European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *URTICA DIOICA* L. AND *URTICA URENS* L., HERBA' (EMEA/HMPC/170261/2006)

Table 1: Organisations providing comments on the draft Community herbal monograph on *Urtica dioica* L. and *Urtica urens* L., herba as released for consultation on 7 September 2007 until 15 December 2007.

	Organisation
1	The European Scientific Cooperative on Phytotherapy (ESCOP)
2	The Association of the European Self-Medication Industry (AESGP)
3	Kooperation Phytopharmaka, Germany
4	PhytoLab, Germany
5	Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Germany

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Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT	
Comment and Rationale	**Outcome**
"The herbal substance is described in the HMPC monograph as following: dried cut or fragmented aerial parts of the plant collected or harvested during the flowering period. According to the Ph.Eur. monograph 5.6. not the herb, but the nettle leaves are described: whole or cut dried leaves of *Urtica dioica* L., *Urtica urens* L. or a mixture of the 2 species. Therefore the used plant material is not in accordance with current pharmacopoeial specification."	This monograph is about nettle herb. A separate monograph will be prepared for nettle leaf.
SPECIFIC COMMENTS ON TEXT	
2 QUALITATIVE AND QUANTITATIVE COMPOSITION	
Paragraph no. **line no.**	**Comment and Rationale**	**Outcome**
ii) Herbal preparations	*To traditional use:* Propose for two additions: Dry aqueous extracts. Dry hydroethanolic extracts. *Reasoning:* There is no reason to exclude either of these types of preparation, nor to specify the potency of the extracts. Clinical studies using a dry hydroethanolic extracts of nettle leaf have been summarised in the ESCOP monograph [1]	Not accepted: This monograph is about nettle herb. A separate monograph will be prepared for nettle leaf.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
ii) Herbal preparations (continued)	*To add to* Well-established–use Dry extract, extraction solvent ethanol 50% V/V, DER 5-10:1. *Reasoning:* These extracts are used with good clinical evidence.	Not accepted: The clinical studies were done with extracts of nettle leaf. This monograph is about nettle herb.
	To add to Traditional use Comminuted herbal substance ***as infusion***	Not accepted: "as infusion" is already mentioned under posology.
	Powdered herbal substance.	Accepted.An interested party and some national competent authorities gave examples.
	Dry extract, extraction solvent 95% 2-propanol, DER 19-33:1	This is a new nettle leaf product, which cannot be accepted.
	Powdered nettle herb and nettle herb dry extract, extraction solvent water, DER 4-7:1	Not accepted. It is a combination product.
	Dry extract (7-9.45:1) extraction solvent: ethanol 45% (V/V) and combination thereof with dried herbal substance.	Not accepted. It is a combination product.
	To add to Traditional use Powdered herbal substance.	An interested party and some national competent authorities gave examples, thus it can be accepted.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
ii) Herbal preparations (continued)	<u>*To add to the well-established use:*</u> Dry extract (8-10:1, ethanol 50%; genuine (native) herbal preparation: 80%) In clinical studies, a dry hydroethanolic extracts of nettle leaf (6,.4-8:1) with a daily dose of 2 x 670 mg (corresponding to about 9.7 g of dried leaf per day) was tested. This preparation corresponds to a daily dose of 2x 536 mg of the above-mentioned dry extracts having a DER of 8-10:1. <u>*To add to traditional use:*</u> • Dry aqueous extract (4-7:1) and combination thereof with dried herbal substance. (This corresponds to the preparation Kneipp Entwasserung Brennessel Dragees, in the German market since 30 September 1961.) • Dry extract (5.5-8.5:1, extraction solvent: ethanol 20% v/v) and combination thereof with dried herbal substance. (This corresponds to the preparation Brennessel Krautertabletten, marketed in Germany by SALUS Haus GmbH Co. KG since 30 June 1978.)	*This monograph is about nettle herb. A separate monograph will be prepared for nettle leaf.* *Not accepted. It is a combination product.* *Not accepted, because according to the letter from interested party this extract is made from nettle root.*
	The wording of the draft monograph for the liquid extracts is not in accordance with the "Declaration" Guideline. It is not clear what is meant by "with 25% ethanol" and with 45/ ethanol." In case it is the concentration of extraction solvent which is an important parameter for characterisation of extracts and tinctures, it should be given as "% (m/m)" or "% (V/V)".	Accepted. The concentration of extraction solvent is given as % (V/V .)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
Footnotes:	Footnotes 2 and 3 lack clarity which be caused by faithful translations into English. Some further information are also missing (e.g. boiling time). Therefore, we suggest completing and clarifying those footnotes or simply making reference to the original text.	Accepted. Reference has been made to the original text.
3. PHARMACEUTICAL FORM		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	To add to the well-established use : Herbal substance or herbal preparation in solid or liquid dosage forms prepared from e.g. dry extracts. Herbal substance for oral use. The pharmaceutical form should be described by the European Pharmacopoeia standard term.	Not accepted. Well-established use is not supported by literature data.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.1. Thera-peutic indications	Well-established use *To add:* **Adjuvant treatment of arthritis, arthroses and/or rheumatic conditions."** *Reasoning:* "This indication is supported by various 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 hydroethanolic extract of nettle leaf (6.4-8:1) at a daily dosage of 2 × 670 mg (corresponding to about 9.7 g of dried leaf per day) which corresponds to a daily dose of 2 x 536 mg of the dry extract having a DER of 8-10:1 mentioned under 2. In each study a proportion of the patients also continued other therapies, primarily non-steroidal anti-inflammatory drugs (NSAIDs), while others received only the nettle leaf extract. Assessments were carried out through patient questionnaires and consultations with physicians. Overall, 80-95% of patients rated the efficacy of the extract, and 93-95% its tolerability, as good or very good. Furthermore, the above mentioned indications are supported by in vitro data (See ESCOP monograph [1] on Page 522, Refrences 35 and 36).	Not accepted. This monograph is about nettle herb, not nettle leaf. Clinical studies were done with an extract of nettle leaf. Not accepted. This monograph is about nettle herb, not nettle leaf. In vitro studies were done with extract of nettle leaf.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.1. Thera-peutic indications (continued)	<u>Traditional use</u> In our view, indication "b", i.e. relief of minor articular pain, is more substantiated by published literature than indication "a". The two indications should be interchanged. We suggest substitution of word "achieve " by enhance". Flushing of the urinary tract can be achieved simply by drinking plenty of water. *Suggestion:* **c, Traditional herbal medicinal product for the treatment of eczema, cutaneous eruptions and seborrheic conditions of the skin.** *Reasoning:* "Nettle herb has also been used orally in the treatment of certain skin condition. • In the officinal French publication "Medicaments á base de plantes" [2] nettle herb is accepted for traditional use in the treatment of seborrheic conditions of skin. • In the British Herbal Pharmacopoeia [3], which reproduces a BHP monograph first published in 1971 and based on the direct experience of UK practitioners, the indications for nettle herb include "cutaneous eruptions, infantile and psychogenic eczema" and as a specific indication, "nervous eczema". These indications have also been mentioned in other texts [4,5]. Studies of the anti-inflammatory activity of nettle herb summarized under in vitro experiments in ESCOP monograph [1] support its use in eczema. **"**	Not accepted. It is right in the case of nettle leaf, but not for nettle herb. Not accepted: The sentence already contains "to increase the amount of urine". It is not necessary to repeat it with "enhance". Accepted. An authority gave an example for a product with this indication.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.1. Thera-peutic indications (continued)	Traditional use *Additional indication.:* "Traditional herbal medicinal product used in seborrhoeic conditions of the skin. *Reasoning*: BHP, Potter's, The Cahier de l' Agence Noº 3 from the French AFSSAPS.	Accepted. See above.
	Traditional use *Suggestion for modification:* b) Traditional herbal medicinal product for relief of minor *muscular and* articular pain *or for relief of localized pain in the musculoskeletal system*	Not accepted. The text is harmonised with other monographs of herbal substances with similar effect.
	Traditional use *Suggestion for modification:* a) Traditional herbal medicinal product to *support the elimination function of the kidney.* b)Traditional herbal medicinal product for relief of *localized pain in the musculoskeletal system*	Not accepted. The text is harmonised with other monographs of herbal substances with similar effect. Not accepted. The text is harmonised with other monographs of herbal substances with similar effect.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.2. Posology and method of administration	*To add to* Traditional use After the entry for "Tincture", in line with the proposal made above under Qualitative and Quantitative Composition, wwe propose the insertion of: **Dry aqueous or hydroethanolic extracts corresponding to 2-4 g of herbal substance as a single dose, up to 3 times.** *Reasoning:* There is no reason to exclude either of these types of preparation, nor to specify the potency of the extracts. Clinical studies using a dry hydroethanolic extracts of **nettle leaf** have been summarised in the ESCOP monograph)	Not accepted. This monograph is about nettle herb, not nettle leaf.
	To add to Well-established use Dry extract, extraction solvent 50% ethanol, DER 5-10:1: up to 540 mg as a single dose, up to 3 times daily.	Not accepted. Well-established use of this extract is not supported properly by literature data.
	To add to Traditional use • Dry extract, extraction solvent 95% 2-propanol, DER: 19-33:1; up to 145 mg as a single dose, up to 3 times daily • Powdered nettle herb and nettle herb dry extract, extraction solvent water, DER 4-7:1	Not accepted. This is a new nettle leaf product. (Hox apha®) Not accepted. It is a combination product.
	To add to traditional use 380 mg nettle herb as powdered herbal substance 3 times daily.	Accepted. An authority gave examples.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.2. Posology and method of administration (continued)	<u>*To add to*</u> Well-established use *Adults and Adolescents over 12 years* **Dry hydroethanolic extract corresponding to 9-10 g** herbal substance (daily dose) in an appropriate pharmaceutical form, e.g. capsule, in 2 single doses	Not accepted. Well-established use of this extract is not supported properly by literature data.
	<u>*To add to Traditional use*</u> • Dry aqueous extract (4-7:1) and combinations thereof with dried herbal substance corresponding to 377.5 - 755.0 mg of the herbal substance 3 times daily.	Not accepted. It is a combination product.
	• Dry extract (5.5 - 8.5 : 1, extraction solvent: ethanol 20 % v/v) and combinations thereof with dried herbal substance corresponding to 1130 mg of the herbal substance 3 times daily.	Not accepted, because it is a combination product and according to the letter sent by an interested party this extract is made from nettle root.
Duration of use	<u>*To add to*</u> Well-estabkished uase Suggestion on modification: Duration of use is not restricted. (See section 4.4. Special warnings and precaution for use.).	Not accepted. Duration of use is harmonised with the monograph of herbal substances with similar effects.
4.3. Contra-indications	<u>*To add to*</u> Well-established use Patients with known hypersensitivity to nettle should not use nettle leaf preparations.	Not accepted. Well-established use is not supported by literature data.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.4. Special warnings and precautions for use	<u>*To add to* Well-established use</u> If symptoms persist or worsen within two weeks, a physician should be consulted. A physician should be consulted in case of acute rheumatic symptoms, e.g. redness, swelling or hyperthermia of rheumatic joints. Nettle leaf preparations may interact with antidiabetic treatment. <u>*To add to* Traditional use</u> We propose deleting the warning stating that "*Patients suffering from diabetes or hypertension …..* This special warning is in line with the following comment "In view of the documented pharmacological actions for nettle, excessive use may interact with concurrent therapy for diabetes, high or low blood pressure, and may potentiate drugs with CNS-depressant actions" [1]. Indeed, some papers listed in the EMEA/HMPC/366106/2007 refer to pharmacological actions as hypoglycaemic action, anti-hyperglycaemic activity and hypotensive effects. Meanwhile, it seems very speculative to support special warnings based on such data. According to [1], these could be considered following "excessive use".	Not accepted. Well-established use is not supported by literature data. Not accepted. Well-established use is not supported by literature data. Accepted.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.4. Special warnings and precautions for use (continued)	Traditional use *To delete*: **"**Patients suffering from diabetes or hypertension…" *Reasoning:* This warning appears to be derived from a sentence in the Nettle monograph by Barnes J et al. (2002) [4] It also appears in the earlier edition of this book [Newal C.A. et al. 1996]: Contra-indication, Warnings: In view of the documented pharmacological actions for nettle, excessive use may interact with concurrent therapy for diabetes, high or low blood pressure, and may potentiate drugs with CNS-depressant action". However, these "documented pharmacological actions" need closer examination: - At high oral dose levels in rodents, nettle herb extracts have produced conflicting results in the oral glucose tolerance test.. Neef H et al [6] reported hyperglycaemic effects in mice, whereas Bnouham M et al. [7] reported anti-hyperglycaemic effects in rats. – In the two in vivo studies reporting hypotensive effects in rodents, nettle herb extracts were administered intravenously; the results can not therefore be considered relevant to oral use. In our view, it would be unreasonable to extrapolate these limited data to the oral use of nettle herb in humans. The proposed contraindication/warnings do not appear elsewhere in the literature and are entirely speculative. Adverse effects experienced after oral use of nettle herb in open clinical studies involving 10,000 patients are summarized in ESCOP monograph under Clinical safety.	Accepted.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.4. Special warnings and precautions for use (continued)	Traditional use *To delete:* "If complaints or 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." *Reasoning:* We know of no literature, which would support this statement, nor can we see any rationale for it. It appears to be unnecessary and alarmist	It is an usual sentence in monographs: „If the symptoms persist during the use of the medicinal products, a doctor or ….." Fever, dysuria ….refer to the illness not to side –effects of nettle herb. Having understood the problem modification was made: If *urinary tract complaints* worsen and symptoms such as fever….
	To add: In case of the concomitant use with synthetic diuretics the diuretic effects may be increased. It is recommended to contact a healthcare professional prior to the concomitant use. *For Reasoning see 4.5 Interaction*	Not accepted. The concomitant use of nettle herb with synthetic diuretics is not mentioned in the final monograph, because there is not a clear proof for the diuretic effect.
4.5. Interactions with other medicinal products and other forms of interaction	*To delete:* Concomitant treatment with synthetic diuretics is not recommended: *Reasoning:* it is not known from clinical evidence that there is in fact a clear documented risk. However, for safety reason a hint may be included in the SPC section 4.4 *special warnings and precautions for use:* In case of the concomitant use with syntehctic diuretics the diuretic effects may be increased. It is recommended to contact a health care professional prior to the concomitant use.	Accepted Not accepted.The concomitant use of nettle herb with synthetic diuretics is not mentioned at all in the final monograph, because there is not a clear proof for the diuretic effect..

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.5. Interactions with other medicinal products and other forms of interaction (continued)	<u>*To delete:*</u> "For preparations other than herbal teas: Patients under anticoagulant therapy should consult their doctor because of the vitamin K content of nettle herb.." *Reasoning*: "As far as we know, the vitamin K content of nettle herb has been reported only once, as 0.16-0.64 mg/100g by Bertok in 1956 [8]. This figure was subsequently mentioned in reviews by Benigni et al (1964) [9] and Bombardelli et al (1997) [10]. Even if we accept that the one determination of vitamin K over 50 years ago gave an accurate figure, the maximum daily dose of a nettle herb preparation, equivalent to about 15g of dried herb, would contain 24-96 µg of vitamin K. this is less than 1% of the therapeutic dosage range of vitamin K_1 (10-20 mg/day) and less than the Adequate Intake of 120 µg/say for a 25-year-old male, as defined under U.S. Dietary Reference Intake system (no Tolerable Upper Intake Level has been set). Vitamin K occurs ion a wide range of foods from leafy green vegetables (e.g. spinach, lettuce) and Brassica vegetables (cabbage, cauliflower, broccoli etc.) to cereals, dairy products, eggs and olive oil – and its intake is unavoidable in the daily diet. On this basis we can not see that the vitamin K content of nettle herb at therapeutic dosage levels presents any hazards to patients under anticoagulant therapy."	Accepted.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.5. Interactions with other medicinal products and other forms of interaction (continued)	<u>*To delete:*</u> *Patients under anticoagulant therapy should….* *Reasoning*: "Vitamin K content described in the literature is 0.16-0.64 mg/100 g [10]. Based on a maximum daily dose equivalent to 15 g, this corresponds to 22.5-90 µg 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. Moreover, according to cited literature [10], given figures refer to very old literature (1954-1956) which as very often in such situation strongly overestimate real content."	Accepted
	<u>*To add:*</u> Patients under anticoagulant therapy should consult their doctor **or control their clotting parameters (INR, Quick's time)** because of the vitamin K content of nettle herb.	Not accepted.
	To add: The preparation contains vitamin K. The herb/leaves preparation can attenuate the efficacy of the anticoagulant preparations like Phenprocoumon or Warfarin.	Not accepted.
4.6. Pregnancy and lactation	<u>*To add to* Well-established use</u> There are no reports of any harmful or deleterious effects during pregnancy and lactation. As there are insufficient systematic data available, use is not recommended during pregnancy and lactation.	Not accepted. Well-established use is not supported by literature data.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.7. Effects on ability to drive and use machines	*To add to* Well-established use No studies on the effect on the ability to drive and use machines have been performed. On the basis of experience hydro-ethanolic extract of nettle leaf has no noticeable effect on ability to drive and use machines	Not accepted. Well-established use is not supported by literature data.
4.8. Undesirable effects	*To add to* Well-established use No serious adverse effects were reported from 5 clinical studies in which a total of 10,368 patients took 2 x 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 upsets or allergic reactions) was 1.2 -2.7 % . ***We therefore propose*:** "*With dry hydro-ethanolic extract of nettle leaf, mild gastrointestinal complaints (e.g. nausea, vomiting, and diarrhoea) and allergic reactions (e.g. itching, exanthema, urticaria) may occasionally occur.* ***Very seldom temporary blood sugar increase in diabetic mellitus patients was observed.*"**	Not accepted. Well-established use is not supported by literature data. This monograph is on nettle herb not on nettle leaf.
	Traditional use: ***Suggestion:*** Mild gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea) and allergic reactions (e.g. itching, exanthema, hives) may occur **in a few individuals** after oral use. The clinical safety data section of the ESCOP monograph states: No serious adverse effects were reported from 5 clinical studies in which a total 10,368 patients took 2 x 670 mg of a dry hydroethanolic 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 upsets or allergic reactions) was 1.2-2.7%. The frequency of undesirable effects is therefore known in a large patient population.	Not accepted. T his monograph is on nettle herb, not on nettle leaf.

5. PHARMACOLOGICAL PROPORTIES		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.8. Undesirable effects (continued)	*To add to* Well-established and to Traditional use Under treatment with nettle herb/leaves preparations diabetic patients reported about increasing blood sugar levels, which normalized after discontinuation of herb/leaves medication.	Not accepted. No details were provided. For example: What was the quantity of the herb or leaves?
4.9. Overdose	*To add to* Well-established use No case of overdose has been reported.	Not accepted. Well-established use is not supported by literature data.
5.1. Pharmaco-dynamic properties	*To add to* well-established use An interested party cited all the text from the ESCOP monograph on Urticae folium/herba under heading: In vitro experiments; Anti-inflammatory activity.	Not accepted. Well-established use is not supported by literature data.
5.2. Pharmaco-kinetic properties	*To add to well-established use* No data available.	Not accepted. Well-established use is not supported by literature data.
5.3. Preclinical safety data	Traditional use The statement is not entirely accurate. The genotoxic potential of several extracts and fractions from Urtica dioica herb has been investigated by Basaran et al.[11] using the standard Ames test. None of the substances produced a positive response in Salmonella typhirium strains TA98 or TA100, with or without metabolic activation. With these reassuring results no further genotoxicity testing may be necessary to satisfy the requirements of the draft Guideline on the Assessment of Genotoxic Constituents in Herbal Substances/Preparations (Document Ref. EMEA/HMPC/107079/2007). COMET assays in human lymphocytes with the same samples produced increases above negative control values, but the authors found the data difficult to interpret and no meaningful conclusions can be derived from them.	The results of the study can not be accepted. There were only two strains investigated. List Entry for nettle herb can not be prepared.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
5.3. Preclinical safety data (continued)	The genotoxic potential of *Urtica dioica* (aerial parts) obtained with different solvents (aqueous and saline extracts) was investigated using the *Salmonella typhimurium* microsomal activation assay. No positive response in strains TA98 and TA100 with or without metabolic activation were observed. A non conventional assay, the alkaline single cell gel electrophoresis (COMET) also investigated the potential genotoxicity. An increase above negative control dose-related increases was observed. According to the authors, results of the COMET assay are difficult to interpret as induction of breaks by an agent is not evidence per se of mutagenic or carcinogenic activity and single strand breaks are among the most innocuous alterations. (Basaran AA et al [11]). Based on the recent draft guideline on the assessment of genotoxic constituents in herbal substances/preparations (EMEA/HMPC/107079/2007), it can be concluded that negative Ames test result described in this study supports the decision that no further genotoxicity testing is required on the basis of HMPC non-clinical guideline (EMEA/HMPC/32116/2005). The traditional use of Urtica herba could then be transferred to an entry to list which could be finalised in light of the existence of genotoxic data. <u>To add to "Well-established use"</u> Toxicity tests in animals have not given cause for concern within the recommended dosage range. 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 f dried drug per kg body weight [12].	The results of the study can not be accepted. There were only two strains investigated. List Entry for nettle herb can not be prepared. Not accepted. Well-established use is not supported by literature data.

[1] Urticae folium/herba. Nettle leaf/herb. In: ESCOP Monographs. 2nd ed. European Scientific Cooperative on Phytotherapy, Thieme, Stuttgart 2003, 521-7
[2] Republique Francaise : Ministére de l' Emploi et de la Solidarité. Médicaments à base de plantes. Ortie dioique, feuilles, parties aérienenes. In : Les Cahiers de l'Agence No.3. Agence du Médicament", Saint-Denis Cedex 1997
[3] Urtica. In: British Herbal Pharmacopoeia. British Herbal Medicine Association, Keighley 1983, 224-5, *which reproduces a BHP monograph first published in 1971*
[4] Barnes J, Anderson LA, Phillipson JD. Nettle. In: Barnes J, Anderson LA, Phillipson JD, eds. Herbal Medicines: A Guide for Health-Care Professionals. Pharmaceutical Press, London 2002, 360-364
[5] Wren RC. Potter's New Cyclopaedia of Botanical Drugs and Preparations. Completely revised by Williamson EM, Evans FJ. Daniel, Saffron Walden, Essex 1988
[6] Neef H, Declercq P, Laekeman G. Hypoglycaemic activity of selected European plants. Phytother Res 1995, 9: 45-8
[7] Bnouham M, Merhfour FZ, Ziyyat A, Mekhfi H, Aziz M, Legssyer A. Antihyperglycemic activity of the aqueous extract of *Urtica dioica*. Fitoterapia 2003, 74: 677–81
[8] Bertok L. A csalán összetétele és táplálóértéke [The composition and the nutritive value of Nettle] Magyar Allatorvosok Lapja 1956, 11: 162-66 (Hungarian) through Chem Abstr 1958, 52:20757b
[9] Benigni R, Capra C, Cattoni PE, Ortica In: Piante Medicinali –Chimica, farmacologia e terapia, Volume 2. Milano: Inverni &della Belfa, 1964>1056-63
[10] Bombardelli E, Morazzoni P. Urtica dioica 1997; 68:387-402
[11] Basaran AA, Yu TW, Plewa MJ, Anderson D. An investigation of some Turkish herbal medicines in *Salmonella typhimurium* and COMET assay in human lymphocytes. Theratog Carcinog Mutagen 1996, 16(2): 125-38
[12] Tita B, Faccendini P, Bello U, Martinoli L, Bolle P. *Urtica dioica* L.: Pharmacological effect of ethanol extract. Pharmacol Res 1993, 27(Suppl. 1): 21-2