14 January 2010
EMA/HMPC/508013/2007
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Urtica dioica* L., *Urtica urens* L., folium

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Whole or cut dried leaves of *Urtica dioica* L., *Urtica urens* L., or a mixture of the 2 species
Herbal preparation(s)	- comminuted herbal substance - liquid extracts - dry aqueous and hydro-ethanolic extracts
Pharmaceutical forms	Herbal substance or herbal preparation in solid or liquid dosage forms for oral and external uses, or as an herbal tea for oral use
Rapporteur	Dr. Susanna Biró-Sándor
Assessor(s)	

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Regulatory status overview[1]

Member State	Regulatory Status				Comments[2]
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
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	☒20 MA	☒1TRAD	☐ Other TRAD	☐ Other Specify:	+ In combination
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	In combination
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	☒1 TRAD	☐ Other TRAD	☐ Other Specify:	
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:	

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

[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

Products on the market:

Name of the Product	Active substance	Indication	Posology	Legal status
Ortica Fitolinea (Sodini) 100 opercles 495 mg/each	*Urtica dioica* L. leaves *Urtica dioica* dry extract	It may favour natural excretion of excessive body fluids	2 opercles 2 times /day with ½ glass of water 1360 mg leaves 240 mg dry extract	Food-supplements 2004 in Italy
Folia Urticae (JSC Riga Pharm. Plant)	Folia urticae	Orally, infusum: slows or stops internal bleeding and used in cases of heavy menstrual bleeding, increases urine production. As supplementary remedy for the treatment of rheumatic pains, arthritis and arthroses conditions. It is a good "spring tonic".	Pour 180 ml of hot water over the 2 tablespoons (~10.0 g) of the leaves, allow them to stand for 10 minutes, and then remove the leaves with strainer. ¼-½ cup of the freshly prepared infusion is drunk 3-5 times daily 30 minutes before eating	Medicinal products registered in Latvia

Overview of the German Market (from German authority)

Active substance	Indication	Posology	Legal status
Urticae folium, cut	As a purging in inflammatory diseases of the urinary tract collection system. As a purging to prevent and support treatment of renal gravel.	4-6 times daily 1 sachet containing 2 g cut Urticae folium in 150 ml of boiling water, let 5 min extract and drink freshly prepared before or to the meals.	at least since 1976 as WEU
Dry extract from Urticae folium (4.7-6:1),extraction solvent: water	For symptomatic treatment of osteoarthritis.	2-3 times daily 2 film-coated tablets containing 375 mg dry extract each	at least since 1976 as WEU
Dry extract from Urticae folium (5-10:1), extraction solvent: water	For symptomatic treatment of osteoarthritis.	3 times daily 3 coated tablets containing 150 mg dry extract each	at least since 1976 as WEU
Liquid extract (tincture) from Urticae folium (1:5),extraction solvent: ethanol 96% (V/V) : water : liqueur wine 16.5 % (V/V) (1.65 :1.35 : 7)	Traditional herbal medicinal product to support the elimination functions of the kidney.	for oral use in adults and adolescents over 12 years, 3-4 times daily 30-40 drops containing 100% oral liquid (26 drops = 1 ml and 101 ml = 100 g)	at least since 1976 as THM
Dry extract from Urticae folium (5-10:1), extraction solvent: ethanol 50% (V/V)	For symptomatic treatment of osteoarthritis. As a purging in inflammatory diseases of the urinary tract collection system. As a purging to prevent renal gravel.	2 times daily 1 coated tablet containing 600 mg dry extract Or 3 times daily 1 coated tablet containing 400 mg dry extract	at least since 2001 as WEU
Dry extract from Urticae folium (8-10:1), extraction solvent: Ethanol 50% (V/V)	For symptomatic treatment of osteoarthritis.	2 times daily 2 hard capsules containing 268 mg dry extract each 2 times daily 1 film-coated tablet containing 600 mg dry extract	at least since 1976 as WEU 2007
Dry extract from Urticae folium (19-33:1), extraction solvent: 2-propanol 95% (V/V)	For symptomatic treatment of osteoarthritis.	3 times daily 1 hard capsule containing 145 mg dry extract	2004

1. Introduction

The assessment of nettle leaf is based on the following literature

- Articles supplied by ESCOP (1997, 2003).
- Mongraphs on Nettle: Hagers Handbuch (*Blaschek W et al 1998*), Commission E Monograph (*Blumenthal 1998*), HerbalGram (*American Botanical Council*), HerbMed, Tropical Plant Database (*Rain Tree Nutrition*), MDidea.
- Review articles to be mentioned: *Chrubasik JE 2007, Setty AR and Sigal LH 2005, Lutomsky J and Speichert H 1983. Szendrei K, Háznagy-Radnai E 2006. Háznagy-Radnai E, Szendrei K. 2006.*
- Articles and references retrieved from databases (*Pubmed, Toxnet*) or internet sources (e.g. Google) until the end of April 2008.

A major problem in assessment of literature on nettle is the issue, that there is not always a clear differentiation between nettle herb and nettle leaf.

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

- Herbal substance(s)

Urticae folium, cut as herbal tea (product on the German market since at least 1976)

ESCOP (*ESCOP 1997, ESCOP 2003*), Hagers Handbuch (*Blaschek W et al, 1998*) Herbal Drugs and Phytopharmaceuticals (*Wichtl M, 2004*)

European Pharmacopoeia 5.6: Whole or cut dried leaves of *Urtica dioica* L., *Urtica urens* L., or a mixture of the 2 species.

Nettle leaf consists of the whole or cut, dried leaves of *Urtica dioica* L., *Urtica urens* L., their hybrids or mixtures. (*Deutsches Arzneibuch 10, Ausgabe 1991*)

- Herbal preparation(s)[3]

Comminuted herbal substance for tea.
Commission E Monograph (*Blumenthal M et al, 1998*)

Liqiud extracts

- (1:5) extraction solvent 96% ethanol: water: wine 16.5% (V/V) (1.65:1.35:7) (product on the German market since at least 1976)
- Tincture/Spiritus (1:10): *(Fintelmann V et al, Phytotherapy Manual 1989*)
  Rapporteur's comment: This preparation is not mentioned in the monograph, because its effect is not plausible. For reasoning see 'II.1.4. Evidence regarding the specified posology'.

Dry extracts prepared with:

- *water*
  dry extract from Urticae folium (4.7-6:1), extraction solvent: water, film-coated tablets containing 375 mg dry extract each (product on the German market since at least 1976).

dry extract from Urticae folium (5-10:1), extraction solvent: water, film-coated tablets containing 150 mg dry extract each (product on the German market since at least 1976).

- *ethanol*
  dry extract from Urticae folium (5-10:1), extraction solvent: 50% (V/V) ethanol, coated tablet containing 400 mg or 600 mg dry extract each (products on the German market since at least 2001)
  dry extract from Urticae folium (8-10:1), extraction solvent: 50% (V/V) ethanol hard capsules containing 268 mg dry extract each (product on the German market since at least 1976).
  or filmcoated tablet containing 600 mg dry extract each (product on the German market since 2007)
- *2-propanol*
  dry extract from Urticae folium (19-33:1), extraction solvent 2-propanol 95% (V/V), hard capsules containing 145 mg dry extract (product on the German market since 2004)

Preparations mentioned in the Monograph because they met the requirement of 30 years:

- Herbal substance

Cut, dried leaves

- Herbal preparation(s)

a) comminuted herbal substance

b) liquid extract from Urticae folium extraction solvent 96% ethanol: water: wine 16.5% (V/V) (1.65:1.35:7)

c) dry extract from Urticae folium (4.7-6:1),extraction solvent: water

d) dry extract from Urticae folium (5-10:1), extraction solvent: water

e) dry extract from Urticae folium (8-10:1), extraction solvent: ethanol 50% (V/V)

f) combinations of herbal substance(s) and/or herbal preparation(s)

g) vitamin(s)

h) mineral(s)[5]

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

Lutomsky J and Speichert H, 1983: "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. In the 16th century Dioscorides's book was the main source of information on the healing characteristics of Nettle. 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. The fresh juice pressed from the leaf was used orally by French doctors as styptic in haemorrhage of the lungs, in haemorrhoids, in heavy menstrual bleeding. Decoctions of the leaves had similar effects."

Herbal Gram: The Journal of the American Botanical Council: Herb and leaf:
"Stinging nettle herb has been used since ancient times. "**Greek physicians** Dioscorides (first century C.E.) and Galen (ca. 130-200 C.E.) reported nettle leaf had diuretic and laxative action and was useful for asthma, pleurisy, and for the treatment of spleen-related illness. **Roman naturalist** Pliny the Elder (ca. 23-79 C.E.) reported hemostatic properties.

In Germany, stinging nettle herb is licensed as a standard herbal tea for diuretic action. It is also used as a component of prepared medicines intended for supportive treatment of rheumatic ailments and irrigation therapy in inflammatory conditions of the lower urinary tract (*Wichtl and Bisset, 1994*). Stinging nettle herb is used in German homeopathy in treatments for urticaria, herpes, eczema, hypersensitive reactions in the skin and joints, and burns (*List and Hörhammer, 1979*).

In traditional **African medicine** the herb is used as a snuff powder for nosebleeds, excessive menstruation, and to treat internal bleeding. It is applied on burns (*List and Hörhammer, 1979*).
In India, the **Ayurvedic Pharmacopoeia** lists stinging nettle herb for uterine hemorrhage, cutaneous eruptions, infantile and psychogenic eczema, and nosebleed, applying dosages of 2-4 g herbal substance or 3-4 ml fluid extract, always in combination with other herbs (*Karnick, 1994*). It is also taken in syrup or tincture form to treat urticaria (nettle rash) (*Nadkarni, 1976).*

Stinging nettle is also widely used in **North American** aboriginal medicines. People of the Hesquiat, Sanpoil, Shuswap, and Tainarna nations use it as an antirheumatic drug (*Moerman, 1998; Palmer, 1975; Smith, 1973; Turner and Efrat, 1982; Ray, 1933*). It is also used as a gynecological aid by women of the Cowlitz, Cree, Kwakiutl, Lummi, Quinault, and Squaxin nations. It is taken as an aqueous infusion during childbirth to relax the muscles. The plant juice is taken by pregnant women who are overdue and the tips of the plant are chewed by women during labour (*Gunther, 1973; Leighton, 1985; Moerman, 1998; Turner and Bell, 1973; Turner and Efrat, 1982*).

In the **United States**, stinging nettle herb is used as a component in a wide range of dietary supplements. It is also used during and following birth and during lactation in traditional women's tonic formulas. It is prescribed by naturopathic physicians and licensed acupuncturists as a component in formulas used to treat hay-fever and other allergies."

Rain tree nutrition: Tropical plant database: "Bandages soaked in a leaf and stem infusion were used in early American medicine to stop the bleeding of wounds; an account of this use was recorded by Dr. Francis P. Procher, a surgeon and physician in the Southern Confederacy during the Civil War. Nettle leaves were also recommended as a nutritious food and as a weight loss aid by the famous American plant forager and naturalist, Euell Gibbons.

In Brazilian herbal medicine the entire plant has been used for excessive menstrual bleeding, diarrhoea, diabetes, urinary disorders and respiratory problems including allergies. Externally, an infusion has been used for skin problems. In Peru nettle has been used against a variety of complaints such as muscular and arthritis pain, eczema, ulcers, asthma, diabetes, intestinal inflammation, nosebleeds and rheumatism. Externally it has been used for inflammations, sciatica, wounds and head lice.

In the United States many remarkable healing properties have been attributed to nettle and the leaf has been utilized for different conditions than the root. The leaves have been used as a diuretic, for arthritis, prostatitis, rheumatism, rheumatoid arthritis, high blood pressure and allergic rhinitis."

Urtica dioica is one of the most commonly used herbal drugs in Turkey and in Jordan (*Kültür S 2007, Gözüm S et al 2007 and Otoom SA et al 2006*)

Complementary alternative treatments

Gözüm et al, 2003: were interested in rapidly growing complementary-alternative medicine therapies in Turkey. Therefore, they investigated the types and prevalence of alternative therapies used by the patients with a diagnosis of cancer and factors influencing the choices of their therapies in Erzurum, Turkey. Approximately 10-minute face-to-face interviews were conducted with each subject in the radiation oncology department. The factors associated with the use of alternative therapies after a diagnosis of cancer were assessed by chi-square analysis. The findings indicated that complementary-alternative medicine therapies were used by 41.1% of the subjects after their diagnosis, and that all of the alternatives they used were herbs. The most commonly used herb was stinging nettle leaf (Urtica dioica) or seed of nettle. Almost all (93.2%) of the herbs used were nettle. In general, especially the women and the younger patients of both genders were more likely to be using alternative therapies. There was no difference in demographic and cancer characteristics between users of alternative therapy and nonusers. More than the half of the patients using alternative therapies (54.5%) reportedly did not discuss the use of herbs with their healthcare professionals. Most of the patients using stinging nettle and other herbs therapies reported that they had heard about the use of herbs from friends or relatives (52.3%), or from the other patients in this clinic (43.2%). This study found that there is a high prevalence of alternative therapies used by patients with cancer in eastern Turkey.

1.3. Type of tradition, where relevant

European tradition. Nettle leaf has also been used in Africa, India, Jordan, North America and Turkey.

1.4. Evidence regarding the indication / traditional use

Four different areas of indication are mentioned in the literature on nettle leaves

Indication 1

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

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

"Externally: Adjuvant treatment of rheumatic conditions." (*Fintelmann V et al, Phytotherapy Manual 1989*)

"When taken internally and used externally: only supportive treatment for rheumatic ailments" (*Blumenthal M et al 1998, Wichtl M, 2004*)

Indication 2

"To increase of the amount of urine and for supportive treatment of complaints associated with urination." (*DAB 10-KOMMENTAR Brennesselblatter 1991, Wichtl M, 2004*)

"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*)

"As irrigation therapy for inflammatory diseases of the lower urinary tract and in the prevention and treatment of kidney gravel." (*Blumenthal M et al, 1998, Wichtl M, 2004*)

Indication 3

"Anti-haemorrhagic" (*Hagers Handbuch 1998*). in "Volkstümliche Anwendung"

"As styptic in haemorrhage of the lungs, in haemorrhoids, in heavy menstrual bleeding." (*Lutomsky J and Speichert H, 1983)*

Indication 4

"for skin complaints, including eczema and skin eruptions" (*Lutomsky J et al, 1983)*

Rapporteur's comment:

From the above mentioned indications, only indication 1 and 2 can be supported as traditional indications and have to be modified according to the requirements of traditional herbal medicinal products.

Indication 1: "Traditional herbal medicinal product for relief of minor articular pain."

Indication 2: "Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints."

Indication 3 and 4 are reported in the literature. However, there are no products on the market supporting thirty years of traditional use with these indications.

1.5. Evidence regarding the specified posology

Internally

Dried herb

3-5 g herbal substance as an infusion up to three times daily (*ESCOP 1997 and 2003*)

Daily 8-12 g herbal substance as infusion (*Blumenthal M et al, 1998, Wichtl M, 2004, Hagers Handbuch 1998*)

Preparation of the tea-infusion:

- "Pour one cup of hot water over 2 teaspoonfuls (approximately 2 g) nettle leaves. Steep for about 10 minutes and then pass through a tea strainer." (*Fintelmann V et al, Phytotherapy Manual 1989*)
- "4 g of nettle leaves for tea preparation three or four times daily" (*DAB 10-KOMMENTAR Brennesselblatter 1991*)
- 4-6 times daily 1 sachet containing 2 g cut herbal substance in 150 ml of boiling water, let 5 min extract and drink freshly prepared before or to the meals. (*Product on the German market since at least 1976*)

Extracts

0.77 g extract (7:1) twice daily (*ESCOP 1997*)

Ethanolic extracts corresponding to 8-12g of nettle leaf daily, divided into 2-3 doses (*ESCOP 2003*)

Liquid extract

- 3-4 times 30-40 oral drops of (26 drops =1 ml and 101 ml = 100 g) liquid extract (1:5) extraction solvent ethanol 96%:water:wine 16.5% (V/V) (1.65:1.35:7) (equivalent to 3-4 times 0.23-0.3 g herbal substance) (Product on the German market since at least 1976)

Dry extracts

- dry extract from Urticae folium (4.7-6:1), extraction solvent: water, 2-3 times daily 2 film-coated tablets containing 375 mg dry extract each, (equivalent to 2-3 times 4013 mg drug, product on the German market since at least 1976)
- dry extract from Urticae folium (5-10:1), extraction solvent: water 3 times daily 3 coated tablets containing 150 mg dry extract each (equivalent to 3 times 3375 mg drug, product on the German market since at least 1976, German market overview)
- dry extract from Urticae folium (8-10:1), extraction solvent: ethanol 50% (V/V) 2 times daily 2 hard capsules containing 268 mg dry extract each (equivalent to 2 times 4824 mg drug, product on the German market since at least 1976)

Accepted posology in the Monograph

i) Herbal substance

2-4 g as single dose for preparation of an herbal tea, 3-6 times daily.

The daily dosage is equivalent to 8-12 g of herbal substance.

ii) Herbal preparations

a) Comminuted herbal substance: 2-4 g as single dose for preparation of an herbal tea, 3-6 times daily. The daily dosage is equivalent to 8-12 g of herbal substance.

b) Liquid extract (1:5): 30-40 oral drops as a single dose, 3-4 times daily.

c) Dry extract (4.7-6:1): 750 mg as a single dose, 2-3 times daily.

d) Dry extract (5-10:1): 450 mg as a single dose, 3 times daily.

e) Dry extract (8-10:1): 540 mg as a single dose, 2 times daily.

f) 2-4 g comminuted dried leaves for preparation of herbal tea as single dose, 3-6 times daily. The daily dosage is equivalent to 8-12 g of herbal substance.
Pour one cup of boiling water over 2-4 teaspoonfuls (approximately 2-4 g) nettle leaves. Steep for about 10 minutes and then pass through a tea strainer)

g) 30-40 oral drops of liquid extracts (1:5) prepared with ethanol 96%:water:wine 16.5% (V/V) (1.65:1.35:7) as a single dose up to 3-4 times daily (equivalent to 3-4 times 0.23-0.3 g herbal substance)

h) 750 mg dry extract from Urticae folium (4.7-6:1) extraction solvent: water as a single dose up to 2-3 times daily (equivalent to 2-3 times 4 g herbal substance)

i) 450 mg dry extract from Urticae folium (5-10:1), extraction solvent: water as a single dose up to 3 times daily (equivalent to 3 times 3.4 g herbal substance)

j) 536 mg dry extract from Urticae folium (8-10:1), extraction solvent: ethanol 50% (V/V) as a single dose up to 2 times daily (equivalent to 2 times 4.8 g herbal substance)

Externally

Tincture/Spiritus (1:10): put one drop onto the aching part of the body and gently rub it. (*Fintelmann V et al, Phytotherapy Manual 1989*)

Fresh nettle leaf applied to the skin in the area of pain for 30 seconds once daily (*ESCOP 2003*).

Rapporteur's comment: It was decided that external application forms were not suitable for consideration in the traditional use part of the monograph. The plausibility of the application of one drop of the tincture is not well justified. Usage of fresh nettle leaves is not convertible to a herbal preparation for herbal medicinal products to be marketed.

1.6. Evidence regarding the route of administration

Nettle leaf has been used internally and as well as externally (*ESCOP 2003*, *Blumenthal M et al 1998*, *Fintelmann V et al, 1989*)

1.7. Evidence regarding the duration of use

Four or six weeks, as a cure. (Hagers Handbuch 1998, page 723)

At the meeting in January 2008 the MLWP decided:
For indication a) 4 weeks (*see Salix monograph EMEA/HMPC/295338/2007*)
For indication b) 2-4 weeks (*see the Solidago monograph EMEA/HMPC/285758/2007*)

1.8. Assessor's overall conclusion on the traditional medicinal use

Nettle leaf has been in medical use for a period of at least 30 years as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product.

2. NON-CLINICAL DATA

2.1. Pharmacology

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)

Principal components of the herbal substance

DAB 10-KOMMENTAR 1991, and Wichtl M, 2004: Nettle leaves contain 1-2% flavonoids, (particularly glycosides and rutosides of quercetin, kaemferol and isohamnetin). The herbal substance contains silicates in a relative big quantity (1-4% SiO_2) partly as water-soluble silicates. Characteristic components are scopoletin, sitosterol with its 3-O-βD-glucoside and caffeic acid esters. Other constituents include chlorophyll (approximately 2.7%), proteins, fats, carbohydrates, traces of nicotine and in the stinging hairs, small amounts of acetylcholine, serotonin and formic acid and leukotrines.

Lutomsky J and Speichert , 1983: Chlorophyll 0.08-0.3% in the fresh substance, 0.3-1% in dried substance, 0.66% in the powdered herbal substance. Further derivatives of porphirine: protoporphyrin and koproporphyrin.
Carotenoids: β-carotin, violaxanthin, xanthophylls, xantophyll-epoxid (eloxantin), lycopene
Vitamins: Ascorbic acid (36-269 mg%), Vitamin B2-lactoflavin-1.5 mg/100g in dried, 0.25 mg in the fresh leaves, panthotenic acid, Vitamin-K1 0.64g/100g.
Minerals: 17.87% ash. It contains. 2.44% K2O, 5.9% CaO, 0.69% MgO, 0.68% P2O5, 2.16% SiO2, 0.83% SO3 095% Cl. Trace-elements: Mn 6.3 mg%, Cu 0.375 mg%, Fe 61 mg%, Al 16 mg%

Szentmihályi K et al, 1998: Potassium sodium ratio has been determined as 63:1 in the medicinal plant and 448:1 in medicinal plant drug decoction.

Fijalek Z et al, 2003: As, Ca, Cd, Cu, Fe, Mg, Mn, Pb and Zn were determined by ICP-MS and ET-AAS in preparations made from peppermint and nettle leaves after microwave high pressure digestion with nitric acid. In preparation from nettle leaves the Ca content was more than three times higher than in preparations made from peppermint leaves. Only very small differences (less than 10%) were observed for all the other elements. In all the samples investigated the content of inorganic elements was below the WHO limit (where existing). Variation coefficients ranged from 0.68% to 10.5% for ICP-MS measurements and from 1.48% to 10.0% for ET-ASS.

Lozak A et al, 2002: The following macro- and microelements were determined in the leaf of peppermint (Mentha piperitae folium) and nettle (Urticae folium) (as tea bags) and in their infusions: As, Ba, Ca, Cd, Co, Cr, Cu, Fe, I, Li, Mg, Mn, Ni, Pb, Se, Sn, Sr, Ti, V and Zn. The determinations were performed using inductively coupled plasma mass spectrometry (ICP-MS) and atomic absorption spectrometry (AAS). From all the determined microelements the highest content found was that of iron, 244 and 107 mg/kg in the leaf of peppermint and nettle, respectively. However, the lowest content found was that of cobalt, 0.10 and 0.08 mg/kg for the leaf of mint and nettle, respectively. The most readily water eluting elements were strontium, selenium and iodine, the most difficult ones - barium and iron.

Guil-Guerrero JL et al, 2003: Several parts (leaves at different maturity stages, stems, roots and seeds) of an edible wild vegetable, Stinging Nettle (*Urtica dioica* L.) were analysed for fatty acids by GLC and carotenoids by reversed-phase HPLC and gradient elution. α-linolenic acid was the predominant fatty acid in leaves, while seeds were richer in linoleic acid. Nine carotenoids were identified in the leaves. For all leaf maturity levels, lutein, lutein isomers, β-carotene and β-carotene isomers were the major carotenoids. Neoxanthin, violaxanthin and lycopene were also important contributors in specific leaf maturity stages.

Pharmacology

In vitro studies

- Anti-inflammatory activity

Obertreis B et al, 1996a: 46:52-56: A nettle leaf hydro-ethanolic extract (6.4-8 :1) (IDS 23, Rheuma-Hek , Strathmann) and its main phenolic constituent caffeoyl malic acid were tested for their inhibitory potential on biosynthesis of arachidonic acid metabolites by rat leukaemic basophilic granulocytes (RBL-1 cells). The extract (0.1 mg/ml) and the isolated acid (1 mg/ml) showed partial inhibitory effects of 20.8% and 68.2% respectively on the 5-lipoxygenase-derived synthesis of leukotriene B4. The isolated acid inhibited the synthesis of leukotriene B4 in a concentration-dependent manner with an IC50 of 85 µg/ml. Both the extract and the acid also showed a strong concentration-dependent inhibition of synthesis of cyclooxygenase-derived prostaglandins (IC50 of 92 µg/ml for extract (PGD2) and 38 µg/ml for the acid (PGD2 and PGF2α). For Indomethacin IC50 was 71.6 µg/ml

in this test system. Calculating the content in the IDS 23 caffeic malic acid was possible but not the only active ingredient of the plant extract. Calculating the content in IDS 23 caffeic malic acid was possible but not the only active ingredients of the plant extract in the tested assay systems. It was demonstrated that the phenolic component showed a different enzymatic target compared with IDS 23.

Obertreis B et al, 1996b: The same extract of *Urtica dioica* folium (IDS 23, Rheuma-Hek, Strathmann) significantly and dose-dependently reduced lipopolysaccharide (LPS)-stimulated release of two pro-inflammatory cytokines, tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in human whole blood from 6 healthy volunteers. After 24 hours, TNF-α concentration was reduced by 50.8 % and IL- 1β concentration by 99.7% using the highest tested extract concentration of 5 mg/ml ($p<0.001$); after 65 hours the inhibition was 38.9% and 99.9% respectively ($p<0.001$). On the other hand, IDS 23 showed no inhibition but stimulated IL-6 secretion in absence of LPS comparable to LPS alone. Simultaneously given LPS and IDS 23 resulted in no further increase. In contrast to described effects on arachidonic acid cascade *in vitro*, Urtica dioica phenol carbonic acid derivates and flavonoids such as caffeic malic acid, caffeic acid, cholorogenic acid, quercetin and rutin did not influence LPS stimulated TNF-α, IL- 1β, IL-6 secretion in the tested concentrations up to 5×10^{-5} mol/l. The cytokine inhibitory substrate or substrates of IDS 23 remained unknown.

Teucher T et al, 1996: Twenty healthy volunteers ingested for 21 days 2 capsules b.i.d. of an IDS 23/1 containing nettle leaf extract (Rheuma-Hek). Before and after 7 and 21 days the basal and the lipopolysaccharide (LPS) stimulated tumour necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1 beta) and interleukin-6 (IL-6) concentrations were measured *ex vivo*. *In vitro* the effects of IDS 23/1 on the release of these cytokines were determined. Additionally, basal interleukin-4 (IL-4) and interleukin-10 (IL-10) levels were recorded. Orally taken the test drug had *ex vivo* no effect on basal levels of TNF-alpha, IL-1 beta, IL-4, IL-6 or IL-10 which were always below detection limits. After ~ 7 and 21 days ingestion *ex vivo* a decrease of LPS stimulated TNF-alpha release of 14.6 and 24.0%, respectively, was observed. IL-1 beta was reduced for 19.2 and 39.3%. *In vitro* IDS 23/1 added to whole blood resulted in an exceeded inhibition of LPS stimulated TNF-alpha and IL-1 beta secretion which correlated with the duration of the drug ingestion. Using the highest tested IDS 23/1 concentration the inhibition reached 50.5 (day 0) to 79.5% (day 21) for TNF-alpha and 90.0 (day 0) to 99.2% (day 21) for IL-1 beta, respectively. IDS 23/1 induced a pronounced release of IL-6 in absence of LPS only *in vitro*. The detected IL-6 concentrations were comparable to those after LPS stimulation, additive effects could not be observed. The absence of detectable IL-6 concentrations in whole blood *ex vivo* after oral ingestion of the tested drug as well as the differences in the inhibition patterns for TNF-alpha and IL-1 beta *ex vivo* and *ex vivo in vitro* suggested that the extract contains different pharmacological effective compounds with varying bioavailabilities.

Riehemann K et al, 1999: Activation of transcription factor NF (nuclear factor)-kappaB is elevated in several chronic inflammatory diseases and is responsible for the enhanced expression of many pro-inflammatory gene products. Extracts from leaves of stinging nettle (Urtica dioica) are used as anti-inflammatory remedies in rheumatoid arthritis. Standardized preparations of these extracts (IDS23) suppress cytokine production, but their mode of action remains unclear. It was demonstrated that treatment of different cells with IDS23 potently inhibits NF-kappa B activation. An inhibitory effect was observed in response to several stimuli, suggesting that IDS23 suppressed a common NF-kappa B pathway. Inhibition of NF-kappa B activation by IDS23 was not mediated by a direct modification of DNA binding, but rather by preventing degradation of its inhibitory subunit I kappa B-alpha. The author suggests that part of the anti-inflammatory effect of Urtica extract may be ascribed to its inhibitory effect on NF-kappa B activation.

Schulze-Tanzil G et al, 2002: The aim of the study was to clarify the effects of Hox alpha (stinging nettle leaf extract) and the mono-substance 13-HOTrE (13-Hydroxyoctadecatrienic acid) on the expression of matrix metalloproteinase-1, -3 and -9 proteins (MMP-1, -3, -9). Human chondrocytes were cultured on collagen type-II-coated petri dishes, exposed to IL-1beta and treated with or without Hox alpha and 13-HOTrE. A close analysis by immunofluorescence microscopy and western blot analysis showed that Hox alpha and 13-HOTrE significantly suppressed IL-1beta-induced expression of matrix metalloproteinase-1, -3 and -9 proteins on the chondrocytes *in vitro*. According to the authors' the potential of Hox alpha and 13-HOTrE to suppress the expression of matrix metalloproteinases may explain the clinical efficacy of stinging nettle leaf extracts in treatment of rheumatoid arthritis. The results suggested that the mono-substance 13-HOTrE was one of the more active anti-inflammatory substances in Hox alpha and that Hox alpha might be a promising remedy for therapy of inflammatory joint diseases.

- Immuno-modulatory activity

Klingelhoefer S et al, 1999: In a whole blood culture system the nettle extract IDS 23 (Rheuma-Hek) inhibited lipopolysaccharide stimulated monocyte cytokine expression, indicating an immunomodulating effect. The immunomodulating effects of IDS 23 on phytohemagglutinin (PHA) stimulated peripheral blood mononuclear cells (PBMC) were investigated *in vitro*. METHODS: Using commercial immunoassays the distinct cytokine patterns of Th1 and Th2 cells were determined. Interleukin 2 (IL-2) and interferon-gamma (IFN-gamma) mRNA expression was evaluated by reverse transcription-polymerase chain reaction (RT-PCR) with PHA stimulated PBMC. RESULTS: IDS 23 inhibited PHA stimulated production of Th1-specific IL-2 and IFN-gamma in PBMC culture (n = 10) in a dose dependent manner up to 50+/-32% and 77+/-14%, respectively. In contrast, IDS 23 stimulated the secretion of Th2-specific IL-4. The dose dependent inhibiting effect on IL-2 and IFN-gamma expression was also detected with RT-PCR, while the amount of actin-specific mRNA transcript was not modified by IDS 23.
CONCLUSION by the authors: The results suggested the effective ingredient of IDS 23 might act by mediating a switch in T helper cell derived cytokine patterns. IDS 23 might inhibit the inflammatory cascade in autoimmune diseases like rheumatoid arthritis.

Broer J and Brehnke B, 2002: The immuno-modulating effect of stinging nettle leaf extract IDS 30 (Hox alpha) on the maturation of hematopoietic dendritic cells was investigated. METHODS: Human dendritic cells were generated from peripheral blood mononuclear cells cultured in granulocyte macrophage-colony stimulating factor and interleukin 4 (IL-4). Dendritic cell maturation was induced by keyhole limped hemocyanin (KLH). Dendritic cell phenotype was characterized by flow cytometric analysis; dendritic cell cytokine production was measured by ELISA. The ability of dendritic cells to activate naive autologous T cells was evaluated by mixed leukocyte reaction. RESULTS: IDS 30 prevented the maturation of dendritic cells, but did not affect their viability. IDS 30 reduced the expression of CD83 and CD86. It increased the expression of chemokine receptor 5 and CD36 in a dose dependent manner. The secretion of tumour necrosis factor-alpha was reduced. Application of IDS 30 to dendritic cells in culture caused a high endocytosis of dextran and a low capacity to stimulate T cell proliferation.
CONCLUSION by the authors: These *in vitro* results showed the suppressive effect of IDS 30 on the maturation of human myeloid dendritic cells, leading to reduced induction of primary T cell responses. This might contribute to the therapeutic effect of IDS 30 on T cell mediated inflammatory diseases like RA.

Galelli A et al, 1995: *Urtica dioica* agglutinin (UDA) has been shown a super antigen that, *in vitro*, binds to specific carbohydrate structures on class II and induces a six fold enrichment of V beta 8.3+ BALB/c mice splenic T cells. Super antigens have pleiotropic effects *in vivo*, causing the activation, proliferation and deletion of specific T cells, but are heterogeneous in regard to their effects on T cell tolerization. Therefore, the responses of peripheral T cells from adult BALB/c mice were compared with the i.v. injection of 50 mg UDA or the bacterial super antigen staphylococcal enterotoxin B (SEB) that also recognizes the V beta 8.3 gene product. The data from this study indicated that activation, clonal expansion, anergy and death of V beta 8.3+ T cells occurred sequentially after UDA administration. Two days after UDA injection, the proportion of V beta 8.3+ T cells in the periphery was elevated to approximately twice that of normal mice. This expansion occurred in both CD4+ and CD8+ subsets. V beta 8.3+ T cells from UDA-primed mice were anergic to UDA restimulation and failed to proliferate or to produce IL-2. Furthermore, the proliferation of V beta 8.3+ T cells was followed by their rapid disappearance concomitant with their specific elimination by apoptosis. In 1 wk, all CD4+ V beta 8.3+ peripheral T cells were deleted. The decline of V beta 8.3+ T cells in the CD4+ subset was more than in the CD8+ subset. This occurred in thymectomized and in thymus-intact animals. Two months after UDA priming, the percentage of V beta 8.3+ T cells was still lower than in control mice.

- Inhibition of platelet aggregation

El Haouari M et al, 2006: The effects of different extracts of *Urtica dioica* leaves on platelet aggregation were investigated. Rat platelets were prepared and incubated *in vitro* with different concentrations of the tested extracts and aggregation was induced by different agonists including thrombin (0.5 U/ml), ADP (10 microm), epinephrine (100 microm) and collagen (5 mg/ml). The crude aqueous extract inhibited thrombin-induced platelet aggregation in a dose-dependent manner. At 1 mg/ml, the percent inhibition was 17.1 +/- 4.2%. Soxhlet extraction of the plant leaves with different successive solvents showed that the ethyl acetate extract exhibited the most anti-aggregant effect with an inhibition of 76.8 +/- 6.1% at 1 mg/ml. Flavonoids isolated from the plant leaves, produced a strong inhibitory effect on thrombin-induced platelet aggregation with an IC(50) of 0.25 +/- 0.05 and 0.40 +/- 0.04 mg/ml for genins and heterosidic flavonoids, respectively. Flavonoids also markedly inhibited platelet aggregation induced by ADP, collagen and epinephrine. It is concluded that *Urtica dioica* has an antiplatelet action in which flavonoids are mainly implicated. These results support the traditional use of *Urtica dioica* in the treatment and/or prevention of cardiovascular disease.

- Influence on insulin secretion

Farzami B et al, 2003: In this report, a perifusion system was arranged in which an exact number of Langerhans Islets were exposed to several fractions of a water extract (5:1) of *Urtica dioica* obtained by thin layer cromatography. . The active ingredient fraction caused a marked increase in insulin secretion. The highest insulin level was obtained at 60 min after the initial time of perfusion. The process was shown to be concentration dependent.

- Inhibition of the protease activity

Gul N et al, 2004: The inhibitory effect of stinging nettle leaf extract on the protease activity of botulinum neurotoxin type A and B light chains was investigated. The nettle leaf infusion was fractionated and HPLC-based enzymatic assays were performed to determine the capacity of each fraction to inhibit the protease activity of botulinum neurotoxin type A and B light chains. Assay results

demonstrated that a water-soluble fraction obtained from the nettle leaf infusion inhibited type A, but did not inhibit type B light chain protease activity. The inhibition mode of water soluble fraction against protease activity of type A light chain was analyzed and found to be a non-competitive.

- Inhibition on adenosine deaminase activity

Durak I et al, 2004: Aqueous extract of *Urtica dioica* showed significant inhibition on adenosine deaminase activity in prostate tissue from patients with prostate cancer. Possible effects of aqueous extract of *Urtica dioica* leaves on adenosine deaminase activity in prostate tissue from patients with prostate cancer were investigated. METHODS: Ten prostate tissues from patients with pathologically proven localized prostate cancer (Gleason scores 4 to 7) were used in the study. In the tissues, ADA activities with and without preincubation with different amounts of *Urtica dioica* extracts were performed. RESULTS: Aqueous extract of *Urtica dioica* showed significant inhibition on adenosine deaminase (ADA) activity of prostate tissue.
CONCLUSION by the authors: ADA inhibition by *Urtica dioica* extract might be one of the mechanisms in the observed beneficial effect of *Urtica dioica* in prostate cancer.

***In vivo* studies**

- Hypoglycaemic effects

Farzami B et al, 2003: A water extract of *Urticae dioica* leaves was purified by using TLC with several changes of solvent to obtain fractions for further *in vivo* studies. A solvent mixture of 30/70% water/isopropanol was found most suitable for initial separation. Fraction F1 was found to increase the insulin content of blood sera in normal and streptozotocin diabetic rats that were injected intraperitoneally (i.p.). The *in vivo* studies showed that not only an increase in insulin level of blood sera was observed in rats after 30 min from the initial point of injection but a simultaneous decrease of blood sugar was detected when similar sera were tested for glucose. The increase in insulin level was 6 times during 120 min. The decrease in blood sugar was found to be similar both in the level and time of initiation. The authors assumed that F(1) was the active ingredient of plant leaves extract. The results showed that the blood lowering effect of the extract was due to the enhancement of insulin secretion by Langerhans Islets.

Rapporteur's comment: The results of this study can not be considered to be relevant for the traditionally applied doses and preparations.

- Uterine muscle activity

The effect of extracts of Urtica dioica leaves on mouse gravid and non-gravid uterus was studied. All of the preparations studied showed a dihydroergotamine like effect. The active constituent was probably a pyranocoumarin (*Broncano FJ. et al. 1987*).

Rapporteur's comment: This article is not taken into consideration because it is on Nettle herb.

- Anti-inflammatory effect

Schoening, 1996: Extract IDS23 (solvent 50% ethanol, 25,100 and 300 mg/kg) produced a dose dependent anti-inflammatory effect in rats with experimental gonarthritis induced by bovine gammaglobulin and silicon particles (diclofenac served as control). Behaviour, foods intake and body weight remained unchanged and mortality was not increased. Histo-pathological evaluation confirmed

a significantly lower lymphocyte infiltration compared to control ($p<0.05$). The effect was similar to diclofenac.

Konrad A et al, 2005: The stinging nettle leaf extract, IDS 30, has been used as an adjuvant remedy in rheumatic diseases dependent on a cytokine suppressive effect. The authors investigated the effect of IDS 30 on disease activity of murine colitis in different models. METHODS: C3H.IL-10-/- and BALB/c mice with colitis induced by dextran sodium sulphate (DSS) were treated with either IDS 30 or water. Mice were monitored for clinical signs of colitis. Inflammation was scored histologically, and faecal IL-1beta and mucosal cytokines were measured by ELISA. Mononuclear cell proliferation of spleen and Peyer's patches were quantified by 3H-thymidine. RESULTS: Mice with chronic DSS colitis or IL-10-/- mice treated with IDS 30 clinically and histologically revealed significantly ($p < 0.05$) fewer signs of colitis than untreated animals. Furthermore, faecal IL-1beta and mucosal TNF-alpha concentrations were significantly lower ($p < 0.05$) in treated mice. Mononuclear cell proliferation after stimulation with lipopolysaccharide was significantly ($p < 0.001$) reduced in mice treated with IDS 30.
CONCLUSIONS by the authors: The long-term use of IDS 30 was effective in the prevention of chronic murine colitis. This effect seemed to be due to a decrease in the Th1 response and might be a new therapeutic option for prolonging remission in inflammatory bowel disease.

- Anti-oxidative effect

Özen and Korkmaz, 2003: The effects of two doses (50 and 100 mg/kg body weight given orally for 14 days) of an ethanolic (80% V/V) extract of *Urtica dioica* L. leaf and butylated hydroxyanisole (BHA) were investigated, for phase I and phase II enzymes, antioxidant enzymes, lactate dehydrogenase, lipid peroxidation and sulfhydryl groups in the liver of Swiss albino mice (8-9 weeks old). A modulatory effect of two doses and BHA was also observed for the activities of glutathione S-transferase, DT-diaphorase, superoxide dismutase and catalase in the kidney, lung and forestomach, as compared with the control group. The activities of cytochrome b5 (cyt b5), NADH-cytochrome b5 reductase (cyt b5 R), glutathione S-transferase (GST), DT-diaphorase (DTD), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD) and catalase (CAT) showed a significant increase in the liver at both dose levels of extract. Both extract-treated mice showed significantly lower activity of cytochrome P450 (cyt P450), lactate dehydrogenase (LDH), NADPH-cytochrome P450 reductase (cyt P450 R), total sulfhydryl groups (T-SH), nonprotein sulfhydryl groups (NP-SH) and protein-bound sulfhydryl groups (PB-SH). BHA-treated Swiss albino mice showed a notable increase in levels of cyt b5, DTD, T-SH, PB-SH, GPx, GR, and SOD in the liver while, LDH, cyt P450, cyt P450 R, Cyt b5 R, GST, NP-SH, and CAT levels were reduced significantly as compared to control values. The extract was effective in inducing GST, DTD, SOD and CAT activity in the fore-stomach and SOD and CAT activity in the lung at both dose levels. BHA-treated Swiss albino mice induced DTD, GST and all antioxidative parameters in the kidney, lung and fore-stomach.

Toldy A et al, 2005: The effects of exercise and nettle supplementation on oxidative stress markers in the rat brain were investigated. Chronic swimming training and phytotherapeutic supplementation have been assumed to alleviate oxidative damage and to support cell survival in the brain. The effect of forced, chronic swimming training, and enriched lab chow containing 1% (W/W) dried nettle (Urtica dioica) leaf were investigated for oxidative stress, inflammation and neurotrophic markers in Wistar rat brains. The rats were divided into groups subjected to swimming training (6 weeks) or to nettle supplementation (8 weeks) or to a combination of these two treatments. The level of oxidative stress was measured by electron spin resonance (EPR), and by the concentration of carbonylated proteins. Nettle supplementation resulted in a decreased concentration of free radicals in both cerebellum and frontal lobe. Swimming, however, did not influence significantly the oxidative damage nor was it

reflected in the carbonyl content. The protein content of nerve growth factor (NGF), and brain-derived neurotrophic factors (BDNF) was evaluated by E-Max ImmunoAssay in the cerebellum. No changes occurred either with exercise or nettle diet treatments. On the other hand, nuclear factor kappa B (NF-kappaB) binding activity to DNA increased with the combined effect of swimming training and nettle diet, while the activator protein1 (AP-1) DNA binding activity showed a more profound elevation in the nettle treated animals. The amount of c-Jun decreased by swimming training. In conclusion, the results suggested that both exercise and nettle influenced physiological brain functions. Nettle supplementation reduced the free radical concentration and increased the DNA binding of AP-1 in the brain. Nettle was found to be an effective antioxidant and possible antiapoptotic supplement promoting cell survival in the brain. Exercise, as a downregulator of c-Jun and in combined group as an upregulator of NF-kappaB, might play also a role in antiapoptotic processes, which is important after brain injury.

Cetnius E et al, 2005: The potential role of *Urtica dioica* (UD) (*Urticaceae*) plant for prevention of oxidative stress in muscle tissues generated by tourniquet application in rats was investigated. Wistar rats were used in this study. The UD extract or 1.15% KCl aqueous solution, in which UD leaf samples (2 g of leaf was homogenized in 10 ml of 1.15% KCl) were homogenized, was given to each group of eight rats once a day for 5 days through an intraesophageal canule. No treatment was applied to untreated group. Tourniquets were applied to the left posterior limb of rats for 1 or 2 h followed by a reperfusion period of 1 h. After the ischemia and reperfusion, the rats were killed with a high dose of anesthetic drug, and malonyldialdehyde (MDA) levels were measured in their tibialis anterior muscles. Basal MDA levels were obtained from tibialis anterior muscles of 8 control rats, which were not exposed to ischemia. MDA levels were lower in the UD-treated rats than those in untreated and KCl-treated rats after either 1 or 2 h of ischemia and 1 h reperfusion. These results indicated that UD had a potential antioxidant effect on ischemic muscle tissues.

2.1.2. Assessor's overall conclusions on pharmacology

Anti-inflammatory and immuno-modulatory activities have been demonstrated in several *in vitro* and *in vivo* experiments.

Anti-inflammatory effects

- A hydro-ethanolic extract of nettle leaf (6.4-8:1) and its main phenolic constituent caffeic malic acid showed partial inhibitory effects of 20.8% and 68.2% respectively on the 5-lipoxygenase-derived synthesis of leukotriene B_4. The isolated acid inhibited the synthesis of leukotriene B_4 in a concentration-dependent manner with an IC_{50} of 85 µg/ml. Both the extract and the acid also showed a strong concentration-dependent inhibition of synthesis of cyclooxygenese-derived prostaglandins [IC_{50} of 92 µg/ml for extract (PGD2) and 38 µg/ml for the acid (PGD2 and PGF2α)]. For Indometacin the IC_{50} was 71.6 µg/ml in this test system (*Obertreis B et al, 1996a*).
- The same extract of *Urtica dioica* folium significantly and dose-dependently reduced lipopolysaccharide (LPS)-stimulated release of two pro-inflammatory cytokines, tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in human whole blood (*Obertreis B et al, 1996a*).
- The treatment of different cells with this extract potently inhibited NF-kappa B activation. Inhibition of NF-kappa B activation by the extract was not mediated by a direct modification of DNA binding, but rather by preventing degradation of its inhibitory subunit I kappa B-alpha (*Teucher T et al, 1996*).

- An iso-propanolic extract (19-33:1) of nettle leaf and one of it components, 13-HOTrE significantly suppressed IL-1beta-induced expression of matrix metalloproteinase-1, -3 and -9 proteins on the chondrocytes *in vitro* (*Schulze-Tanzil G et al, 2002*).
- The hydro-ethanolic extract (25, 100 and 300 mg/kg) produced a dose dependent anti-inflammatory effect in rats with experimental gonarthritis induced by bovine gammaglobulin and silicon particles (diclofenac served as control) (*Schoening U, 1996*).
- Mice with chronic DSS colitis or IL-10-/- mice treated with iso-propanolic extract clinically and histologically revealed significantly ($p < 0.05$) fewer signs of colitis than untreated animals. Furthermore, faecal IL-1beta and mucosal TNF-alpha concentrations were significantly lower ($p < 0.05$) in treated mice. Mononuclear cell proliferation after stimulation with lipopolysaccharide was significantly ($p < 0.001$) reduced in mice treated with this extract (*Konrad A et al, 2005*).

Immono-modulatory effects

- In an *in vitro* study a hydro-ethanolic extract of nettle leaf (6.4-8:1) mediated a switch in T helper cell derived cytokine pattern (*Klingelhoefer S et al, 1999*).
- *In vitro* results showed the suppressive effect of iso-propanolic extract on the maturation of human myeloid dendritic cells, leading to reduced induction of primary T cell responses (*Broer J and Behnke B, 2002*).

Thus the traditional use of nettle leaves for treatment of minor rheumatic disorders is plausible. There are no studies addressing possible diuretic effects of nettle leaf. Unfortunately it can not be found any study which investigates the diuretic effect of nettle leaf, but only for nettle herb. Because of the similarity of nettle herb and nettle leaf data existing for nettle herb may also be considered to support the traditional use of nettle leaf in this therapeutic area.

2.2. Pharmacokinetics

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)

There is no pharmacokinetic study with nettle leaf.

2.2.2. Assessor's overall conclusions on pharmacokinetics

Not applicable.

2.3. Toxicology

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)

Turker Au and Usta C, 2008: Screening of antibacterial activity and toxicity of 22 aqueous plant extracts from 17 Turkish plants was conducted. Antibacterial activity was performed with six bacteria including *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Streptococcus pyogenes,*

Staphylococcus aureus and Staphylococcus epidermidis. Extracts of *Tussilago farfara* leaves, *Helichyrsum plicatum* flowers, *Solanum dulcamara* aerial parts and *Urtica dioica* leaves gave the best inhibitory activity against *Streptococcus pyogenes, Staphylococcus aureus and Staphylococcus epidermidis*. Of the 22 plant extracts, 20 extracts displayed toxicity (LC_{50}) was <1000 mg/l) in the brine shrimp bioassay. For radish seed bioassay, two different determinations (root length and seed germination) were performed with a comparison between two concentrations (50,000 mg/l) and 10,000 mg/l). At low concentration (10,000 mg/l), *Solanum dulcamara* aerial parts and *Primula vulgaris* leaf extracts were observed to inhibit the root length more than the other plant extracts. Also, the most inhibitive plant extract for seed germination was obtained with S*olanum* dulcamara aerial parts.

Özen and Korkmaz, 2003: Two doses (50 and 100 mg/kg body weight) of an ethanol-water extract (80-20%) extract of the leaves of *Urtica dioica* L. were given orally for 14 days to Swiss albino mice (8-9 weeks old). Distilled water and BHA (butylated hydroxyanisole) served as controls. No undesirable side effects could be observed.

2.3.2. Assessor's overall conclusions on toxicology

Specific data on the toxicology of nettle leaf are limited.

3. CLINICAL DATA

3.1. Clinical Pharmacology

3.1.1. Pharmacodynamics

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

There are no relevant data.

3.1.1.2. Assessor's overall conclusions on pharmacodynamics

There are no relevant data.

3.1.2. Pharmacokinetics

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

There are no relevant data.

3.1.2.2. Assessor's overall conclusions on pharmacokinetics

There are no relevant data.

3.2. Clinical Efficacy

3.2.1. Dose response studies

There are no studies available.

3.2.2. Clinical studies (case studies and clinical trials)

Extracts of Nettle leaf were studied in osteoarthritis.

According to the Points to consider on clinical investigation of medicinal products used in the treatment of osteoarthritis (CPMP/EWP/784/97) osteoarthritis is a disorder which can potentially affect all synovial joints. It is characterised by degradation and regeneration of articular cartilage and bone. The pathological changes can be focal or more generalized and these changes often correlate poorly with clinical symptoms and signs. However, it has been suggested that asymptomatic osteoarthritis, diagnosed radiologically, is a precursor of symptomatic disease. Osteoarthritis, particularly of the large joints of lower limbs – for example, knees and hips – is now widely recognized as a major cause of the chronic disability in the population.

Medication for osteoarthritis may affect symptoms and/or modify structures. Three classes of drugs act in osteoarthritis: fast-acting drugs that induce symptomatic relief, slow-acting drugs that induce symptomatic relief and disease-modifying drugs.

- Open studies

Five open, multicentric, post marketing surveillance studies have been carried out on patients with arthritic or rheumatic complaints using a preparation containing a dry hydro-alcoholic extract of nettle leaf (6.4-8:1) at a daily dosage of 2 times 670 mg (corresponding to 9.648 g of dried leaf per day.)

Ramm S and Hansen C, 1995: An extract preparation was tested in a multicentric 3-week study on 152 patients suffering from various rheumatic, mainly degenerative, diseases at a daily dose of 1.54 g of dried extract (6.4-8:1, corresponding to 9.648 g of dried leaf per a day, *Urtica dioica folia hydroethanolic extract 335 mg IDS 23*, Rheuma-Hek capsule). 121 patients from the 152 (79.6%) were pre-treated with non-steroidal anti-inflammatory drug (NSAID), mainly Diclofenac. 106 patients continued taking NSAID and 19 patients, who were not pre-treated took Rhema-Hek together with NSAID. Only 12 patients were treated with Rheuma-Hek alone. The latter patients experienced a weaker effect than patients with combined therapy. Pain symptoms assessed by a visual analogue scale (VAS) improved in 70% of patients with combined therapy (n= 98) by at least one third: pain at rest by 50%, movement pain by 51%. In patients receiving only nettle leaf extract (n=12) pain decreased by 43%.The authors suggested the mono-therapy with Rheuma Hek was a suitable treatment only for incipient or weaker rheumatic complaints. While only 17% of physicians evaluated the monotherapy with NSAID as good or very good, 78% of them rated the combination therapy - NSAID + Rheuma Hek - good or very good. The tolerability of the combined therapy was qualified good or very good by 95% of the physicians and the patients. Only one patient stopped the therapy because of an allergic reaction. The authors thought that the importance of adjuvant therapy with nettle leaf extract could be a reduction of dosage of NSAID and a better tolerability.

Hansen C, 1996 and Sommer R-G and Sinner B, 1996: 219 patients (142 women, average age: 67; 77 men average age: 53), mainly (60%) with degenerative (60%) or inflammatory (16%) joint disorders, were treated with IDS 23 (2 times 2 capsules) in a 3-week study. Pain symptoms (VAS) improved by at least one-third in 70% of patients; in patients with pain of degenerative origin by about 50%. Patients (n=71) taking only nettle leaf extract considered it as effective as the extract + NSAIDs.

Ramm S and Hansen C, 1996: The results of a 3 week post marketing surveillance study in 1528 patients (1392 arthrose, 268 rheumatoid arthritis) showed that the herbal medicinal product Rheuma-Hek (335 mg/capsule IDS 23 2 times 2 capsules) was very well tolerated and effective in alleviating rheumatic complaints. The dose of the existing treatment with NSAIDs given in parallel with IDS 23 could be reduced in 42.8% of the patients and could be stopped in additional 19.75 % of the patients.

Ramm S and Hansen C, 1997: The previously mentioned Urticae folium extract was tested in an open, multicentric clinical trial. The patient number was 8955, and they suffered from osteoarthrosis or rheumatoid arthritis. The patients took 2 times 2 capsules nettle leaf extract (335 mg/caps. IDS 23, Rheuma- Hek) for three weeks. About half of the patients (49.5%) were pre-treated with NSAID to relief their acute complaints. (Diclofenac 82.2%, Ibuprofen 19.5%, Piroxicam 12.6%). Further 7.7% of the patients were pre-treated with alternative treatments, mainly with physiotherapy. There were three therapy-groups during the study: Rheuma-Hek monotherapy (n= 4996), Rheuma-Hek + NSAID combination-therapy and Rheuma- Hek + other therapy (n=643). The evaluation was focused on how the intensity of the pain in rest and in motion changed, or how the patient's ability to move improved. In the Rheuma-Hek + NSAID group the moving pain was stronger than in the other two groups at the beginning of the study. The same applied to the resting pain and the physical disability.

Results: 2754 patients (64%) could markedly reduce the dose of the parallel NSAID. 26.2% of the patients could stop treatment with NSAID, and further 37.8% of the patients could reduce the dose of them about by 50%. NSAID therapy did not change in 28.4% of the cases and only 7.6% of the patients needed NSAID parallel to Rheuma-Hek later. The rest pain decreased about by about 55%, the moving pain by 45%, the moving ability improved by 38%. 82.5% of the patients thought that their state improved (50.2% very good, 32.3% good). Only 11.7% of the patients were categorised as non-responders. Clinically relevant differences between the three therapy-groups could not be demonstrated. The tolerability was also very good. Only 1.2% of the patients experienced adverse effects, mainly gastro-intestinal complaints (0.64%) and allergic reactions (0.13%).

Wolf F, 1998: The long-term efficacy and tolerability of an Urticae folium extract (IDS 23, Rheuma Hek) was investigated in an open post-marketing-surveillance study. 819 patients received 2 times 2 capsules Rheuma-Hek/day for one year. 101 of these patients did not take the medicine continuously, they had four-week's breaks once or twice a year. 244 patients got only Rheuma-Hek, the others got Rheuma-Hek + NSAID. 64% of the patients were pre-treated (58% with NSAID) for at least three weeks.
The efficacy of the product was evaluated with the help of a gonarthrose specific patient questionnaire. There were 5 questions about pain on the joints (warmth, swelling, sensitivity to pressure, redness), 2 question about rigidity of the joints and 17 questions about function of the joint. It was also investigated how the product influenced the process of the illness (frequency and duration of painful schubs).
Under continuous therapy with Rheuma-Hek the pain decreased on average 73.5% during the year. The rigidity of the joints reduced on average 63.2% and the function of the joint improved 63.5%. The degree of the improvement was the highest in the first three months, then it went on with lower intensity. The results were similar in the group getting the product intermittently. The frequency of painful schubs also reduced markedly. 90% of the physicians and 88% of the patients rated the effectiveness as good or very good. The tolerability was rated as good or very good by 95% of the physicians and the patients. Side effects occurred only at 2.7% of the patients (allergic reactions, gastro-intestinal complaints).
As IDS 23 was shown to reduce formation of cytokinin IL-1β and TNF-α, which play an important role in the pathogenesis of arthrosis, the authors argued that not only the symptoms improved but the progress of illness slowed down. IDS 23 might produce a cartilage -protective effect.

Open studies with other preparations

Wolf F et al, 2001: In an observational study the clinical effectiveness of an extract of nettle leaf (145 mg dry extract of nettle leaves (19-33:1) prepared with 2-propanol 95% V/V) was investigated. Twenty patients suffering from painful arthrosis took 3 times 1 capsule of STRAT 59 (Hox alpha) for 3 months. The pain was measured by using a rating scale (O-5) in a patient-diary and decreased by

42%. Joint- function was evaluated with the help of WOMAX-questionnaire, and it improved by 32%, the rigidity by 35%.

Randall C et al, 1999: An exploratory study was carried out on the alleviation of pain by external application of fresh nettle leaves, which causes urtication. From analysis of recorded semi-structured interviews between a doctor and 18 people who had tried this self-treatment for joint or muscle pains, 15 out of 18 claimed that nettle treatment worked on every application; 17 out of 18 reported pain relief after the first course of treatment and had found no other treatment as effective as nettle leaf. Onset of pain relief occurred in less than 24 hours in 11 out of 18 patients. The stinging sensation was reported by 14 out of 18 as "not painful, with a not unpleasant warmth" and other than 3 cases of localised numbness for 6-24 hours and few rashes, no side effects were reported. This exploratory study supported the hypothesis that nettle sting might be a useful, safe and cheap therapy which needs further study.

- Controlled studies:

Chrubasik S et al, 1997: Forty individuals suffering from an acute attack of chronic joint disease (acute arthritis) took part in an open randomised study comparing the effects of 50 mg diclofenac and 50 g of a prepacked stewed nettle leaf purée (*Urtica dioica* L., water content 95.5%, caffeoyl malic acid content 20 mg, patient's number=19) with 2 times 100 mg diclofenac (n=17). Both groups also received the gastro protective prostaglandin analogue misoprostol. The assessment was based on the decrease of the elevated C-reactive protein (CRP) concentrations (main criterion) and the clinical signs of acute arthritis, physical impairment, subjective pain and pressure pain (patient assessment) and stiffness (physician assessment). All assessments were based on a verbal rating scale from 0 to 4. C-reactive protein and total joint scores improved significantly in both groups (Wilcoxon paired rank sum) with a median score change of about 70% relative to the initial value. Only minor adverse effects occurred during treatment (group D 200: diarrhoea over 2 days n=2, abdominal pain over 3 days n=1; group D50+U: meteorism n=3). The authors concluded, that 50 mg diclofenac together with 50 g stewed nettle leaf may significantly decrease elevated acute phase proteins and the clinical symptoms of acute arthritis as effectively as 200 mg diclofenac. The authors concluded that 50 mg diclofenac were unlikely to produce such a profound effect. A dose finding study revealed that 75 mg/d diclofenac proved inadequate in 16 out of 18 patients with rheumatoid arthritis. To date, 150 to 200 mg diclofenac are usually administered as daily dosage for the improvement of rheumatic complaints. *Urtica dioica* ingredients' synergistic antirheumatic efficacy might, thus, account for the clinical effect in the 50 mg diclofenac group and the enhancement of the NSAID antirheumatic effectiveness.

Rapporteur's comment: This article is not considered because it is assumed that it is about nettle herb.

Randall C et al, 2000: A randomized controlled double-blind crossover study was conducted in 27 patients with osteoarthritic pain at the base of the thumb or index finger. Patients applied stinging nettle leaf (Urtica dioica) daily for one week to the painful area. Patients were instructed how to cut a leaf (with hand in plastic bag) and apply the lower surface to the painful area of thumb or index finger base with gentle pressure for about 30 seconds, moving the leaf twice. The effect of this treatment was compared with that of placebo, white deadnettle leaf (Lamium album), for one week after a five-week washout period. Observations of pain and disability were recorded for the twelve weeks of the study. After one week's treatment with nettle sting, score reductions on both visual analogue scale (pain) and health assessment questionnaire (disability) were significantly greater than with placebo ($P = 0.026$ and $P = 0.0027$). After one week's treatment daily use of analgesic and anti-inflammatory drugs showed a decline in the stinging nettle group but the difference versus placebo was not significant. No serious side-effects were reported or observed. The localized rash and slight itching associated with stinging nettle was acceptable to 23 of 27 patients; 2 patients reported the sting as unpleasant but not

distressing. 1 patient had a persistent rash on her forearms after treatment but this had occurred before and was not necessarily due to stinging nettle. The stinging nettle treatment caused a rash on the hand of one patient who discontinued treatment because he needed heavy gloves for his job. The result of this trial demonstrated an analgesic effect and reduction of disability after one week treatment with stinging nettle. A weakness of the design was that the "blinding" of both doctor and patients was incomplete; one patient reported stinging and rash with the application of one plant treatment. Patients were not, however, given to understand that any benefit might be associated with the sting, and the patients did not seem to make this assumption. The sample size was small, but crossover of treatment considerably increased the power of the results. Patients' compliance was high.

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

There is no study available.

3.2.4. Assessor's overall conclusions on clinical efficacy

The quality of above mentioned clinical studies with nettle leaf in osteoarthritis is poor, not convincing. They all show a trend of effectiveness in the domains investigated, which needs, however, to be proven in confirmatory studies. They do not fulfil the requirements of the above mentioned CHMP guideline. Three-arm, placebo and active controlled studies are recommended. Thus well-established use can not be supported.

3.3. Clinical Safety/Pharmacovigilance

3.3.1. Patient exposure

3.3.2. Adverse events

The stinging nettle (*Urtica dioica*) is a common weed that can cause a wide range of cutaneous reactions. Contact with the hairs or spines on the stems and leaves of the stinging nettle causes the release of several biologically active substances. The released chemicals act to cause itching, dermatitis, and urticaria within moments of contact. (*Anderson BE et al, 2003*)

Mild gastrointestinal complaints (e.g. nausea, vomiting and diarrhoea) and allergic reactions (e.g. itching, exanthema and hives) may occur. The frequency is not known. (Data resulting from market overview)

In clinical studies

Allergic reaction

Only 1.2% of the patients experienced adverse effects, mainly gastro-intestinal complaints (0.64%) and allergic reactions (0.13%). (*Ramm S, Hansen C, 1997*)

No serious adverse effects were reported from 5 clinical studies in which in total 10,368 patients took 2 times 670 mg of a dry hydro-ethanolic extract of nettle leaf (6.4-8:1), corresponding to about 9.7 g of dried leaf, daily for periods varying from 3 weeks to 12 months; the incidence of minor adverse effects mainly gastrointestinal upset or allergic reactions) was 1.2-2.7%. In a study where 19 patients received 50 g stewed nettle leaf purée daily for 14 days, 3 patients reported meteorism. (*ESCOP 2nd ed, 2003*)

Spontaneous case reports for the iso-propanolic extract (Hox Alpha, WHO database):

Allergy, dry skin, Urticaria, pruritus, rash erythematous, rush postular, dyspepsia, nausea, faecal incontinence, diarrhoea, sleep disorders, dizziness.

3.3.3. Serious adverse events and deaths

None reported.

3.3.4. Laboratory findings

No data available.

3.3.5. Safety in special populations and situations

No data available.

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

No data available.

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

ESCOP: None known.

Blumenthal M et al, 1998; Wichtl M, 2004: None known.
Note: No irrigation therapy in cases of oedema due to impaired cardiac or renal function.

Hagers Handbuch: Water retention (oedema) as a results as a result of impaired cardiac and renal function.

Tropical Plant database

- Nettle has been documented in animal studies to lower blood pressure and heart rate. Those with heart conditions should seek the advice and supervision of a health practitioner to determine if nettle is suitable for their condition and monitor its effects.
- Nettle has been documented to have diuretic effects. Chronic use of this plant may be contraindicated in various medical conditions where diuretics are not advised. Chronic long-term use of any diuretic can cause electrolyte and mineral imbalances. Consult your doctor if you choose to use this plant chronically for longer than 30 days concerning possible side effects of long term diuretic use.

Contraindications in the Monograph

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

3.3.5.3. Warning

Blumenthal M et al, 1998; Hagers Handbuch 1998; Wichtl M, 2004

In irrigation therapy, care must be taken to ensure an abundant fluid intake.
Excessive use may influence the treatment of hypertension and diabetes.

Rapporteur's comment: There are no data (clinical or preclinical) which support this statement.

Articular pain accompanied by swelling of joint, redness or fever should be examined by a doctor.

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

If minor 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.

3.3.5.4. Drug interactions

None reported. (*ESCOP 1997, 2003; Blumenthal M et al, 1998*)

Due to the content of vitamin K in nettle leaf the herbal substance or preparations thereof could attenuate the efficacy of anticoagulants like phenprocumon or warfarin (labelling applied by the German authority). According to data provided during public consultation, the Vitamin K content described in the literature is 0.16-0.64 mg/100 g [*Bertok L 1956, Benigni R 1964, Bombardelli E 1997*]. Based on a maximum daily dose equivalent to 15 g, this corresponds to 24-96 µg of vitamin K. Therapeutic dosage of vitamin K1 (oral use) is 10-20 mg daily. This means that vitamin K brought by nettle preparations would represent at a maximum less than 1 percent the effective dose.

Because there have been no reports on clinically observed drug interactions with nettle leaf it was decided to introduce the wording "none reported" into the monograph.

3.3.5.5. Use in pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

3.3.5.6. Overdose

No case of overdose has been reported.

3.3.5.7. Drug abuse

No data available.

3.3.5.8. Withdrawal and rebound

No data available.

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.

3.3.6. Assessor's overall conclusions on clinical safety

Nettle leaf preparations are well-tolerated.

4. ASSESSOR'S OVERALL CONCLUSIONS

The traditional use of nettle leaf in minor articular pain is supported by pharmacological data, as IDS 23 hinders the building of cytokinin IL-1β and TNF-α, which play an important role in the pathogenesis of arthrosis, so the use of the nettle leaf extract might be useful. NSAIDs acting by inhibition of COX1 enzyme cause serious gastrointestinal adverse effects and NSAIDs acting by inhibition of COX2 enzyme have cardiovascular risks, so that their use should be restricted, if possible (see CHMP opinion EMEA/CHMP/410051/2006). Results of clinical studies in this therapeutic area are not sufficient to attribute an indication under well-established use. Nevertheless, the results support the plausibility of the traditional use in minor articular pain. The traditional use of nettle leaf as adjuvant in minor urinary complaints is plausible due to the tradition and the data existing for nettle herb which are to be taken into account because of the high similarity of nettle herb and nettle leaf.

ANNEXES

List of references