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EMA/HMPC/584060/2010
Committee on Herbal Medicinal Products (HMPC)

# Overview of comments received on Community herbal monograph on *Urtica dioica* L.; *Urtica urens* L., folium (EMA/HMPC/508015/2007)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Urtica dioica* L.; *Urtica urens* L., folium as released for public consultation on 8 May 2008 until 15 September 2008

| | **Organisations and/or individuals** |
|---|---|
| 1 | The European Scientific Cooperative on Phytotherapy (ESCOP) |
| 2 | The Association of the European Self-Medication Industry (AESGP) |
| 3 | Kneipp Gruppe, Germany |

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Table 2: Discussion of comments

## General comments to draft document

| Interested party | Comment and Rationale | Outcome |
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| ESCOP | The HPMPC has prepared separate draft monograph for Urticae herba (nettle herb) and Urticae folium (nettle leaf). Since the herb contains a very high proportion of leaf material (even during the flowering season), from a phytotherapeutic viewpoint we doubt whether any notable phytochemical or pharmacological distinction could be made between herb and leaf. However, we accept that various pharmacological and clinical studies have been carried out using specifically leaf material and preparations from it, which could be considered to justify a separate monograph for the leaf.<br><br>Apart from one double-blind, placebo-controlled study [1] which is not relevant to commercial products since fresh nettle leaf was applied directly to the skin as a treatment for osteoarthritis, published clinical evidence supporting the therapeutic indications for nettle leaf appears to consist primarily of the uncontrolled studies summarized in the ESCOP monograph on Urticae folium/herba [2]. | Separate monographs have been prepared for nettle herb and nettle leaf. The similarities of both herbal substances as well as the problems of differentiation in the existing literature have been taken into account during assessment as far as possible. |
| AESGP | With regard to preparation eligible for the well-established medicinal use we fully refer to our comments already submitted on the draft monograph on Nettle herb. Our comments were based on several studies which have mainly been performed with nettle leaf preparation. The herb normally contains a very high proportion of leaf material. Therefore from our point of view a phytochemical or pharmacological distinction between herb and leaf should not be made. That means that our proposal for well-established use preparations already submitted for Nettle herb applies for Nettle leaf as well. | Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed.<br><br>Separate monographs have been prepared for nettle herb and nettle leaf. The similarities of both herbal substances as well as the problems of differentiation in the existing literature have been taken into account during assessment as far as possible. |

## SPECIFIC COMMENTS ON TEXT

| Section number and heading | Comment and Rationale | Interested party | Outcome |
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| 2. Qualitative and quantitative composition | The precisely defined herbal preparations, A,B,C, and D are adequate as examples. However, there is no scientific evidence to justify those specific preparations to the exclusion of any other comparable preparations. More flexibility is needed for traditional use in the absence of controlled studies.<br><br>We propose an additional sentence: Other comparable hydro-alcoholic or aqueous extracts. | ESCOP | Not accepted. According to the market overview only products containing herbal preparations A, B, C and D have been on the market far more than 30 years. |
| 2. Qualitative and quantitative composition | For well-established Use:<br><br>Dry extract (8-10:1, ethanol 50%; genuine (native) herbal preparation: 80%)<br><br>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 2 x 536 mg of the above-mentioned dry extracts having a DER of 8-10:1.<br><br>For traditional use:<br><br>Tincture(1:10) of fresh whole flowering plant, extraction solvent ethanol 45% (V/V) (Date of first marketing: 1965) | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed.<br><br>Not accepted. This monograph is on nettle leaf. |
| 2. Qualitative and quantitative composition | Dried powdered herbal substance and dry extracts (4-7:1) prepared with water and combined preparations thereof. | Kneipp Gruppe | Not accepted. The suggestion refers to a combination product which is not within the scope of the monograph. |

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| 3. Pharmaceutical form | To add to the well-established use :<br><br>Herbal substance or herbal preparation in solid or liquid dosage forms prepared from e.g. dry extracts.<br><br>The pharmaceutical form should be described by the European<br><br>Phaemacopoeia standard term. | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |
| 4.1 Therapeutic indications | b) Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as anadjuvant in minor urinary complaints.<br><br>We suggest substitution of the word “achieve” by “enhance”. Flushing of the urinary tract can be achieved simply by drinking plenty of water. | ESCOP | Not accepted: The sentence already contains “to increase the amount of urine”. It is not necessary to repeat it with “enhance”. |
| 4.1 Therapeutic indications | To well-established use<br><br>We suggest: “Adjuvant treatment of arthritis, arthroses and/or rheumatic conditions."<br><br>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 | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |

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| | 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.<br><br>To Traditional use<br><br>a) Traditional herbal medicinal product traditionally used in the symptomatic treatment of articular pain symptoms.<br><br>b) Traditional herbal medicinal product used to facilitate renal elimination of water. | | Not accepted. The wording is harmonised with the indication of other herbal substances with similar effects. |
| 4.1 Therapeutic indications | The indication “to increase the amount of the urine achieve flushing of the urinary tract” should not be reduced to “minor urinary complaints” but should also include the general preventive form “to support the excretory function of the kidneys.” The general preventive form of indication is in long-standing use as so called “Frühjahrskur”(spring cure) in colloquial language. | Kneipp Gruppe | Not accepted. The wording is harmonised with the indication of other herbal substances with similar effects. |
| 4.2. Posology and method of administration | When the number of times a single dose should be taken daily is given as a range (e.g.) 3-6 times daily, 3-4 times daily, 2-3 times daily) the words “up to” are inappropriate. For example, the text under Herbal substance should read”…..as a single dose 3-6 times daily”<br><br>Daily dosages stated for the herbal substance and herbal preparations B, C, and D correspond to 8-12 g of herbal substance. In the case of herbal preparation A daily dosage appears to be considerably and inexplicably lower than for | ESCOP | Endorsed.<br><br>Preparation A): 30-40 oral drops of liquid extracts (1:5) prepared with 96% ethanol: water: wine 16.5% (V/V) (1.65:1.35:7) as a single dose 3-4 times daily (equivalent with 3-4 times 0.23-0.3g herbal substance). There is an existing product |

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| | the others, and no figure is given for "(equivalent to x g of herbal substance").<br><br>In line with the point made under Qualitative and quantitative Composition, we propose an additional sentence:<br><br>Other hydro-alcoholic or aqueous extract at daily dosages corresponding to 8-12g of herbal substance. | | with the specified posology.<br><br>Not accepted. According to the market overview only products containing herbal preparations A, B, C and D have been on the market since more than 30 years. |
| 4.2. Posology and method of administration | To well-established use<br><br>Adults and Adolescents over 12 years<br>Dry hydroethanolic extract corresponding to 9-10 g herbal substance (daily dose) in an appropriate pharmaceutical form, e.g. capsule, in 2 single doses<br><br>Method of administration: As described in the package leaflet due to pharmaceutical form, e.g. 2 x 2 capsules per day, with a sufficient amount of water after meals.<br><br>Duration of use: Duration of use is not restricted. (See section 4.4. Special warnings and precaution for use.).<br><br>To traditional use<br><br>100-150 drops of tincture in ethanol 45% V/V (1:10) daily, as a single dose up to 3-4 times daily. | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed.<br><br>Not accepted. This is a nettle herb preparation. |
| 4.3.Contraindication | To well-established use:<br><br>Patients with known hypersensitivity to nettle should not use nettle leaf preparations. | AESGP | Not accepted. Well-established use is not supported by proper literature data. |

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| 4.4. Special warnings and precaution for use | "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.<br><br>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.<br><br>We recommended deletion of the sentence. | ESCOP | Not accepted. This wording refers to the disease to be treated and is reflecting the limitations of treatment with a traditional herbal medicinal product. |
| 4.4. Special warnings and precaution for use | Well-established use<br><br>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. | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |
| 4.5 Interactions | Well-established use<br><br>Nettle leaf preparations may interact with antidiabetic treatment. | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |
| 4.6 Pregnancy and lactation | Well-established use<br><br>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. | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |

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| 4.7. Effects on ability to drive and use machines | Well-established use<br><br>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. | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |
| 4.8 Undesirable effects | "Mild gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea) and allergic reactions (e.g. itching, exanthema, hives) may occur. The frequency is not known."<br><br>The Clinical safety data section of the ESCOP monograph [2] states:<br><br>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 9.7g of dried leaf, daily for periods varying from 3 weeks to 12 months; the incidence of minor adverse effects (mainly gastro-intestinal upset or allergic reactions) was 1.2-2.7%.<br><br>The frequency of undesirable effects is therefore known in large patients' population.<br><br>We propose amendment of statement to read:<br><br>"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." | ESCOP | Not accepted. These adverse effects are reported in 1.2 - 2.7 % of the patients in clinical trials. Consequently, the frequency is calculated. |

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| 4.8 Undesirable effects | Well-established use<br><br>We 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.<br><br>Reasoning:<br><br>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 9.7g of dried leaf, daily for periods varying from 3 weeks to 12 months; the incidence of minor adverse effects (mainly gastro-intestinal upset or allergic reactions) was 1.2-2.7%. | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |
| 4.9. Overdose | Well-established use<br><br>No case of overdose has been reported. | | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |
| 5.1. Pharmacodynamic properties | Well-established use<br><br>In vitro experiments<br><br>Anti-inflammatory activity<br><br>AESGP gave detailed description of 5 experiments. | AESGP | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |

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| 5.2. Pharmacokinetic properties | Well-established use<br><br>No data available. | | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |
| 5.3. Preclinical safety data | "Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed."<br><br>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. [3] using the standard Ames test. None of the substances produced a positive response in *Salmonella typhimurium* strains TA98 or TA 100, with or without metabolic activation. With these reassuring results no further genotoxicity may be necessary to satisfy the requirements of the draft Guideline on Assessment of Genotoxic Constituents in Herbal Substances/Preparations (Document Ref. EMEA/HMPC/107079/2007).<br><br>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. | ESCOP | The results of the study can not be accepted because only two strains were investigated. |
| 5.3. Preclinical safety data | Well-established use<br><br>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 dried drug per kg body weight [4]. | | Not accepted. Well-established use is not supported by proper literature data. Only uncontrolled studies have been performed. |

REFERENCES:


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