et al. 2002)*

Indication 4:

" Mild hypoglycaemic activity." (*Wren 1988, Bradley 1992. Barnes et al. 2002)*

Indication 5:

"Skin complaints, including eczema and skin eruptions, usually as an infusion." (*Wren 1988*)

"Cutaneous eruption, infantile and psychogenic eczema, and specifically for nervous eczema." (*British Herbal Pharmacopoeia 1983, Barnes et al. 2002*).

In the officinal French publication "Médicaments à base de plantes" (République Française Ministère de l'Emploi et de la Solidarité, 1997) nettle herb is accepted for traditional use in the treatment of seborrhoeic conditions of skin.

Indication 6:

Allergic rhinitis *(Bradley 1992)*.

Accepted indications in the Monograph:

a) Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.
b) Traditional herbal medicinal product for relief of minor articular pain.
c) Traditional herbal medicinal product used in seborrhoeic skin conditions.

- **Evidence regarding the specified posology**

1. In indication a) and b)

Dried herb:

Thrice daily 2-4 g or by infusion. (*BHP 1983, Barnes et al. 2002)*

Three times daily 3-6g or in infusion. *(Bradley 1992)*

Daily 8-12 g herbal substance as infusion *(Blumenthal et al. 1998, Blaschek et al. 1998)*

"Making the tea: 1.5g of the finely cut herbal substance is put into cold water and boiled for a short time, or boiling water is poured directly on to it, and after 10 min. strained. As a diuretic, a cupful is drunk several times day. 1 teaspoon=ca. 0.8g, 1 tablespoon=ca. 2.2 g.
Herbal preparations: The herbal substance is also available in tea bags (1.0-1.8g)." *(Bisset 1994)*

Powdered herb:
380-570 mg powdered herbal substance as single dose up to 3-4 times daily

Expressed juice from fresh herb:
(1:0.5-1.1) 10-15 ml as a single dose up to 3 times daily.

(1.36-1.96:1) 3.5 ml as a single dose up to 3-4 times daily

Liquid extracts with ethanol:

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

Three times daily 3-4 ml (*BHP 1983, Barnes et al. 2002)*

Three times daily 2-4 ml (*Bradley 1992)*

Liquid extract (1:1.8-2.2), extraction solvent: ethanol 30% V/V:
Up to four times daily 100 drops

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

Three times daily 2-6 ml *(BHP 1983, Barnes et al. 2002*).

Dry extracts:

Dry extract from Urticae herba (5-10:1), extraction solvent: water; corresponding to 2-4 g of herbal substance as a single dose up to 3 times daily.

2. In indication c)

275 mg powdered dried aerial parts of nettle as single dose up to 3-4 times daily

- **Evidence regarding the route of administration**

Internally:

British Herbal Pharmacopoeia 1983
Commission E Monograph (*Blumenthal et al. 1998*)
Wren1988
British Herbal Compendium (*Bradley 1992*),
Barnes et al. 2002
Hagers Handbuch (*Blaschek et al. 1998*)

Cutaneous use:

British Herbal Pharmacopoeia 1983
Wren1988
Bisset 1994
Commission E Monograph (*Blumenthal et al. 1998*)
ESCOP 2003

Method of administration in the Monograph:

Oral use.

Cutaneous use is not mentioned, because there is no product on the market for more than 30 years.

- **Evidence regarding the duration of use**

Four or six weeks, as a cure (*Blaschek et al. 1998*).

Duration of use in the Monograph is harmonised with that in other monographs on herbal substances with similar effects.

Indication a) and c)

The herbal substance is traditionally used over a period of 2 up to 4 weeks.

If symptoms persist or do not improve within one week, a doctor or a qualified health care practitioner should be consulted.

Indication b)

Not to be taken for more than 4 weeks.

If symptoms persist or do not improve within one month, a doctor or a qualified health care practitioner should be consulted.

I.2 NON-CLINICAL DATA

For all studies cited, it should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.

I.2.1 Pharmacology

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

(e.g. primary pharmacodynamics, secondary pharmacodynamics, safety pharmacology, pharmacodynamic interactions)

***In vitro* experiments:**

- ***Anti-inflammatory activity***

An extract of nettle herb, prepared as 0.25 mg/ml of a lyophilized aqueous extract in water, produced 93% inhibition of platelet activating factor (PAF)-induced exocytosis of elastase from human neutrophils. The same extract (0.2 mg/ml) showed no activity in a test for inhibition of the biosynthesis of prostaglandins from ^{14}C-arachidonic acid (Tunón *et al.* 1995).

- ***Immuno-modulatory activity***

The major compounds isolated from the methanolic extract of the aerial parts of *Urtica dioica* L. were determined as quercetin-3-O-rutinoside (1), kaempherol-3-O-rutinoside (2) and isorhamnetin-3-O-glucoside (3) by chromatographic, chemical (acidic hydrolysis) and spectral (UV, IR, H-NMR, C-NMR) methods. Their immuno-modulatory activities were studied *in vitro* by chemotaxis (Boyden Migration Chamber) and intracellular killing activity (nitroblue tetrazolium (NBT) reduction test). Compounds 1, 2, 3 and the total flavonoid fraction were determined to have significant chemotatic effects in 4, 8, 16 g doses. According to the results of the NBT reduction test, all flavonoid glycosides showed high intracellular killing activity. The results of both assays confirmed the immuno-stimulatory activity of the flavonoid fraction and the isolated flavonoid glycosides on neutrophilis suggesting that they could possibly be useful for treating patients suffering from neutrophil function deficiency and chronic granulomatous diseases (Akbay *et al.* 2003).

Czarnetzki *et al. 1990:* In order to clarify the mechanisms of urtication after contact with stinging plants, nettle (*Urtica urens*) hair and whole-plant extracts were examined for the presence of leukotriene (LT) B4 and LTC4 by reverse phase high-pressure liquid chromatography (RP-HPLC) and radioimmunoassay (RIA) and for *in vitro* neutrophil chemotactic activity and histamine contents. Both hair and plant extracts contained high levels of LTB4 and LTC4 by RIA as well as histamine. The presence of LTB4 was supported by RP-HPLC elution profiles and by *in vitro* chemotaxis. Nettle hairs therefore resemble insect venoms and cutaneous mast cells with regard to their spectrum of mediators.

- ***Cardiovascular effects***

Urtica dioica L. is widely used in oriental Morocco to treat hypertension. Aqueous extract of nettle herb (AEN) also exerts a hypotensive action in the rat *in vivo*. The aim of this work was to characterize the specific cardiac and vascular effects of AEN (10 g plant was infused in 100 ml of boiled distilled water and incubated for 20 min. The aqueous extract was filtered and dried at 50°C.) In the isolated Langedorff perfused rat heart, AEN (1 and 2 g/l) markedly decreased heart rate and increased left ventricular pressure. Higher concentration (5 g/l) even led to cardiac arrest. Although carbachol mimicked the bradycardiac effect of AEN, atropine (1 μM) did not modify the response. Beside its action on myocardium, AEN also affected vascular contractility. Indeed, AEN (0.1-5 g/l) produced a dose dependent increase in basal tone of isolated rat aorta. This effect was endothelium independent and was abolished by 1 μM prazosin (an α_1-adrenergic antagonist). AEN had little additional effects when the aorta was preconcentrated by noradrenaline (1 μM) or KCL (40 mM). Data indicate that AEN produces a vasoconstriction of the aorta which is due to activation of α_1-adrenergic receptors. However, AEN also induces a strong bradycardia

through non-cholinergic pathways which might compensate for its vascular effect and account for the hypotensive action of *Urtica dioica* L. described *in vivo* (Legssyer *et al.* 2002).

- ***Effect on platelet aggregation***

Aqueous nettle extract (ten grams of aerial parts before flowering in 100 ml of boiled distilled water for 30 min.) demonstrated weak inhibition of thrombin 1 U/ml and ADP 10 µM-induced platelet aggregation (IC_{50} 15.5 and 12.8 mg/ml, respectively (Mekhfi *et al.* 2004*)*.

A methanolic extract had only weak antithrombotic activity (200 g aerial parts of the plant collected in period June-September 1999 were extracted in sequence with methylene chloride [24 h] and ethanol [24h]. The solvent was removed under vacuum to yield the methylene chloride extract and then the methanol extract) (Goun *et al.* 2002).

Antonopoulou *et al.* (1996) identified in the nettle herb collected in spring 1989 from Marousi (Attica Greece) a phospholipid fraction that was able to induce platelet aggregation in dose-dependent manner, five orders of magnitude less potent than the platelet-aggregating factor (PAF). The effect was not inhibited by indometacin but by a PAF receptor-specific agent indicating that a receptor is involved in the effect mechanism.

- ***Antioxidative effect***

An aqueous nettle extract was prepared the following way: 20 g dried aerial parts of nettle collected in May in Turkey, powdered and mixed with 400 ml boiling water during 15 min. The filtrate was frozen and lyophilized; 20 mg was dissolved in 20 ml water. 50, 100 and 250 µg amounts of this water extract showed 39, 66 and 98% inhibition on peroxidation of linoleic acid emulsion, respectively, while 60 µg/ml of α-tocopherol, exhibited only 30% inhibition. Moreover the aqueous nettle extract had effective reducing power, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, and metal chelating activities at the same concentration (Gülcin *et al.* 2004).

Likewise, Mavi *et al.* (2004) found some antioxidative activity for aqueous (5% decoction) and for methanolic (solvent 5% methanol) nettle extracts (concentrations tested 50-500 mg/l).

Lipopolysaccharide-stimulated NO_2-production was inhibited by the aqueous nettle extract in a dose-dependent manner without affecting cell viability (dose range tested 12.5-800 µg/ml). The expression of induced nitric oxide synthetase (iNOS) was not affected (Harput *et al.* 2005). Aqueous nettle extract: 10 g air-dried aerial parts were boiled with water for 1 h. The aqueous solution was clarified by filtration and evaporated under reduced pressure at 40°C. Freeze-drying and solvent elimination under reduced pressure finally yielded 2.4 g of powdery, crude aqueous extract.

- ***Uterine muscle activity***

An aqueous extract of nettle herb caused slight contraction followed by relaxation in isolated uterine smooth muscle from the non-pregnant mouse. Application of the extracts to uterine muscle from the pregnant mouse produced a diametrically opposed effect, increase of muscular tone and contractions of considerable amplitude. The authors concluded that extracts had adrenolytic activity, similar to the action of dihydroergotamine (40 mg extract = 0.132 mg dried plant = 0.8 mg dihydroergotamine) and inhibited the effect of adrenaline (2 µg). The active principle responsible of the action was isolated (Broncano *et al.* 1987a).

- ***Inhibition of α-Glucosidase***

Investigation of water extracts of some medicinal herbs: *Urtica dioica*, *Taraxacum officinale*, *Viscum album* and *Myrtus communis* with α-glucosidase inhibitor activity was conducted to identify a

prophylactic effect for diabetes *in vitro*. The inhibitory effect of these plants and some common antidiabetic herbal substances against the enzyme source (baker's yeast, rabbit leaver and small intestine) were searched (Önal *et al.* 2005).

Table 3: α-Glucosidase inhibitory activity of some plant crude extracts and drugs

IC_{50} (mg/ml) *			
A-glucosidase	Baker's yeast	Rabbit liver	Rabbit intestine
Viscum album	11.7	10.1	19.2
Urtica dioica	**3.7**	**2.3**	**2.3**
Myrtus communis	0.038	0.5	0.31
Taraxacum officinale	2.3	3.5	1.83
Amaryl (glymerid)	0.4	0.88	0.5
Betanorm (gliclazide)	0.8	1.4	0.8
Glycobay (acarbose)	0.5	0.75	0.25

*Plants extracts; mg plant/ml, herbal substance samples; mg active material/ml

The concentration of the α-glucosidase inhibitor required to inhibit 50% of the α-glucosidase activity under the assay condition is defined as the IC_{50} value.

***In vivo* experiment:**

- ***Diuretic effects***

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 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, the arterial blood pressure was reduced proportionally to the dose of the perfusion of the plant extract (15 and 38%, $p<0.001$, respectively). These effects were accompanied by a correlative increase of diuresis (11 and 84% $p<0.001$, respectively) and natriuresis (28 and 143%, $p< 0.001$, respectively). 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 lower dose of the plant extract and furosemide, while the effect of the higher dose was persistent, indicating a possible toxic effect. The results demonstrate an acute hypotensive action of *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 higher dose (Tahri *et al.* 2000).

No effect on diuresis or ion excretion could be demonstrated in rats after **oral** administration of an aqueous extract 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. 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*).*

- ***CNS –depressant activity***

A nettle herb infusion (i.p. in doses of 1.66 g/kg, and 3.33 g/kg) and an aqueous extract (drug extract ratio 3:1, i.p. in doses of 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.* 1987b).

- ***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 intraperitoneally 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.* 1987b).

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

- ***Hypotensive effects***

In the ***i.v.*** perfusion experiments on rats described above under diuretic effects (Tahri *et al.* 2000), the diuretic and natriuretic effects were accompanied by a dose-dependent hypotensive effect. Compared to control periods (perfusion of isotonic 0.9% saline only) perfusion of dry aqueous extract from nettle herb (in isotonic saline) reduced arterial blood pressure by 15% at 4 mg/kg/hour and 38% at 24 mg/kg/hour (both $p<0.001$), while furosemide at 2 mg/kg/h reduced arterial blood pressure by 28% ($p<0.001$). The hypotensive effect was reversible within about 1 h of recovery after the lower dose of nettle herb extract or furosemide, but was persistent after the higher dose of nettle herb extract, indicating a possible toxic effect at that dose level (Tahri *et al.* 2000).

Nettle herb produced a rapid but only transient decrease of 31.7% in the blood pressure of anaesthetized rats after ***i.v.*** 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 dihydroergotamine 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 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 occurred during the study period (Daher *et al.* 2006).

Table 4: Effect of *U. dioica* aqueous and petroleum ether extracts on serum triacylglycerol, total cholesterol, HDL cholesterol, LDL cholesterol and LDL/HDL ratio

Lipids (mg/dl)	Regular diet			High fat diet		
	Control	Petroleum Ether extract[a]	Water extract [b]	Control	Petroleum Ether extract[a]	Water extract [b]
Triacyl-glycerol	62 ± 4.5	58 ± 4.2	56 ±2.9	84 ± 4.6	78 ± 4.6	63*,**±2.9
Total cholesterol	86 ± 4.1	74* ± 4.2	71*± 2.6	97 ± 4.1	86 ± 2.5	78* ± 3.1
HDL cholesterol	40 ± 2.1	38 ± 2.1	42± 2.2	39 ± 1.9	37 ± 2.1	40 ± 2.1
LDL cholesterol	32 ± 2.7	25* ± 4.2	20*,**± 2.1	40 ± 2.7	33*±2.3	27*,**± 2.4
LDL/HDL	0.8 ±0.06	0.66*±0,05	0.48*,**±0.04	1 ± 0.06	0.89 ± 0.06	0.68*,** ± 0.07

N=10

[a] 20 mg/kg/day extract [100 g plant material was macerated with petroleum ether (1 l), evaporated *in vacuo*] for 30 days.

[b]150 mg/kg/day extract [10 g plant material was macerated with hot water (1 l), evaporated *in vacuo*] for 30 days.

* $p<0.05$ Significant difference with respect to control group

** $p<0.05$ Significant difference between water and petroleum ether groups

- ***Hyperglycaemic and hypoglycaemic activity***

Nettle is stated to contain both hypoglycaemic and hyperglycaemic principles. The hypoglycaemic component has been termed 'urticin' and nettle has been reported to lower the blood-sugar concentration in hyperglycaemic rabbits (Barnes et al. 2002).

Bever & Zahnd (1979) in their article listed the herbal substances having hypoglycaemic action into three categories. *Urtica dioica* L. plant was listed into the Group II.: Plants with more or less confirmed hypoglycaemic action but with as yet unknown active constituents. According to the author, the known chemical components are: "Hypoglycaemic principle='urticin. Contains chlorophyll; flavonoids are found in allied *spp*.

In oral glucose tolerance test (OGTT) animals (male Wistar rats) were fasted for 16 hours, before glucose (1g/kg) was administered by gavage 30 min after oral administration of 250 mg/kg a water extract. [This extract was prepared the following way: Dried aerial material (10 g) was infused in 100 ml of distilled water for 20 min. The extract evaporated *in vacuo* gave a crude residue (yield: 21%), *(drug extract ratio: ~5:1)*]. The decrease of glycaemia has 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 (500mg/kg) did not show hypoglycaemic effect in alloxan-induced diabetic rats (intra-peritoneally 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 (250mg/kg) vs. 11.11 ± 0.75 mg in control rats (perfusing solution) during 2 hours ($p<0.05$). The results indicate that nettle herb at high dose has a significant anti-hyperglycaemic effect in OGTT model. This effect may be caused in part by the reduction of intestinal glucose absorption (Bnouham *et al.* 2003).

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 herbal substance/kg body weight 2 h prior to glucose load, produced hyperglycaemic effects in an OGTT (Neef *et al.* 1995).

- ***Analgesic activity***

After administration of nettle herb aqueous extract at a dose of 1200 mg/kg mice 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).

On the other hand, no analgesic activity was noted in hot plate test after oral or intraperitoneal administration to rats of an unspecified ethanolic extract of nettle, although this extract reduced the writhing response to phenylquinone in rats after oral (1 g/g) and intraperitoneal (500 mg/kg) treatment (Tita *et al.* 1993).

In the acetic acid-induced writhing test in mice, aqueous nettle extract (20 g dried aerial parts of nettle collected in May in Turkey, powdered and mixed with 400 ml boiling water during 15 min. The filtrate was frozen and lyophilized; 20 mg was dissolved in 20 ml water. Doses 50-250 µg were used in the tests.) in a dose of 50, 100 and 200 mg/kg i.p. produced a dose-dependant inhibition in writhing which was more pronounced than that of metamizole (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).

I.2.1.2 Assessor's overall conclusions on pharmacology

Indication a: Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

If we consider the possible traditional use of nettle herb, the diuretic effect is not unambiguous. It was clearly demonstrated only by intra-venous administration. For oral use there are some studies with negative results. One study has positive effect only, but due to the lack of statistical analysis and great variation of data, further studies are necessary to clarify the diuretic effect of nettle herb. Nevertheless nettle herb has high mineral content which may explain its diuretic effect.

Indication b: Traditional herbal medicinal product for relief of minor articular pain.

The analgesic and anti-inflammatory characteristics can be supported only very weakly.

Nettle herb did not inhibit the biosynthesis of prostaglandins, but had activity in PAF-test. Its flavonoid fractions showed *in vitro* immuno-modulatory activity in chemotaxis and intracellular killing activity tests. Its analgesic doses are high.

Indication c: Traditional herbal medicinal product used in seborrhoeic skin conditions.

The anti-inflammatory effect of nettle herb (the flavonoid fractions of it) can support this indication.

I.2.2 Pharmacokinetics

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

(e.g. absorption, distribution, metabolism, elimination, pharmacokinetic interactions with other medicinal products)

No relevant data available.

I.2.2.2 Assessor's overall conclusions on pharmacokinetics

No relevant data available.

I.2.3 Toxicology

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

(e.g. single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, local tolerance, other special studies)

Single/repeat 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).
LD_{50} (i.v. 72 h) of an infusion (100 mg/ml) of nettle herb in rats has been found 1928 mg herbal substance/kg body weight. Subacute LD_{50} of this infusion in rats (p.o.) has been found 1310 mg/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 of *Urtica dioica* herb showed low toxicity in both rats and mice after oral and intraperitoneal administration at the equivalent of up to 2 g of dried herbal substance/kg body weight (Tita *et al.* 1993).

Three horses with an apparent neurological disorder resulting from nettle rush showed signs of ataxia, distress and muscle weakness, and two of them had urticaria. The condition resolved within 4 h (Bathe 1994).

Reproductive toxicity:

A nettle extract (whole plant without root, prepared with 90% ethanol) 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).

Genotoxicity:

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 their study Basaran *et al.* (1996) investigated various Turkish medicinal herbs for their genotoxic potential in the *Salmonella typhimurium* microsomal activation assay and the alkaline single cell gel electrophoresis (COMET) assay. Among others the aerial parts of *Urtica dioica* were examined. The plant extract was prepared by weight 1 g of plant sample in either 100 ml saline or 100 ml deionised water and extracted twice at 50ºC 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.

The plant extracts and fractions investigated, none produced a positive response in strains TA98 and TA100 with or without metabolic activation, but all produced an increase above negative control values in the COMET assay. *Urtica* extract was investigated further and produced dose-related increases. 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. It is known that flavonoids in the glycoside form can act under certain conditions in antigenotoxic capacity. The breaks that were detected in the COMET assay could be alkali-labile adenosine phosphate-sites and intermediates in base- or nucleotide-excision repair and are difficult to interpret in terms of hazard for man. Further studies with additional genotoxicity assays would be required to make such a prediction.

I.2.3.2. Assessor's overall conclusions on toxicology

Two Ames strains are not enough for evaluating of the genotoxicity. The COMET assay has not been validated and consequently it is not known how specifically and reliably it could differentiate between genotoxicants and non-genotoxicants. It is also sensitive to artefacts and false positives. Thus a Community list entry for nettle herb cannot be prepared.

The accepted wording in the Monograph: Tests on reproductive toxicity and carcinogenicity have not been performed. Adequate tests on genotoxicity have not been performed.

I.3 CLINICAL DATA

For all studies cited, it should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.

I.3.1 Clinical Pharmacology

I.3.1.1 Pharmacodynamics

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

No relevant data available.

I.3.1.1.2 Assessor's overall conclusions on pharmacodynamics

No relevant data available.

I.3.1.2 Pharmacokinetics

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

No relevant data available.

I.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

No relevant data available.

I.3.2 Clinical Efficacy

I.3.2.1 Dose response studies

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

Diuretic effect

In an open 2-week study, 32 patients suffering from either myocardial or chronic venous insufficiency were treated three times daily with 15 ml of nettle herb juice *(afterwards the dosage changed for once a day in the morning)*. A significant increase in the daily volume of urine was observed throughout the treatment, 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. Minor decreases in body weights (about 1%) and systolic blood pressure were observed. Serum parameters were unaffected and the treatment was well tolerated apart from the tendency towards diarrhoea (Kirchhoff 1983).

Results in myocardial insufficiency:

Table 5: Urine volume and bodyweight under the therapy with expressed juice from nettle herb (n=19)

Treatment days	0	2	4	6	14
Urine volume (ml/24 h)	1674	1828***	1825***	1795**	1781***
Bodyweight (kg)	76.55	76.38^{oo}	76.23^{ooo}	76.03^{oo}	75.53^{ooo}
** $p < 0.005$ *** $p < 0.0005$ comparing with the baseline ^{oo} $p < 0.005$ ^{ooo} $p < 0.0005$ comparing with the previous value					

Results in venous insufficiency:

Table 6: Urine volume and bodyweight under the therapy with expressed juice from nettle herb (n=13)

Treatment days	0	2	4	6	14
Urine volume (ml/24 h)	1483	1837*	1809**	1828*	1770*
Bodyweight (kg)	70.2	70.15	69.91^{oo}	69.85	69.32^{ooo}
* $p <0.05$ ** $p <0.005$ comparing with the baseline ^{oo} $p <0.005$ ^{ooo} $p <0.0005$ comparing with the previous value					

Anti-inflammatory effect

Previous research had established that 1340 mg of powdered extract of nettle leaves (*Urtica dioica*) allows a 50% reduction in the dose of non-steroidal anti-inflammatory analgesics (NSAID) used to treat arthritis. In a German study, 40 subjects suffering from an acute attack of chronic joint disease participated in an open randomized study comparing the effectiveness of a combination of **stewed stinging nettle** and 50 mg of diclofenac to the standard 200 mg dosage of diclofenac. Diclofenac is an NSAID commonly prescribed in dosages of 150 to 200 mg per day for the treatment of rheumatoid and osteoarthritis. The subjects were randomly assigned to the nettle and 50 mg of diclofenac group (group D50+U) or the 200 mg diclofenac group (group D200). Extensive pre-screening eliminated patients with diseases, conditions, medications, or allergies that could influence the outcome of the study.

Group D200 received a semi-synthetic gastric protective prostaglandin analogue misoprostol in addition to the diclofenac. Gastric bleeding is a common side effect of NSAID use. Both groups received the same nutrition over the study period of 14 days. The primary measure of effectiveness was the improvement (decrease) in serum concentrations of C-reactive protein (CRP). Other criteria were total joint scores for physical impairment, subjective pain, pain on pressure, and stiffness. CRP and total joint scores improved dramatically (70% median score change) in both treatment groups. The treatment was well tolerated over the two-week period, with only six participants (3 from D200 and 3 from D50+U) reporting side effects. The D200 group reported minor side effects of diarrhoea and abdominal pain during the treatment period. The D50+U group reported the side effect of meteorism [abnormal distention due to the presence of gas or air in the intestine or the peritoneal cavity], intestinal gas with bloating.

This study indicates that 50 mg of stewed stinging nettle plus 50 mg of diclofenac is as effective as 200 mg of diclofenac at reducing the clinical symptoms of acute arthritis. This could be great news for those who cannot tolerate NSAIDs because of ulcers or other gastric problems. Further study is needed to determine if stinging nettle could be effective without the use of NSAIDs (Chrubasik *et al.* 1997).

Anti-allergic effect

Ninety-eight individuals took part in a double-blind randomized study comparing the effects of a freeze-dried preparation of *Urtica dioica* herba (2 times 300 mg) with placebo on allergic rhinitis. Sixty-nine individuals completed the study. Assessment was based on daily symptom diaries, and global response recorded at the follow-up visit after one week of therapy. *Urtica dioica* was rated higher than placebo in the global assessments. Comparing the diary data, *Urtica dioica* was rated only slightly higher (Mittman 1990).

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

There have been no studies in special populations.

I.3.2.4 Assessor's overall conclusions on clinical efficacy

The indications (myocardial or chronic venous insufficiently, acute attack of chronic joint disease, allergic rhinitis) in these four clinical studies are not proper for traditional use. These indications are relevant only for well-established use, but the results of these trials cannot be used because they are hardly acceptable. The studies are not double blind (except Mittman's study), the data are not detailed enough, and the results are not persuasive. They may only contribute to the plausibility of the diuretic and anti-inflammatory effect, in such way they may support the traditional indications.

I.3.3 Clinical Safety/Pharmacovigilance

I.3.3.1 Patient exposure

I.3.3.2 Adverse events

ESCOP 1997, 2003: "None reported."

Blumenthal et al. 1998, Blaschek et al 1998: "Not known."

Bisset 1994: "Occasionally (rare) after taking nettle tea, allergies (cutaneous affections, oedema, oliguria, gastric irritation) have been observed."

Bradley 1992: "Occasional (rare) allergic reactions have been observed. "

Barnes et al. 2002: "Consumption of nettle tea has caused gastric irritation, a burning sensation of the skin, oedema, and oliguria."

The accepted wording in the Monograph: Mild gastrointestinal complaints, e.g. nausea, diarrhoea, vomiting and allergic reactions (e.g. itching, exanthema, hives) may occur. The frequency is not known.

I.3.3.3 Serious adverse events and deaths

I.3.3.4 Laboratory findings

I.3.3.5 Safety in special populations and situations

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

No data available.

I.3.3.5.2 Contra indications (hypersensitivity and allergic potential to be both covered)

Not known. (ESCOP 1997, 2003; Blumenthal et al. 1998, Bradley 1992)

Water retention (oedema) as a result of impaired cardiac and renal function. (Blaschek *et al*. 1998, Bisset 1994)

The accepted wording in the Monograph:

Hypersensitivity to the active substance.

Condition where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease).

I.3.3.5.3. Warnings and precautions for use

"In irrigation therapy, care must be taken *to ensure an abundant fluid intake."*

(Blumenthal et al. 1998*,* Blaschek *et al*. 1998, Bisset 1994).

"Excessive use may interact with concurrent therapy for diabetes, high or low blood pressure, and may potentiate drugs with CNS depressant actions." (Barnes et al. 2002)

Assessor's comment: The above mentioned sentence was not taken into consideration for reasoning see I.3.3.5.4 Drug interactions)

The accepted wording in the Monograph:

The product is not intended to be used in case of acute arthritis as this condition requires medical advice.

The use is not recommended in children under 12 years of age because of lack of available experience.

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 professional should be consulted.

I.3.3.5.4 Drug interactions

"Not known. "(Blumenthal et al. 1998*,* Blaschek *et al*. 1998, Bisset 1994)

"None reported." (ESCOP 1997, 2003)

"Excessive use of nettle preparation may interact with concurrent therapy for diabetes or high blood pressure, and may potentiate drugs with CNS depressant action." (Barnes et al. 2002)

Assessor's comment: It is not necessary to mention these actions under the "Interaction" section of the Monograph.

See studies I.2.1 Pharmacology for reasoning:

- *Inhibition of α-glucosidase, hyperglycaemic and hypoglycaemic activity: the applied doses are very high; they are far from the therapeutic doses.*
- *Hypotensive effects: There was an in vitro study (Cardiovascular effects, Legssyer et al. 2002) at high concentration 1 g - 2 g/l or two in vivo studies, where the preparation was applied intravenously (Tahri et al. 2000, Lasheras et al. 1986).*
  In one study an aqueous extract was given to cats and rats by canula, but the applied doses are again too high (88 mg/kg, 16 6mg or 333 mg/kg) (Broncano et al. 1983).
- *the CNS depressant should not be mentioned as well because it was experienced only by intra-peritoneal application (Broncano et al. 1987b).*

Other question may be the vitamin K content of the nettle herb: It is very low, 0.16-0.64 mg/100g (Bertok 1956). The maximum daily dose of a nettle herb preparation, equivalent to about 15 g of dried herb, contains 24-96 microgramm of vitamin K. These values are less than 1% of the therapeutic dosage range of vitamin K (10-20 mg/day).

The accepted wording in the Monograph:

None reported.

I.3.3.5.5 Use in pregnancy and lactation

Nettle is reputed to be an abortifacient and to affect the menstrual cycle. Uteroactivity has been documented in animal studies. In view of this, the use of nettle during pregnancy should be avoided. It is best to avoid excessive use during lactation (*Barnes et al. 2002*).

Assessor's comment: Utero-activity was described only in an in vitro study [Broncano et al1987(1a)] see I.2.1. Pharmacology]. A nettle extract was reported to be devoid of antifertility activity following oral administration to mice (250 mg/kg). [Sharma et al 1983, See I.2.3.Toxicology)
It is the reason why it is not necessary to mention it in the Monograph.

ESCOP 1997, 2003: "No data available. In accordance with general medical practiced, the product should not be used during pregnancy and lactation without medical advice."

The wording in the Monograph is the general one:
Safety during pregnancy and lactation has not been established.
In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

I.3.3.5.6 Overdose

No case of overdose has been reported.

I.3.3.5.7 Drug abuse

I.3.3.5.8 Withdrawal and rebound

I.3.3.5.9 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.

I.3.3.6 Assessor's 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 and in children under 12 years of age due to lack of adequate data.
The use of nettle herb is contraindicated in patients with hypersensitivity to nettle herb and in condition where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease).
Nettle herb is not intended to be used in case of acute arthritis as this condition requires medical advice.
The establishment of a Community list entry for nettle herb is not possible because tests on reproductive toxicity and carcinogenicity have not been performed and adequate tests on genotoxicity have not been performed.

I.4 ASSESSOR'S OVERALL CONCLUSIONS

For nettle herb has been in medicinal use for a period of at least 30 years as requested by Directive 2004/24/EC, this requirement for the qualification as a traditional herbal medicinal product is fulfilled (long-standing use dating back to ancient time).

From the viewpoint of traditional indication the diuretic effect (flavonoids and the high mineral content may contribute to the diuretic action; supported somehow by the clinical study), and the anti-inflammatory and analgesic effect (polyphenol content; supported somehow by the pharmacodynamic experiments) can be considered plausible.

Thus the three endorsed indications are the following:

a) Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

b) Traditional herbal medicinal product for relief of minor articular pain.

c) Traditional herbal medicinal product used in seborrhoeic skin conditions

The use of nettle herb is considered safe in the recommended dosage. However, nettle herb cannot be recommended during pregnancy or lactation and in children under 12 years of age due to lack of adequate data.

The establishment of a Community list entry for nettle herb is not possible because tests on reproductive toxicity and carcinogenicity have not been performed and adequate tests on genotoxicity have not been performed.

ANNEXES

Community herbal monograph on *Urtica dioica* L. and *Urtica urens* L., herba

Literature references