European Medicines Agency
Evaluation of Medicines for Human Use

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***Equisetum arvense* L., herba**

ASSESSMENT REPORT FOR THE DEVELOPMENT OF COMMUNITY MONOGRAPHS AND FOR INCLUSION OF HERBAL SUBSTANCE(S), PREPARATION(S) OR COMBINATIONS THEREOF IN THE LIST

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I. REGULATORY STATUS OVERVIEW[1]

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'

Member State	Regulatory Status				Comments[2]
Austria	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No preparations
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Finland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No preparations
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Lithuania	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Norway	☐ MA	☐ TRAD	☒ Other TRAD	☒ Other Specify:	No information
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No preparations
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	

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

Member State	Regulatory Status				Comments[2]
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	

II. ASSESSMENT REPORT FOR HERBAL SUBSTANCE(S), HERBAL PREPARATIONS OR COMBINATIONS THEREOF WITH TRADITIONAL USE

Equisetum arvense L., herba

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Equisetum arvense* L., whole or cut dried, sterile aerial parts of the plant
Herbal preparation(s)	a) comminuted herbal substance b) expressed juice (1 : 1.6 - 2.0) c) liquid extract (1 : 4-5) extraction solvent: ethanol 31.5 % d) liquid extract (1 : 5) extraction solvent: ethanol 96 % (V/V)/water/ sweet wine (16.5:13.5 : 70) (m/m) e) liquid extract (1 : 5.5) extraction solvent: sweet wine: ethanol 96 % (V/V) (91 : 9) (m/m) f) dry extract (4 - 7 : 1) extraction solvent: water g) dry extract (7.5-10.5 : 1) extraction solvent: ethanol 70 % (V/V)
Pharmaceutical forms	Herbal preparation in solid or liquid dosage forms or as herbal tea for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.
Rapporteur	Dr Werner Knöss

II.1 INTRODUCTION

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

- Herbal substance(s) [3]: *Equisetum arvense* L., whole or cut dried, sterile aerial parts of the plant

Herba Equiseti is known under the synonyms:

German: Equisetum-arvense-Kraut, Kannenkraut, Pferdeschwanzkraut, Schachtelhalmkraut, Scheuerkraut, Tannenkraut, Zinnkraut;

English.: Herb of field horse-tail, Herb of horse-tail;

French.: Herbe de prêle, Herbe de champs;

Italian: Erba d'equiseto dei campi;

Spanish.: Yerba de cola de caballo,

Croatian: Zelen preslice,

Czech Republic: Preslicova nat,

Danish: Agerpadderokke,

Lituanian: Asiukliu zole,

Norvegian: Kjerringrokk.

The drug consists of the whole or cut dried sterile aerials parts of *Equisetum arvense* L. The primary stem of horsetail is hollow and about 1-3.5 mm thick, separated by nodes into 2-6 cm long segments (internodes) with about 6-19, but generally 9-13 pronounced, longitudinal ridges. The main stem and lateral branches are green to greyish green, rough and brittle. The herb is almost odourless. The taste is insipid, grates between the teeth when chewed.

Equisetum is widely distributed throughout the temperate zones of the northern hemisphere. The material of commerce is imported of China, as well as from eastern and south-eastern European countries.

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

It contains about 10 % inorganic constituents with two-third silicic acid (or silicates respectively) of with 10 % are water-soluble. Flavonoids (0.2 -0.9 %) are present with mostly caempferol and quercetin glycosides and their malonyl esters. There are apparently two chemotypes. Asian and North American varieties contain luteolin-5-glycoside, which is absent from European plants. Also caffeic acid derivates and small amounts of a styrylpyrone glycoside, polyenic acid, sterols, rare dicarboxylic acids and traces of alkaloids including nicotin have been detected. The supposed saponin-complex which has previously been known as "equisetonin", has been identified as a mixture of sugars and flavonoids (Wichtl M, 2004). Schneider (1989) also proposed to cancel "Equisetonin" from the list of compounds of Equisetum arvense.

- Herbal preparation(s):
  - comminuted herbal substance
  - expressed juice (1 : 1.6 – 2.0)
  - dry extract (4 - 7 : 1) extraction solvent: water
  - dry extract (8 - 10 : 1) extraction solvent: ethanol 70 % (V/V)
  - dry extract (7.5-10.5 :1) extraction solvent: ethanol 70 % (V/V)
  - liquid extract (1 : 4 - 5) extraction solvent: ethanol 31,5 %
  - liquid extract (1 : 5) extraction solvent: ethanol 96 % (V/V)/water/ sweet wine (16.5 : 13.5 : 70) (m/m)
  - liquid extract (1 : 5.5) extraction solvent: sweet wine: ethanol 96 % (V/V) (91 : 9) (m/m)
  - extract from fresh herb (1 : 9) extraction solvent water

  (Sweet wine is monographed in the German Pharmacopoea EB 6.)

- Combinations of herbal substance(s) and/or herbal preparation(s)[4]

  For combination products there is often lack of 30 years of tradition, unclear composition (unclear number of composition partners, unclear content of composition partner) or unclear declaration of the extracts. Because of the number of composition partners an extrapolation to a plausible dosage for a

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

single preparation is not possible. Therefore the combinations of horsetail are not proposed for the monograph/list.

- Vitamin(s)[5]: not applicable
- Mineral(s): not applicable

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

The following herbal substances and herbal preparations are since a period of 30 years on the European market and are proposed for the monograph on traditional use.

i) comminuted herbal substance

ii) expressed juice (1 : 1.6 - 2.0)

iii) liquid extract (1 : 4-5) extraction solvent: ethanol 31.5 %

iv) liquid extract (1:5) extraction solvent: ethanol 96 % (V/V)/water/ sweet wine (16.5:13.5:70) (m/m)

v) liquid extract (1:5,5) extraction solvent: sweet wine: ethanol 96 % (V/V) (91 : 9) (m/m)

vi) dry extract (4-7 : 1) extraction solvent: water

vii) dry extract (7.5-10.5 : 1) extraction solvent: ethanol 70 % (V/V)

The dry extract (8-10 : 1) extraction solvent: ethanol 70 % (V/V) is included in the dry extract (7.5-10.5 : 1) extraction solvent: ethanol 70 % (V/V).

Posology and indications of the traditional herbal substance and preparations of horsetail:

- comminuted herbal substance in tablets

Indication: traditionally used to promote the renal elimination of water

[5] Only applicable to traditional use

Posology: 3 times daily 3 coated tablets with 190 mg herb

Single dose: corresponding to 570 mg herbal substance

Daily dose: corresponding to 1.71 g herbal substance

- comminuted herbal substance for tea preparation

Indication:

Czech Republic:

Oral use: adjuvant in treatment of kidney and urinary tract inflammation and infections.

Topical use: for compresses and ablution of superficial wounds with tendency to poor healing, for lavage in case of nose bleeding.

Croatia: oral use: diuretic

Lituania: oral use: for improvement diuresis

Germany:

Commission E monograph, published 18.09.1986: Equisetum herba:

Oral use: Posttraumatic and static oedema, irrigation therapy in bacterial and inflammatory diseases of the lower urinary tract and the renal gravel.

Topical use: supportive treatment for poorly healing wounds.

Posology for oral use:

Germany: Daily dose 6 g herbal substance. (3 times daily an infuse of 2 g herbal substance or 4 times daily 1.5 g herbal substance)

Single dose: corresponding to 2 g herbal substance

Daily dose: corresponding to 6 g herbal substance

Croatia: 3 times daily a tea preparation of 1 tea spoon herb (ca. 2 g) in 250 ml water

Czech Republic: 2-3 times daily a tea preparation of 1 tea spoon herb (ca. 2 g) in 250 ml water

Lithuania: 3 times daily a tea prepared with 3-5 g herbal substance

Conclusion:

Range of posology: Daily dose: 4-15 g herbal substance

Recommendation: The most common posology of all countries is 3 times daily a tea prepared with 2-3 g herbal substance (Daily dose: 6-9 g herbal substance)

Posology for topical use as compresses:

Germany: 10 g herbal substance in 1 l hot water.

Czech Republic: 1 table spoon herbal substance in 250 ml water.

- expressed juice (1 : 1.6-2.0)

Indication

Oral use: Posttraumatic and static oedema. Irrigation therapy in bacterial and inflammatory diseases of the lower urinary tract and the renal gravel.

Topical use: supportive treatment for poorly healing wounds.

Posology for oral use:

2-3 times daily 20 ml (single dose corresponding 11 g fresh herb, daily dose corresponding 22-33 g fresh herb)

Posology for topical use as compresses:

40 ml expressed juice in 500 ml water (corresponding 22 g fresh herb)

- liquid extract (1 : 4 - 5) extraction solvent: ethanol 31.5 %

Indication: Oral use: Traditionally used to promote the renal elimination function.

Posology for oral use: 3 times daily 20 drops (single dose corresponding to 0.155 g herbal substance, daily dose corresponding to 0.465 g herbal substance).

- liquid extract (1:5) extraction solvent: Ethanol 96 % (V/V)/water/ sweet wine (16.5:13.7:70) (m/m)

Indication: Oral use: Traditionally used to promote the renal elimination function.

Posology for oral use: 3 - 4 times daily 30-40 drops (single dose corresponding to 0.2 g herbal substance, daily dose corresponding to 0.6-1.04 g herbal substance).

- liquid extract (1 : 5.5) extraction solvent: Sweet wine: ethanol 96 % (V/V) (91:9) (m/m)

Indication: Oral use: Traditionally used to promote the renal elimination function.

Posology for oral use: 3 times daily 25 drops (single dose corresponding to 0.2 g herbal substance, daily dose corresponding to 0.6 g herbal substance).

- dry extract (4 - 7 : 1) extraction solvent: water

Indication: Oral use: Irrigation therapy for bacterial and inflammatory diseases of the lower urinary tract and renal gravel.

Posology for oral use: 3 times daily 185 mg (single dose corresponding to 2 g herbal substance, daily dose corresponding to 6 g herbal substance) or 2 times daily 272 mg (single dose corresponding to 2 g herbal substance, daily dose corresponding to 6 g herbal substance).

- dry extract (8-10 : 1) extraction solvent: ethanol 70 % (V/V),

Indication: Oral use: Irrigation therapy for bacterial and inflammatory diseases of the lower urinary tract and renal gravel.

Posology for oral use: 3 times daily 200 mg (single dose corresponding to 1.8 g herbal substance, daily dose corresponding to 5.4 g herbal substance).

- dry extract (7.5-10.5 : 1) extraction solvent: ethanol 70 % (V/V),

Indication: Oral use: Irrigation therapy for bacterial and inflammatory diseases of the lower urinary tract and renal gravel.

Posology for oral use: 3 times daily 225 mg (single dose corresponding to 2 g herbal substance, daily dose corresponding to 6 g herbal substance).

The following list shows combinations containing horsetail, existing on the European market, and their indications.

- Equiseti herba extract (4:1) extraction solvent: ethanol 70 % (corresponding to 540 mg herb) and an extract of dandelion herb and root (Taraxacum officinale) solvent unknown, corresponding to 600 mg of plant (Uvalette® of Denmark, not 30 years of tradition, no clinical data for well established use)

  Indication: Herbal medicinal product for the increase of the diuresis in minor oedemas

- (Equisetum arvense L., herba) 13 g/100g in a fixed combination product with other herbal substances in a herbal tea (Horsetail Salus tea (Denmark), not 30 years of tradition, no clinical data for well established use, unclear composition)

  Indication: Herbal medicinal product for the increase of the diuresis, especially in situations with irritations in the urinary system.

- Echinamin® (Denmark): Unclear composition and indication
- 135 mg Equiseti fruct. extr. sicc. resp. (5 : 1), extraction solvent unknown and 120 mg Tarataci rad. extr. sicc. resp. (5 : 1) extraction solvent unknown (from Finland: not 30 years tradition)
- Indication: Minor enhancing effect on urinary secretion.
- Equiseti herba dry extract, ext. solvent: aqua purificata; DER= (4.7-5.7 : 1) combined whith Uvae ursi folii extractum siccum, and other supportive active ingredients Betulae folii extractum siccum and Ononidis radicis extractum siccum. (Product from Croatia, unclear composition, more than 15 years on the market, but unclear if 30 years traditional use)

  Indication: Uncomplicated urinary infections, urinary tract disorders relief with prescribed medicines

- Equiseti herba dry extract (other data not available) combined with Juniperus communis (fruit), Arctostaphylos uva ursi (leaf), Pepper fruit, Petroselenium sativum (aerial), Ananas comusus, and Potassium Citrate (from Croatia, unclear composition)

  Indication: Improvement and health maintenance of urinary tract

- Herbal tea – Visci albi herba 40 g, Hyperici herba 20 g, Crataegi folium cum flore 16.5 g, Crataegi fructus 10 g, Equiseti herba 7.5 g, Menthae piperitae herba 2 g, Melissae herba 2 g, Matricariae flos 2 g/100 g of the herbal tea. On the market in Czech Republic since 1969 – for oral use

  Indication: In presclerotic states, as an adjuvant in mild forms of hypertension.

- Herbal tea – Filipendulae ulmariae herba 450 mg, Equiseti herba 150 mg, Violae tricoloris herba 225 mg, Harpagophyti radix 150 mg, Salicis cortex 225 mg, Solidaginis virgaureae herba 150 mg, Callunae herba 150 mg/tea bag – on the market in Czech Republic since 1999 – for oral use

Indications: As an adjuvant for inflammatory and degenerative diseases of the locomotor apparatus (rheumatism, arthrosis, arthritis and gout), adjuvant therapy in flu like symptoms

- Herbal tea – Uvae ursi folium 375 mg, Matricariae flos 150 mg, Sambuci nigrae flos 150 mg, Equiseti herba 300 mg, Myrtilli herba 225 mg, Solidaginis virgaureae herba 150 mg, Thymi herba 150 mg/tea bag - on the market in Czech Republic since 1989, for oral use,

  Indications: As an adjuvant therapy in acute and chronic infections and inflammations of the urinary tract

- Equisetum arvense (unknown extract) and Taraxacum officinale (unknown extract), unknown composition, is approved as a natural remedy in Sweden with the following indication: "Traditionally used to relieve a sensation of swelling, for example due to PMS (premenstrual syndrome)".

- Germany: On the German market there are many combination products containing horsetail as mild diuretics. The average number of combination substances is 3-5. The main combination substances are Betulae folium, Urticae herba, Solidaginis herba, Juniperi fructus, Ortosiphonis folium and Ononidis radix. Two extracts [Equiseti herba dry extract (6 - 8 : 1) extraction solvent: water and Equiseti herba dry extract (4 - 6 : 1) extraction solvent: water] are combined with crude drug.

- Austria: In Austria Equiseti herba is authorised / registered only in homoeopathics, in a herbal combination with Plantago and Thyme (Pneumopan - Sirup) for the treatment of cough, and in several tea preparations (in combination with other herbal substances) for mild urinary tract disorders.

Documentation of tradition in the European context:

Horsetail has an old tradition in the European context. [Madaus 1938] describes horsetail as an "additional important area of this medicine is diseases of the urinary organs". He notes, that horsetail is mentioned in phytotherapeutical books since the 16th Century. He gives detailed information about old European literature to the traditional medicinal use in a lot of different indications, for example Magnus 12th century, in Germany (Agricola, 16th century, Kneipp 19th century), in Poland and Russia at the beginning of the 20th century.

Equisetum arvense is described detailed in a lot of newer phytotherapeutical books, for example Bézanger-Beauquesne (1986, 1990), British Herbal Medicine Association (1996,

2003), Duke JA (1985, 2002), Garnier (1961), Hänsel (1993), Hager ROM (2003, 2006), Hoppe (1975), LaGow PDR for Herbal Medicines (2004), Paris (1976), Saint-Paul (1980), Van Hellemont (1986) and Wichtl (2003, 2004).

Hiermann (2006) describes as traditional indications for the oral use, to promote the elimination of water in catarrhs of kidneys and bladder, as an haemostyptic at nose, stomach, lung and strong menstruation, as an adjuvant in the treatment of tuberculosis, fissured nails and loss of hair. Horsetail was traditionally used in form of a bath at gynaecological diseases, rheumatic diseases, gout, and treatment of poorly healing wounds, tumescence and break of bones.

It is interesting that the characteristics from the traditional use in the indications involving the plant's inorganic content of silicon, the potential to heal broken bones, connective tissue and nail injuries in patients needing remineralisation, and to treat osteoporosis, led to the French patent application for the use of silicon compounds isolated from E. arvense (Hamon, 1992).

Only a few of these traditional uses of horsetail have been introduced into Pharmacopoeias or accepted collections in the European countries:

Great Britain:

- Equisetum. In: British Herbal Pharmacopoeia Part One, British Herbal Medicinal Association, 1976, 75.: dried herb, or infusion or decoction of the dried herb (thrice daily the single dosage: 1-4 g), liquid extract (1 : 1) in 25 % alcohol (thrice daily the single dosage 1-4 ml): Indications: Enuresis, prostatic disease, cystitis with haematuria, urethritis. Specific indications: Inflammation or benign enlargement of the prostate gland; urinary incontinence; enuresis of children
- Equisetum. In: Ainley Wade, Martindale The Extra Pharmacopoeia, 27th Ed, Pharmaceutical Society of Great Britain 1977, 1754.: Dried herb: Weak diuretic

Germany:

- Herba Equiseti. Ergänzungsbuch zum Deutschen Arzneibuch 6. Ausgabe, DAV Stuttgart, 1953, 244-245
- Equiseti herba, Schachtelhalmkraut, Monographie der Kommission E. In: Bundesanzeiger Nr. 173 vom 18.09.1986. (Equisetum herba. Commission E

monograph, published in Bundesanzeiger Nr. 173, 18.09.1986 and Blumenthal, 1998):

Orally: Comminuted herbal substance for tea preparation and other oral galenic combinations; Dosage: Corresponding to 6 g herbal substance daily. Indications: Posttraumatic and static oedema. For irrigation therapy in bacterial and inflammatory diseases of the lower urinary tract and the renal gravel.

External use: Comminuted herbal substance for tea preparation and other galenic combinations; Dosage: 10 g herbal substance in 1 l water. Indication: supportive treatment for poorly healing wounds.

- Schachtelhalmkraut Standardzulassung No. 1239.99.99 published 12.03.1986 (Equivalent to: Schachtelhalmkraut. In: Braun R Standardzulassungen für Fertigarzneimittel, DAV Stuttgart Govi Verlag GmbH Frankfurt 2004): dried herb for tea preparation;

Dosage: three times daily the single dose: an infusion of 2 teaspoons (ca. 2 g) herb in 150 ml hot water.

Indication: Posttraumatic and static oedema. For irrigation therapy in bacterial and inflammatory diseases of the lower urinary tract and the renal gravel.

External use: comminuted herbal substance for tea preparation and other galenic combinations; Dosage: 10 g herbal substance in 1 l water. Indication: Supportive treatment for poorly healing wounds.

<u>Belgium:</u>

- Circulaire Nr. 367 1990: Equisetum arvense, herba. Indication: Traditionally used to promote the renal elimination of water, although its activity has not been proven in accordance with the current evaluation criteria for medicines (Bradley, 1992).

<u>France:</u>

- Agency Instructions No. 3 (Bulletin Officieal Nr. 19/22, 1990): Equisetum arvense: Therapeutic Indications Nr.

045: Traditionally used to promote renal and digestive elimination functions

085: Traditionally used as an adjuvant in slimming diets/to assist loss of weight, complementary to dietary measures.

151: Traditionally used to promote renal elimination of water

Switzerland:

- Equiseti herba. Pharmacopoea Helvetica, Verlag Eidgenössische Drucksachen- und Materialzentrale Bern 1971: Equisetum arvense L.: dried herb: Indication: “Species diureticae”

Europa:

- Conseil de l Europe, (1989): Equisetum arvense L. :Glycolic extract E/D=2:1; Dosage up to 10 per cent in products of massage, skin restoring elasticity (striae, wrinkles) antiperspirants, hair lotions (hair loss), greasy skins; remineralisating agent, antihaemorrhagic, disinfiltrating agent, tissue drainage.
- Current Pharmacopoeial Monographs: Equisetum Stem Ph. Eur. 01/2008: 1825 corrected 6.0. In European Pharmacopoeia, 6.0 Vol 2 Council of Europe, 2008, 1794-5.

For horsetail herb a period of at least 30 years in medical use as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is fulfilled.

Altogether the literature data support the traditional use for the following indications:

Oral use:

i) Traditionally used to promote renal elimination function

ii) Posttraumatic and static oedema

iii) For irrigation therapy in bacterial and inflammatory diseases of the lower urinary tract and the renal gravel/kidney and bladder stones

The topical use is based only on one preparation (expressed juice 1:1.6-2.0) and the German Commission E monograph (Willuhn, 1995). Therefore this indication is not recommended for the monograph.

Assessor’s comments:

From the above mentioned indications only the following indications are appropriate for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment:

Oral use: Traditionally used to promote renal elimination function.

Diuretics are a group of drugs that block normal solute reabsorption (not water reabsorption directly) along the nephron, inducing solute diuresis.They decrease the extra cellular fluid volume, and are primarily used to produce a negative extra cellular fluid balance. The data for efficacy of horsetail are not appropriate to document a diuretic mechanism of activity with a negative extracellular fluid balance. Therefore the following wording is proposed:

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

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

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

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

In-vitro tests:

Antioxidant effect:

Amarowitcz (2004): Different ethanolic extracts from the roots of wild liquorice (Glycyrrhiza lepidota), narrow-leaved echinacea (Echinacea angustifolia), senega (Polygala senega), leaves of bearberry (Arctostaphylos uvae-ursi) and aerial parts of two varieties of horsetail (Equisetum spp.) (dry extract, DER unclear, extraction solvent 95 % ethanol) were prepared and evaluated for their free-radical scavenging capacity and their antioxidant activity by a number of chemical assays. Assays employed included a beta-carotene-linoleic acid (linoleate) model system, reducing power, scavenging effect on the DPPH free radical and capacity to scavenge hydroxyl free radicals (HO), by use of electron paramagnetic resonance (EPR) spectroscopy. The bearberry-leaf extract, followed by horsetail exhibited the highest antioxidant activity based on the tests performed. The polyphenolic constituents appear to be responsible, at least in part, for the extract's radical-scavenging capacity.

Katalinic (2006): The total phenolic content and related total antioxidant capacity of 70 medicinal plant infusions was analyzed. Aqueousus extracts were prepared as infusion, (3 g of the herb with 200 ml boiled water). The total phenolics were measured by Folin-Ciocalteau assay. The total antioxidant capacity was estimated by Ferric Reducing/Antioxidant Power (FRAP) assay. To make a practical comparison of the relative antioxidant potential of phenolics extracted from selected medicinal plants, the phenol antioxidant coefficient (PAC) was calculated for each infusion. There was a significant linear correlation between total phenolic content and FRAP. The best results were obtained for Melissae folium infusions. Equisetum herba had a Phenol antioxidant coefficient of 2.5 (The PAC was ranging from 1.1 to 3.9).

Nagai (2005): Water extract and ethanol extract from top and body portions of field horsetail Equisetum arvense (tsukushi) were prepared, and the antioxidative activity was investigated using four different methods. (5 g herb were extracted by 5 volumes water or ethanol (unknown concentration), devaporated and solved in 1 ml ethanol (unknown concentration). 0.1 and 1.0 sample solutions were used.) The contents of total phenolic components were richer in the ethanol extract fractions of each portion than in the water extracts. The protein contents were much lower in ethanol extract fractions than in water extract fractions. The ethanolic fractions had antioxidative activities, similar to that of 5 mM ascorbic acid. Water extracts of both portions showed high superoxide anion radical-scavenging activities. Hydroxyl radicals were effectively scavenged by ethanol extracts. The authors concluded that field horsetail (tsukushi) is rich in vitamins C and E. Moreover it contains high levels of copper and zinc. These are essential elements for superoxide dismutase to act against active oxygen species.

Stajner (2006): The scavenger activities of Equisetum arvense, Equisetum ramosissimum and Equisetum telmateia above ground parts phosphate buffer (pH 7) aqueous extracts (1 g of fresh plant material in 5 ml 0,1 mol/l K2HPO4) were evaluated using three different methods: DPPH assay, ESR and NO radical inhibition assay. The total reducing power was determined by FRAP assay. The E. telmateia extract demonstrated the most relevant scavenger and antioxidant properties. ESR signal of DMPO-OH radical adducts in the presence of E. telmateia phosphate buffer (pH 7) extract was reduced to 98.9 %, E. ramosissimum 97.8 % and Equisetum arvense 73.5 %.

Trouillas (2003): The paper presents the antioxidant, anti-inflammatory and antiproliferative capabilities of 16 plants, including E. arvense. The biological properties of the water-soluble fractions (“5 g of hydroalcoholic plant extracts were extracted by 50 ml water addition”) were measured. Antioxidant properties were evaluated by the electron spin resonance (ESR)

method in order to visualize the inhibition of the DPPH, superoxide and hydroxyl radicals. E. arvense had by comparison with reference molecules, e.g. vitamin E and quercetin only low antioxidant properties. Antioxidant effects were correlated with the total amount of phenolic compounds contained in the extracts. Also measured were the anti-inflammatory activities of the 16 water-soluble fractions, by evaluating inhibition of lipoxygenase activity. E. arvense belonged to the group with the second highest activity. (IC50 1.5 mg/ml). Equisetum arvense showed for high concentrations (> 0,5 mg/ml) a significant antiproliferative effect on the proliferation of melanoma B16 cells.

Inhibitory activity on nitric oxide synthesis in LPS-activated macrophages:

Ryu (2003): Nitric oxide (NO) produced in large amounts by inducible nitric oxide synthase (iNOS) is known to be responsible for the vasodilation and hypotension observed in septic shock and inflammation. Inhibitors of iNOS, thus, may be useful candidates for the treatment of inflammatory diseases accompanied by overproduction of NO. The authors prepared extracts ("stem bark and woody plant material were extracted with MeOH, dispersed in water and extracted with ethyl ether") of woody 23 different plants, including E. hyemale and screened the inhibitory activity of NO production in lipopolysaccharide (LPS)-activated macrophages after the treatment of these extracts. Among 83 kinds of plant extracts, 23 kinds of extracts showed potent inhibitory activity of NO production above 60% at the concentration of 80 mcg/ml. Some of potent extracts showed dose dependent inhibition of NO production of LPS-activated macrophages at the concentration of 80, 40, 20 mcg/ml. Artemisia iwayomogi, Machilus thunbergii, Populus davidiana and Populus maximowiczii showed the most potent inhibition (above 70%) at the concentration of 40 mcg/ml. Inhibitory activity of NO production was concentrated to nonpolar solvent fractions (ethyl ether and/or ethyl acetate soluble fractions) of Artemisia iwayomogi, Machilus thunbergii and Morus bombycis. E. hyemale showed a potent inhibition above 50.1 %.

Antimicrobial effects:

Heisey (1992): Extracts (1 : 1) (v/v), extraction solvent methanol/dichlormethan (1 : 10) (g/ml) from 54 plant species, including E. arvense, were tested for antimicrobial activity against E. coli, Staph. aureus, Strept. mutans, Candida albicans, Fusarium oxysporum and Trichophyton rubrum. Antimicrobial activity was noted in extracts of Celastrus scandens, Chamaebatia foliolosa, Cheledonium majus, Chenopodium ambrosioides, Digitaria sanguinalis, Echinochloa crusgalli, Ginkgo biloba, Juglans nigra, Juniperus virginiana, Kalmia latifolia, Lindera benzoin, Oenothera biennis, Rhus glabra, Pelargonium xhortorum and Thuja occidentalis. In a secondary screen, 10 of the above were tested against Bac.

cereus, Erwinia carotovora, Micrococcus luteus, Proteus vulgaris, Strept. salivarius, Asp. niger, Pen. notatum, Pythium ultimum, Rhizopus nigricans and Sacch. cerevisiae. Equisetum arvense showed no antimicrobial activity.

Aswal (1984): 292 Plant extracts (not described) were tested for antibacterial, antifungal, antiprotozoal, anthelmintic, antiviral, antifertility (abortifacient and contraceptive), neuromuscular blocking, cytostatic, sedative, vulnerary, hypoglycemic, respiratory, cardiovascular, spasmolytic, analgesic, utertonic, hypothermic, anticonvulsant, diuretic and antiinflammatory effects. LD50s were also determined. Organisms used included E. coli, Strept., Ps., Klebs., Proteus, Candida, Cryptococcus, Asp., Entamoeba, Nippostrongylus, Vaccinia virus, and Ranikhet disease virus. E. arvense was tested for antibacterial, antifungal, antiprozoal and antiviral activity. It showed no activity. The LD50 was > 1000 mg /kg i.p. in mice.

Antibacterial activity:

Kloucek (2005): Nine ethanol extracts of Brunfelsia grandiflora (Solanaceae), Caesalpinia spinosa (Caesalpiniaceae), Dracontium loretense (Araceae), *Equisetum giganteum* (Equisetaceae), Maytenus macrocarpa (Celastraceae), Phyllanthus amarus (Euphorbiaceae), Piper aduncum (Piperaceae), Terminalia catappa (Combretaceae), and Uncaria tomentosa (Rubiaceae), medicinal plants traditionally used in Callería District for treating conditions likely to be associated with microorganisms, were screened for antimicrobial activity against nine bacterial strains using the broth microdilution method. Among the plants tested, Phyllanthus amarus and Terminalia catappa showed the most promising antibacterial properties, inhibiting all of the strains tested with minimum inhibitory concentrations (MICs) ranging from 0.25 to 16 mg/ml. The extract from aerial part of Piper aduncum was significantly more active against Gram-positive (MICs ranging from 1 to 2 mg/ml) than against Gram-negative bacteria (MICs>16 mg/ml).

Antifungal activity:

Guerin (1984): 41 Plant extracts (water extract of Equisetum arvense herba (1:6))were tested against 9 fungi species. Extracts of Piper methysticum, Illicium verum, Rhamnus frangula, Ruscus aculeatus, Hibiscus sabdariffa, Tamarindus indica, Eschscholtzia californica, Zingiber officinale, Tilia cordata and Viola tricolor were found to have antifungal activity against 1 or more of Sacch. pastorianus, Candida albicans, Rhizopus nigricans, Asp. niger, A. Fumigatus, Botrytis cinerea, Penicillium digitatum, Fusarium oxysporum and Trichophyton mentagrophytes, in vitro. P. methysticum extract was active against all 9 fungi. Other extracts

tested were from Fucus, *Equisetum*, Cupressus, Acorus, Allium, Salix, Betula, Castanea, Urtica, Humulus, Beta, Peumus, Erysimum, Raphanus, Hypericum, Aesculus, Vitis, Cassia, Trigonella, Lespedeza, Lotus, Melilotus, Medicago, Glycyrrhiza, Alchemilla, Crataegus, Rosa and Spiraea species. E. arvense showed no antifungal activity.

Parihar (2002): The antifungal properties of the aqueous and acetone extracts of pinnules, petioles and rhizomes of Adiantum lunulatum; stems and roots of *Equisetum ramosissimum*; and leaflets, petioles and rhizomes of Marsilea minuta against Candida albicans were studied in vitro. All the tested plants exhibited antifungal properties against C. albicans, although the inhibitory properties of the extracts varied depending on the type of extract and plant part used. The aqueous stem extract of E. ramosissimum recorded the highest inhibitory effect.

Antiviral effect:

Husson (1986): A test for antiviral properties using cell cultures and the results with a series of plant extracts (alcoholic (content unclear) extract of fresh plant of E. arvense (5 : 1)) are described. Equisetum arvense showed an antiviral effect.

Suganda (1983): Ethanolic extracts of 41 species of plant indigenous to France were screened for antiviral activity. Extracts of Matricaria chamomilla, M. inodora and Anthyllis vulneraria inhibited in vitro replication of human polio virus type 2 and human herpes virus type 1. Extracts of Bryonia dioica inhibited human polio virus replication. E. arvense had no antiviral effect.

Assessor's comments:

A lot of in vitro test have been performed in order to examine the mechanism of the effects which attribute to the use in diseases of the urinary tract. From the in vitro tests the antioxidant effect may contribute to the efficacy. The anti-inflammatory activity could be at least in part due to the presence of compounds with antioxidant activity. E. arvense shows in the majority of tests performed an antioxidant activity for which the polyphenolic constituents appear to be responsible. The tests show that other Equisetum species (E. telmateia, E. ramosissimum) may be more potent antioxidants.

Equisetum arvense showed no antimicrobial activity in the tests performed. Additionally E. arvense showed no reproducible antiviral and antifungal effect. An antimicrobial contribution to the efficacy is implausible.

Anticancer and antithrombin activity:

Goun (2002): A chromogenic bioassay was utilized to determine the antithrombin activity of the methylene chloride and methanol extracts prepared from forty-five plants of Russia, including E. arvense. Mouse leukemia cells (L1210) were utilized to screen these extracts ("200 g plants, dry weight extracted in sequence with methylen chloride (24 h) and ethanol"), for activity against cancer. The results indicated that eight plant extracts demonstrated 90 % or higher activity in the inhibition of thrombin. Also, nine methanol extracts demonstrated activity of 90 % or higher in the inhibition of mouse leukemia L1210 cells. The methylen cloride extracts of E. arvense demonstrated high activity against both thrombin and cancer (84/99 %). The ethanol extracts of E. arvense demonstrated 45/38 % activity against thrombin and mouse leukemia L1210 cells.

Assessor's comments:

The anticancer effect and antithrombin activity correspond with the traditional use as anticancer preparation and in hematopoietic diseases. A negative point of the study is the fact that the DER of the extracts and the ethanol content (%) is not described clearly. The results show a strong dependence of the effect from the used vehicle methylene chloride or ethanol. The methylene chloride extract had approximately the double power in the anticancer activity as compared with the ethanolic fraction. The results indicate that the lipid fraction may contribute to the effect. A water extract, or an ethanolic water extract were not tested. For the clinical relevance additional in vivo studies must be conducted. The effects must be taken into consideration at the toxicological assessment.

Hepatoprotective activity:

Oh (2004): The hepatoprotective activity-guided fractionation of the MeOH extract of Equisetum arvense L. (Equisetaceae) resulted in the isolation of two phenolic petrosins, onitin (1) and onitin-9-O-glucoside (2), along with four flavonoids, apigenin (3), luteolin (4), kaempferol-3-O-glucoside (5), and quercetin-3-O-glucoside (6). Among these, compounds 1 and 4 exhibited hepatoprotective activities on tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, displaying EC(50) values of 85.8 +/ -9.3 microM and 20.2 +/- 1.4 microM, respectively. Silybin, used as a positive control, showed the EC(50) value of 69.0 +/- 3.3 microM. Compounds 1 and 4 also showed superoxide scavenging effects (IC(50) = 35.3 +/- 0.2 microM and 5.9 +/- 0.3 microM, respectively) and DPPH free radical scavenging effect (IC(50) of 35.8 +/- 0.4 microM and 22.7 +/- 2.8 microM, respectively). The authors concluded that these results support the use of this plant for the treatment of hepatitis in oriental traditional medicine.

Selenium content:

Lovkova (1993): A total of 192 plant species belonging to 44 families were screened for their selenium contents. The highest selenium contents were found in the rhizomes of Siberian liquorice [Glycyrrhiza sp.] (1.12 mug/g DM), the leaves of ash gum [Myrtaceae] (0.64 mu/g), the buds of weeping birch [Betula sp.] (0.70 mug/g), and the shoots of common melilot [Melilotus], joint fir [Ephedra sp.] and meadow horsetail [Equisetum arvense](0.80, 0.68 and 0.60 mug/g, respectively). Based on plant and soil analyses, the highest coefficients of biological accumulation, defined as the ratio of plant selenium content versus soil selenium content, were calculated for ash gum (53.3) and meadow horsetail (30.0). It is suggested that these species might be of therapeutic value in the treatment of selenium deficiency.

Assessor's comment:

The results of the studies on Selenium content and the hepatoprotective activity do not highlight any specific activity for the relevant indication or safety concerns.

Pharmacological interactions:

Schauss (2006): A bacterial reverse mutagenicity assay has shown that Urologic (TM), a dietary supplement containing Crateva nurvala bark extract and standardized Equisetum arvense (composition unknown), is non-mutagenic in all six strains. To determine if Urologic is a potential inducer of human cytochrome P450 (CYP1A2 and CYP3A4), an assay using immortalized human hepatocytes (Fa2N-4 cells) found a lack of interference of P450 cytochromes as preliminary evidence of its safety when taken with other medications.

Scott (2006): High-throughput enzyme inhibition screening assays were used to quantify the effect of ethanol extracts (1:5) extraction solvent ethanol: water 55 % (v/v)) of 2 accessions of 10 North American (NA) botanicals against the activity of the human cytochrome P450s: CYP3A4, CYP19, and CYP2C19. The fluorescence readings were measured by a Cytofluor 4000 Fluorescence Measurement System plate reader with excitation and emission at 485/20 and 535/25 with two gains (50 and 75). In addition, phytochemical biomarkers within each extract were identified and quantified using HPLC-MS or GC. Extracts containing uncharacterized phytochemicals were identified taxonomically. The overall objective was to describe the relationship between types and quantities of phytochemicals in ethanol extracts and their ability to inhibit CYP activity. The top three inhibitors of CYP3A4 were Gaultheria procumbens L. leaf > Rhodiola rosea L. root > Arctostaphylos uva-ursi L. Spreng leaf; of

CYP19 were R. rosea root > Rhododendron groenlandicum (Oeder) Kron & Judd leaf > A. uvae-ursi leaf; and of CYP2C19 were Achillea millefolium L. leaf and flower > Vaccinium sp. L. leaf > Polygala senega L. root. Equisetum arvense L. leaf, Arctium lappa L. root, and P. senega root had the lowest effect on CYP3A4 and CYP19 activity. Furthermore, the concentration of certain phytochemical markers varied significantly between accessions (i.e., rosarin and essential oils), suggesting that the extent of metabolic inhibition is directly dependent upon the concentration of bioactive constituents in an extract.

Assessor's comments:

The two studies have shown contradictory results. Since Schauss (2006) describes results of a combination preparation with limited data to the extracts, the results of the study from Scott (2006) are of more interest. They show a low inhibitory effect on CYP3A4 and CYP19 activity. The data have to be taken into consideration at the risk assessment of clinical interactions. (see II.3.3.5.2)

In-vivo tests

Diuretic effect:

The diuretic effect of E. arvense was tested in older in vivo studies. In a study published in 1912 an E. arvense preparation showed a diuretic effect on dogs about 15-20 % compared with water [Cow, 1912].

About 650 diuretic trials on rats were prepared by Wachter (1938). The diuretic effect of a 6 % infuse was tested in 210 rats. Compared with water, after 30 minutes the effect was about 196 % higher, after 45 min 79 % and after 60 min about 39 %. The speed of the elimination of urine was much higher in the tea group compared with the water group. A negative fluid balance after 4 hours could not be determined. The author concluded that horsetail is a fast and good diuretic. Similar were the experiments of Kreitmair (1936 and 1953) and Herre (1937).

Lower diuretic effects of an E. arvense decoct were shown by Volmer (1937, 1939, 1940, 1941) on 55 mice (39 % diuretic effect), 20 rats (13 % diuretic effect), 20 rabbits (23-50 % diuretic effect and about 30 % chloride). The authors compared the collected urine of 24 hours of the tea group with the water group. The content of 0,948 % chloride in Equisetum arvense was considered.

No diuretic effect was detected by Jaretzky (1938, 1940) and Breitwieser (1939).

Assessor's comments:

The results of Wachter (1938) indicate a faster excretion of the urine and no negative fluid balance. The results of Volmer (1937) indicate a diuretic mechanism with negative cellular fluid volume, and the data from Jaretzky (1938, 1940) and Breitwieser (1939) do not show any effect. In summary the mechanism of the diuretic activity of Equisetum arvense is not known, but a low diuretic effect was shown in three different animal species.

Pérez Gutierrez (1985): Chloroform extracts of 4 Equisetum spp. (20 g herb /250 ml chloroform, vacuum evaporated, suspended in ml water; single dose 50 mg extract /kg mice, corresponding ca. 4 mg herb/kg mice) were compared for activity with standard diuretics in studies with mice. The most active was in E. hiemale [hyemale] var. affine, followed by E. fluviatile, E. giganteum and E. myriochaetum. E. hiemale was a more effective diuretic than any of the three standards. The tested dosage showed significant increase in sodium, potassium and chloride excretion, as well as a rise in the urine pH level. The authors concluded that the mechanism of action may be similar to that of hydrochlorothiazide.

Assessor's comments:

From the point of view of the wide traditional use, different Equisetum species have been used as diuretics. The study indicates that the E. species have different potential in diuretic activity. The current study does not analyze E. arvense, the relevant E. species used in Europe. It cannot be concluded whether other E. species might be more potent diuretics.

<u>Antiurolithiasic effect:</u>

Grases (1994): The effects of seven plants that have been applied to prevent and treat kidney stone formation (Verbena officinalis, Lithospermum officinale, Taraxacum officinale, *Equisetum arvense*, Arctostaphylos uvae-ursi, Arctium lappa and Silene saxifraga) have been studied using 12 female Wistar rats for each plant. The studied herbs were given by infusion. E. arvense infusion was prepared from 3 g herb/l water. Variations of the main urolithiasis risk factors (citraturia, calciuria, phosphaturia, pH and diuresis) have been evaluated. No relevant difference was found in diuresis. None of the studied infusions affect calciuria and citraturia values. The authors concluded that beneficial effects caused by these herb infusions

on urolithiasis can be attributed to some disinfectant action, and tentatively to the presence of saponins. Some solvent action can be postulated with respect to uric stones or heterogeneous uric nucleus, due to the pH -increasing capacity of some herb infusions.

Assessor's comments: The results of the study do not support the use for prevention and treatment in kidney stone formation. The results are also contrary to the use as diuretic. From the point of view that only 12 rats were tested for each plant, the results are only of minimal value.

Antinociceptive and anti-inflammatory properties:

Do Monte (2004): In this study antinociceptive and anti-inflammatory effects of hydroalcoholic extract of stems from Equisetum arvense ("the dried stems were extracted with 50 % ethanol-water, the ethanol was evaporated and the extract was stored in the concentration of 5 %") in mice were evaluated. The extract (10, 25, 50 and 100 mg kg-1, i.p.), reduced the writhing induced by acetic acid in 49, 57, 93 and 98 %, respectively, compared with the control group treated with saline. In the formalin test, 50 and 100 mg kg-1 (i.p.) extract reduced the licking activity in 80 and 95 % of the animals in the first phase, but in the second phase only the latter dose diminished the licking time (in 35% of the animals). In both phases, naloxone failed to revert the analgesic effect of the extract.

In the hot-plate test, the extract at 100 and 200 mg kg-1 did not change the latency to licking or jumping. In the carrageenan-induced rat paw oedema, the extract at 50 mg kg-1 reduced the paw oedema 2 h (25 %) and 4 h (30 %) after carrageenan administration. The dose of 100 mg kg-1 caused reduction of the paw oedema (29 %) only 4 h after carrageenan administration. The authors concluded that this extract exhibits an antinociceptive (analgesic) effect in chemical models of nociception which is not related to the opioid system, as well as significant anti-inflammatory properties.

Assessor's comments:

The results of the studies may contribute to the plausibility of the traditional global use in diseases of the urinary tract (not for the use as diuretic). The anti-inflammatory effect may contribute to the traditional topical use.

Sedative and anticonvulsant effects:

Dos Santos (2005): The hydroalcoholic extract of Equisetum arvense (HAE) ("the dried stems were extracted with 50 % ethanol-water, DER unclear") tested i.p. at the doses of 200 and 400 mg/kg showed a significant activity on the open-field, enhanced the number of falls in the rota-rod reducing the time of permanence in the bar and increased the sleeping time (46 % and 74 %) in the barbiturate-induced sleeping time. On the contrary, in the elevated plus maze, the doses of 50, 100 and 150 mg/kg did not affect the evaluated parameters. HAE presented anticonvulsant and sedative effects.

In the pentylenetetrazole-seizure test the hydroalcoholic extract of Equisetum arvense increased the first convulsion latency, diminished the severity of convulsions, reduced the percentage of animals which developed convulsion (50% and 25 %) and protected animals from death.

An acute toxicity study showed that in rats the extract at doses of 2 and 5 g /kg i.p. induced mortality in 12 % and 37,5 % of the animals. Because the LD50 values were higher than 5 g/kg, the extract was considered as non-toxic.

A phytochemical analysis detected the presence of tannins, saponins, sterols and flavonoids.

Cognitive enhancement effects:

Dos Santos Junior (2005)(2) has investigated if the chronic administration of the hydroalcoholic extract of stems from *Equisetum arvense* (HAE) reverses the cognitive impairment in aged rats; moreover the in vitro antioxidant properties were evaluated. The chronic administration of HAE at dose of 50 mg/kg, i.p. improved both short- and long-term retention of inhibitory avoidance task and ameliorated the cognitive performance in reference and working memory version of the Morris Water Maze. No differences were found between all three groups of young controls, aged controls and EHA-treated animals with regard to the open field and elevated plus maze tests. No toxicity manifestations were observed during the treatment for eight weeks. In vitro assays revealed that HAE diminished the thiobarbituric acid reactive substances as well as the nitrite formation, but did not alter the catalase activity. Thus, the cognitive enhancement effects of the HAE may be attributed, at least in part, to the antioxidant action.

Assessor's comments:

The anticonvulsant, sedative and enhancement effects were examined intraperitoneally. The effects were dose dependent. The i.p. administration is one point to make it impossible to extrapolate the data to the human use. A further point is the unknown dosage because the

extract is not described in detail. The DER of the administered extract is unknown. The relevance for the clinical use is to be examined in the clinical assessment.

The results of the studies conducted by the Brazil investigators referring the anticonvulsant, sedative and enhancement effects do not highlight any specific activity for the relevant indication. Under clinical conditions the symptoms were not described. In summary it is proposed not to include the effects in the text referring the "use of machines" or "special warnings".

Tumor-damaging capacity:

Belkin (1952): Materials from 30 plants, used as diuretics, were tested at a single subcutaneous dose for necrotisizing capacity against Sarcoma 37 implanted in CAF1 mice. Four preparations were used for each plant material: An aqueous suspension, an olive-oil suspension, an alcohol extract, and an acid extract.

From E. arvense was used the aqueous suspension (1mg/g mouse), olive-oil suspension (1mg/g mouse), alcoholic extract ((1mg/g mouse) and an acid extract (0.02 ml pro g mouse, 0.01 ml acid extract represents about 5 mg per g of the original plant material).

Materials from 12 plants produced grossly and histologically demonstrable damage. A relatively pronounced effect was induced with: Dioscorea villosa, Oxydendrum arboreum and Spiraea ulmaria. Tumor damage of lesser degree was exhibited by 9 other plants: Apocynum androsaemifolium, Asparagus officinalis, Capsella bursa-pastoris, *Equisetum arvense*, E. hyemale, Hydrangea arborescens, Juniperus communis, Parietaria officinalis, and Polytrichum juniperum. E. arvense aqueous suspension, olive-oil suspension, alcohol extract showed no tumour damaging capacity. The acid extract showed "a lesser degree of induced effect".

Assessor's comments: The results for E. arvense aqueous suspension, olive-oil suspension and alcohol extract are negative. The effect of the acid extract was equivocal.. The tests were performed with a subcutaneous single dose. The results do not highlight any specific activity for the relevant indication or safety concerns on the oral use.

Hypoglycaemic effect:

Cetto (2000): The hypoglycaemic effect of water extracts as well as of butanolic extracts prepared from the aerial parts of Equisetum myriochaetum was examined in streptozotocin-induced diabetic rats. A single oral administration of the water extract (WE) at doses of 7 and 13 mg/kg and of the butanol extract (BE) at doses of 8 and 16 mg/kg significantly ($P<0.001$) lowered the plasma glucose levels in diabetic rats within three hours of administration. As a reference drug, glibenclamide was used and showed, at a dose of 3 mg/kg, similar hypoglycaemic effects to the tested extracts. Three kaempferol glucosides and one caffeoyl glucoside were isolated from the drug and were shown to be the main constituents in both extracts.

Assessor's comments:

The hypoglycaemic effect was realized by oral administration of aqueous extracts. The result is to be considered in the clinical assessment.(See II.3.1.1.2)

II.2.1.2 Assessor's overall conclusions on pharmacology

Indication: Oral use: Traditionally used to promote renal elimination function

Assessors comments:

A diuretic is any drug that tends to increase the flow of urine from the body. Diuretics also decrease the extracellular fluid volume and are primarily used to produce a negative extracellular fluid balance.

In summary the data for the efficacy of horsetail are not appropriate to document a diuretic aaction with a negative extracellular fluid balance. The results of Wachter (1938) indicate a faster excretion of the urine and no negative fluid balance. The results of Vollmer (1937) indicate a diuretic mechanism with negative cellular fluid volume and the data of Jaretzky (1938, 1940) and Breitwieser (1939) did not show any effect. Since then no in-vivo studies addressing the diuretic effect of E. arvense have been performed.

For horsetail it is shown that saponins, which are regarded as effective diuretic constituents in the literature, are absent. Pharmacological and pharmacokinetical data of flavonoids and other phenolics as possible effective constituents have been presented. Flavonoids and the high potassium content may contribute to the efficacy.

Therefore the following wording is proposed:

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

In summary the pharmacological data support the traditional indication but they are not sufficient to demonstrate well established use. The pharmacological effects and efficacy are only plausible on the basis of long standing use and experience (traditional use) (Veit, 1994). The following wording is recommended in the monograph:

"Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended."

II.2.2 Pharmacokinetics

II.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)

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

In vivo data on pharmacokinetics are absent. See II.3.1.2

II.2.3 Toxicology

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

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

Single and repeat dose toxicity:

Aswal (1984): The LD50 for an undefined extract of E. arvense was > 1000 mg /kg i.p. in mice.

Maeda (1997): The effects of dietary field horsetail (Equisetum arvense L.) powder on lipid components were examined in male Sprague-Dawley rats fed on a 20 % casein diet with or without cholesterol (0.5 % cholesterol and 0.15 % sodium cholate) for 14 days. The rats were given free access for diet. The ingestion of E. arvense L. powder, 0.4 or 4.0 %, did not influence food intake or growth. However, a cholesterol diet with E. arvense L. at 4 % caused dermatitis at the neck, head and back in about 20-65 % of the rats. This dermatitis was

reversed when the diet was changed to a standard commercial pelleted diet. There were no apparent effects on serum or liver lipids in the rats fed with E. arvense L. irrespective of the dietary cholesterol. Serum immunoglobulin E (IgE) concentrations, measured by enzyme-linked immunoassay, revealed that the induction of IgE may not necessarily be involved in the dermatitis caused by the intake of E. arvense L. It was concluded that the ingestion of large amounts of E. arvense L. as cooking material is not recommended for those on a cholesterol-rich diet.

Dos Santos (2005): The acute toxicity study of the hydroalcoholic extract of Equisetum arvense (HAE) ("the dried stems were extracted with 50 % ethanol-water, DER unclear") showed that in the dose of 2 and 5 g /kg i.p. rat the extract induced mortality in 12 % and 37.5 % of the animals. Because the LD50s was higher than 5 g/kg the extract was considered as non-toxic. The author noted that chronic administration of the dose utilized in the study did not result in toxicity which may support the intense, chronic and popular use.

Dos Santos (2005)(2): No toxicity manifestations were observed during treatment of eight weeks of HAE (hydroalcoholic extract of stems from Equisetum arvense, DER unclear) at a dose of 50 mg/kg, i.p. in rats.

Genotoxicity:

Joksic (2003): The authors assessed the in vitro cytogenetic effects of extracts of the commonly used medicinal plants Equiseti herba, Ononidis radix, and Uvae ursi on irradiated human blood lymphocytes. They examined the acquired micronucleus formation in unirradiated and irradiated samples of cultured blood lymphocytes using the cytochalasin block micronucleus test (CBMN).

An alcoholic extract of *Equiseti herba* had weak clastogenic properties, increasing the yield of micronuclei in unirradiated samples and reducing the level of radiation-induced micronuclei in a concentration-dependent manner. In the control, unirradiated samples, 36.8% of micronuclei were centromere-positive (MNC+), while in the irradiated ones the percentage of MNC+ ranged from 10.8-15.3%, indicating a clastogenic mechanism for the micronuclei formation.

Schauss (2006): A bacterial reverse mutagenicity assay has shown that Urologic (TM), a dietary supplement containing Crateva nurvala bark extract and standardized Equisetum arvense, is non-mutagenic in all six strains investigated.

Other toxicity studies have not been performed

II.2.3.2 Assessor's overall conclusions on toxicology

Single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies do not exist according to the state of the art and the relevant guidelines. The few data are only results from studies with other intention. The cited studies give less information on the acute and chronic toxicity since the DER of the extracts is unclear and the route of administration was mostly i.p. and not oral.

In the cytochalasin block micronucleus test (CBMN) an alcoholic extract of Equiseti herba had weak clastogenic properties, increasing the yield of micronuclei in unirradiated samples and reducing the level of radiation-induced micronuclei in a concentration-dependent manner (Joksic, 2003). The study was performed to detect the mechanism of action of the tested plants. The blood from only one person was tested. In the highest concentration 4.2 % of cells had micronuclei. In the range of 4-5 % the test is often cut off. The effect is in the borderline range.

In an in vivo study (Belkin, 1952) E. arvense aqueous suspension, olive-oil suspension or alcohol extract did not show any tumour damaging capacity. The acid extract showed "a lesser degree of induced effect". In animals, in the chronic administration of the hydroalcoholic extract of stems from Equisetum arvense in rats no toxicity manifestations were observed during treatment (Dos Santos 2005(2)).

The dermatitis caused by the intake of E. arvense in a cholesterol-rich diet is not relevant with respect to the therapeutic use. The rats consumed E. arvense powder in "free access". In Japan E. arvense is consumed as food.

In summary the data on toxicity are insufficient. Therefore for horsetail a traditional monograph and no list entry are recommended.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

II.3.1.1 Pharmacodynamics

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

Lemus (1996): A 10 % infusion of Equisetum bogotense (collected in San Juan de Pirque, Chile) was administered to 25 healthy volunteers at a single daily dose equivalent to 0.75 g plant/person for 2 consecutive days during a 6-day study. Effects on water balance and urinary biochemical parameters were determined. The infusion showed a significant diuretic effect. The analysis of urinary electrolytes showed a significant increase in sodium, potassium and chloride excretion with respect to the control group, but within normal physiological limits. No adverse effects were noted.

Revilla (2002): The hypoglycaemic effect of a water extract from aerial parts (0.33 g/kg) of Equisetum myriochaetum was analyzed in 11 recently diagnosed type 2 diabetic patients. A single dose of this extract was orally administered. Glucose and insulin were determined at 0, 30, 60, 90,120 and 180 min after administration. The same patients served as the control group and received only coloured water as placebo. The administration of the extract significantly reduced the blood glucose levels of the type 2 diabetic patients within 90, 120 and 180 min. There were no significant changes in the insulin levels. The results demonstrate that the water extract of the aerial parts of E. myriochaetum shows a hypoglycaemic effect in type 2 diabetic patients, starting 90 min after its administration.

Sparavigna (2006) : Two clinical trials were carried out with a new formulation based on Equisetum arvense and a sulfur donor in a hydro-alcoholic solution, with the aim to evaluate the efficacy and preventive activity of this new formulation on nail alterations. For the first study, 36 women with nail plate alterations applied the test product every night on the nails of one hand, randomly assigned for 28 days. The results demonstrated a significant reduction in longitudinal grooves as well as an 85% reduction in patients reporting lamellar splitting of treated nails, while no significant change was observed in untreated controls. In the second study, 22 women with nail plate alterations applied the test product randomly on the nails of one hand only, on alternating days, preferably in the evening, for 14 days. After drying, a common nail polish was applied on the finger nails of both hands and removed by an organic solvent every other day before the application of the next product . The results from this

study showed a significant decrease (P< .001) of lamellar splitting compared to baseline with the test product (82 % of cases).

II.3.1.1.2 Assessor's overall conclusions on pharmacodynamics

Clinical pharmacological data of Equisetum arvense preparations do not exist. The plausibility of the efficacy is based on the traditional medicinal use and supported by the non clinical data.

One Study with a different Equisetum species, E. bogotense, showed a diuretic effect (Lemus, 1996). The clinical study is consistent with results of in-vivo studies that indicate that the E. species have different potential in diuretic activity. The current study does not analyze E. arvense, the relevant E. species used in Europe.

A human study on Equisetum (E. myriochaetum) showed a hypoglycaemic effect (Revilla, 2002). It is a disadvantage that the study was conducted only with one single dose, and the analyzed product contains a different Equisetum species. In summary the data are consistent with the in vivo data, based on Equisetum myriochaetum. General data on the base of other plant species are not considered in the labelling. From the traditional use of E. arvense no clinical hypoglycaemic effects are reported.

The study by Sparavigna (2006) has been conducted with a new formulation. The results are not relevant for the traditional use indications.

II.3.1.2 Pharmacokinetics

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

Graefe, 1999): Flavonoids and hydroxycinnamic acids are polyphenolic compounds present in our daily diet in form of tea and vegetables as well as in herbal remedies used in phytomedicine. In order to examine the metabolism and renal excretion of these compounds a standardized extract from horsetail (Equisetum arvense) was administered to 11 volunteers following a flavonoid-free diet for 8 days. 24 h urine samples were collected and analyzed by HPLC-DAD. The putative quercetin metabolites, 3.4-dihydroxyphenylacetic acid or 3,4-dihydroxytoluene could not be detected in urine in any sample. The endogenous amount of homovanillic acid, generally regarded as one of the main quercetin metabolites, was 4 +/- 1 mg/d and did not increase significantly. Hippuric acid, the glycine conjugate of benzoic acid, increased twofold after drug intake. Thus, the degradation to benzoic acid derivatives rather

than phenylacetic acid derivatives seems to be a predominant route of metabolism. The results of this pilot study should give rise to additional pharmacokinetic investigations in humans.

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

Clinical data on absorption, distribution and pharmacokinetic interactions are few. The data show that flavonoids and hydroxycinnamic acids seem to be predominantly metabolized to benzoic acid derivates than to phenylacetic derivates.

II.3.2 Clinical Efficacy[6]

II.3.2.1 Dose response studies

Not available.

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

Hesse, 1985): Harntee 400 is recommended for the stone carrier's daily fluid intake programme. Consitutents include Calendula, Equisetum, Fotniculum, Juniperus, Glycyrrhiza, Ononidis, Orthosiphonis and Betulus extracts, and arbutin. In 20 calcium oxalate stone carriers the p.o. treatment with Harntee 400 (TAD) resulted in diuresis and a leveling of concentration peaks of most urinary parameters investigated. Citric acid elimination in urine increased, and urine pH stabilized in a range supporting litholysis. No intolerance was noted.

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

Not available.

II.3.2.4 Assessor's overall conclusions on clinical efficacy

The data do not fulfil the requirements of a well-established medicinal use with recognised efficacy and are not eligible for a marketing authorisation. The only clinical study has been conducted with a combination product in 20 patients only. The efficacy is plausible on the basis of long standing use and experience.

II.3.3 Clinical Safety/Pharmacovigilance

II.3.3.1 Patient exposure

[6] In case of traditional use the long-standing use and experience should be assessed.

II.3.3.1 Adverse events

The national database of Germany contains 3 reports (database request from 21.06.2007 on adverse events (AE) connected to preparations with a single herbal preparation containing horsetail. Subsumed are all horsetail species in all pharmaceutical forms. Two cases refer to allergic reactions e.g. rash (BfArM case nr. 03015301 and 91009533). The case 91009533 refers to a local allergic reaction after horsetail bath. In the case 03015301 (oral consumption), because of negative rechallange it was concluded the rash was not related to the consumption of the E. arvense product.

There is one case of an adverse event of two (elder) people with gastrointestinal reactions as nausea and diarrhoea and sleep disorder and weariness after horsetail tea consumption (BfArM case nr.97001924). The patients told their pharmacist that they have also diverse "complaints of old age", which are unknown. Also it is unknown if the patients took other concomitant preparations for these complaints. There is no hint on none-drug related explanations as infectious diseases. The patients considered the adverse reactions as toxic reactions. Adulteration with E. palustre was ruled out. It was considered that the intake of horsetail is not related to the adverse event. The case is insufficiently documented.

The adverse events are labelled: "Mild gastrointestinal complaints and allergic reactions (e.g. rash) have been reported. The frequency is not known."

II.3.3.2 Serious adverse events and deaths

Kolettis (2005): The authors report a case of a transient complete atrioventricular block in a 38-year-old man, after intake of a mixture of herbs (not trade name, Ribes nigrum, Helicrysum italicum, Taraxacum officinale, Uncaria tomentosa, Vitamin C, Vitamin E, Fumaria officinalis, Melissa officinalis, Equisetum arvense in unclear composition and DER) for two days, intended to aid cigarette smoking cessation. Since all other causes of conduction disturbances were excluded, a side effect of the herbal remedy was suspected as the most likely explanation.

Assessor's comments:

The patient has a consumption of various other plants preparations with not known medicinal ingredients (Helicrysum italicum,). From Uncaria tomentosa it is well known that it contains oxindol alkaloids which are associated to have a negative chronotropic and inotropic cardiac effect. (Länger,2002). Because of the concomitant plants taken by the patient, a

causal relationship between the ingestion of Equisetum arvense and the transient complete atrioventricular block is unlikely.

Whiting (2002): Six patients have been presented with clinical, biochemical and histological evidence of severe hepatitis after taking herbal remedies. Five patients took a combination of herbs (one patient took a combination of chaperal, dandelion, Whitania somnifera, horsetail and Echinacea) and presented with jaundice, fatigue and pruritus. The authors concluded that healthcare providers and members of the public should be aware of the potential adverse effects of these remedies.

Assessor's comment:

A causal relation to horsetail is not probably, because the medication contained other hepatotoxic plants.

Perazella (2002): Certain medical herbs (such as Equisetum arvense) may induce potentially life threatening hyperkalemia in patients with underlying risk factors (chronic renal insufficiency, hypoaldosteronism, and use of other potassium altering medication).

Agustin-Ubide MP 2004]: A patient reported contact dermatitis when preparing a meal from carrot. She tolerated food ingestion. While she used Equisetum arvense for loss of weight, she showed a sensation of pharyngeal occupation, cough, breathing difficulty and itching after the ingestion of cooked carrots. The authors concluded that Equisetum arvense (with a similar protein as carrots) possibly increased the symptoms.

Assessor's comments:

Patients with known hypersensitivity to Equisetum arvense and decreased cardiac and renal function are ruled out under contraindications. Because there is only one case with a hypothetical relation to horsetail it is proposed not to give information about a possible increase of the allergy symptoms from carrots under "Special warnings and precautions for use":

Other events:

Henderson (1952): The field occurrence of Equisetum poisoning was observed in 3 horses. Two of these responded favourably to daily subcutaneous injections of 100 mg of thiamine hydrochloride for 4 days. Similar symptoms were produced in a 2-year old colt fed for 35 days on a ration consisting solely of Equisetum-containing hay from the same field. Thiamine

injections which were begun after the animal was unable to rise failed to bring about recovery. In vitro experiments demonstrated that the Equisetum caused an almost complete destruction of thiamine and of the thiamine content of oats and dried brewer's yeast. The enzymatic nature of this destruction was indicated.

Assessor's comments:

In the literature there are reports on a "thiamine like factor" which is discussed to be responsible for toxicity in animals, particularly in horses, as muscle weakness, weight loss, abnormal pulse rate, cold extremities and fever, symptoms similar to nicotine poisoning (Pohl, 1955), (Hamon, 1992), (Jean-Blain, 1973). The Canadian government department decided that, the manufacturers must prove that their E. arvense products are free of thiaminase activity, because the "thiamine like factor" destroys thiamine in the stomach of monogastric animals, including man, which can lead to irreversible brain damage in thiamine deficient people (Hamon, 1992).

For the toxicity in horses and cows the presence of aconitic acid and the presence of one ore more alkaloids is discussed by Rapp (1954). Palustrin, an ingredient of E. palustre, is also dicussed (Frohne, 1984). Veit (1987) noted that 1 % of E. palustre in the hay can cause heavy damages. The minimal content of alkaloids which are well soluble in water (tea) does not seem to be the reason for the toxicology of animals, because in humans such adverse reactions have not been registered.

Enzymes are inactivated by preparing ethanolic extracts or at high temperatures which are used at the preparation of tea or commercial expressed juice (Fabre, 1993). In Europe adverse events such as brain damage in thiamine deficient people, or toxic reactions similar to nicotine poisoning have not been observed.

II.3.3.3 Laboratory findings

No data available.

II.3.3.4 Safety in special populations and situations

No data available.

II.3.3.4.1 Intrinsic (including elderly and children) /extrinsic factors

No special studies about the use in children under 12 years or elderly exist. For children under 12 years the use of diuretic drugs in self medication is not appropriate. Therefore the use for children is not recommended.

II.3.3.4.2 Drug interactions

Validated interaction studies do not exist for horsetail preparations. The Commission E monograph, published 18.09.1986 for Equisetum herba, gives the information “not known”.

The above mentioned “interaction studies” are insufficient to rule out any interaction. Clinical interactions with other drugs have not been reported (Mills, 2005).

An in-vitro study gives the information that Equisetum arvense has a low effect on CYP3A4 and CYP19 activity (Scott, 2006). A clinical interaction study was conducted with a combination of Crateva nurvala bark extract and Equisetum arvense in undefined composition and dosage. There was a lack of interference with CYP450 (Schauss, 2006).

II.3.3.4.3 Use in pregnancy and lactation

Studies to carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies do not exist. In the cytochalasin block micronucleus test (CBMN) Equiseti herba had weak clastogenic properties. The Commission E monograph, published 18.09.1986 for Equisetum herba, does not give a contraindication in pregnancy and lactation. From the traditional use no negative clinical observations in pregnancy and lactation exist (Mills, 2005).

In summary, the safety data for use in pregnancy and during lactation are not sufficient; therefore it is proposed that E. arvense preparations should not be recommended.

The following text is proposed in the monograph:

“In the absence of sufficient data the use during pregnancy and lactation is not recommended.”

II.3.3.4.4 Overdose

No case of overdose has been reported.

II.3.3.4.5 Drug abuse

Drug abuse has not been reported

II.3.3.4.6 Withdrawal and rebound

None reported.

II.3.3.4.7 Effects on ability to drive or operate machinery or impairment of mental ability

Not relevant

II.3.3.5 Assessor's overall conclusions on clinical safety

The efficacy of Equisetum products is plausible on the basis of long standing use and experience. The traditional use over a long period has shown that E. arvense is not harmful when it is used in the specified conditions. However a long standing use does not exclude the possibility that there may be concerns with regard to the product safety. Therefore E. arvense should not be used in children under 12 years, during pregnancy and lactation, and in patients suffering from conditions where a reduced fluid intake is recommended (e.g.cardiac or renal diseases) or in patients with known hypersensitivity to horsetail. Interactions are considered as clinical irrelevant and are not mentioned in the monograph. Special warnings to undesirable effects are given. The herbal substance is traditionally used over a period of two to four weeks. The duration of use is limited to one week if the symptoms persist during the use of the medicinal product.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

Despite of their long tradition, horsetail products do not fulfil the requirements of a well-established medicinal use with recognised efficacy and an acceptable level of safety.. Horsetail is considered to have an impact on the protection of public health on the basis of the long medicinal tradition in the specified conditions. Therefore horsetail products may be considered as traditional herbal medicinal products.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH ON EQUISETUM *ARVENSE* L., HERBA

III.2 LITERATURE REFERENCES