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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Herniaria glabra* L., *H. hirsuta* L., *H. incana* Lam., herba

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

Draft

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|---|--|
| Herbal substance(s) (binomial scientific name of the plant, including plant part) | <i>Herniaria glabra</i> L., <i>H. hirsuta</i> L., <i>H. incana</i> Lam., herba |
| Herbal preparation(s) | Comminuted herbal substance |
| Pharmaceutical form(s) | Comminuted herbal substance as herbal tea for oral use |
| Rapporteur(s) | R Länger |
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Herniaria glabra* L., *H. hirsuta* L., *H. incana* Lam., herba. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

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

- Herbal substance(s)

According to the monograph 2010/056 in the Austrian Pharmacopoeia the herbal substance is defined as the dried, flowering aerial parts of *Herniaria glabra* L., *H. hirsuta* L., *H. incana* Lam. or a mixture of them (Austrian Pharmacopoeia 2017).

There is no Ph. Eur. monograph published.

During the update of the monograph for the Austrian Pharmacopoeia commercial samples with defined origin were investigated. It became evident that beside *H. glabra* two hirsute species can be detected. Comparison with authenticated herbarium specimen revealed that *H. hirsuta* and additionally the densely grey hairy *H. incana* is in use as plant source. The descriptions and tests in previous pharmacopoeia monographs (like in Austrian Pharmacopoeia 1960) did not allow a differentiation between *H. hirsuta* and *H. incana*. Therefore also the historical medicinal use of *H. incana* is highly probable. Current commercial samples consist mainly of parts of *H. glabra* and *H. incana* (Strasser 2011).

- Herbal preparation(s)

Comminuted herbal substance.

Constituents:

Triterpenesaponins: 3-9%, mono- and bisdesmosidic derivatives of medicagenic acid (Wichtl 2016). After complete hydrolysis Kozachok *et al.* (2016) determined as sugar components D-rhamnose, D-arabinose, D-fucose, D-xylose, D-mannose, D-glucose, D-galactose, D-pinitol, myo-inositol, D-mannitol, D-dulcitol. Glucose was found as the predominant sugar with 33.4 mg/g in *H. glabra*.

Flavonoids: 0.2-1.2%, mainly derivatives of quercetine and isorhamnetine (Maleš *et al.* 2013, Wichtl 2016).

Coumarins: 0.1-0.4%, e.g. herniarine, umbelliferone (Wichtl 2016).

Tannins: small amounts (Wichtl 2016).

Essential oil: Lazari *et al.* (2000) investigated *H. incana* collected in Greece. The content determined by steam distillation was 0.1%. Main components were 6,10,14-trimethyl-2-pentadecanone and tridecanal.

Maltol-derivatives (Kozachok *et al.* 2018)

Phenolic acids: caffeic and chlorogenic acid (0.34% in *H. glabra*, Maleš *et al.* 2013)

Amino acids: alanine, asparaginic acid, glutaminic acid, glycine, histidine, isoleucine, leucine, phenylalanine and threonine (*H. glabra*, Maleš *et al.* 2013)

Van Dooren *et al.* (2016) investigated the composition of an infusion of *H. hirsuta* (80 g dried material in 4 litres water) collected in Morocco. The decoction yielded 15 g lyophilisate. The authors isolated 2 saponins (medicagenic acid derivatives) and 3 flavonoids (rutin, narcissin, quercetin-3-O-(2'' -O- α -L-rhamnopyranosyl)- β -D-glucuronopyranoside) as the main constituents.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Herniariae herba is mainly used in diuretic tea combinations (see sections 2.1 and 2.2), however these combinations are not covered by this assessment.

1.2. Search and assessment methodology

Standard handbooks of phytotherapy were screened manually for relevant information.

Scientific databases: Scifinder, Scopus, PubMed; search date 6.8.2018; key word: Herniaria.

Data from EU and non-EU regulatory authorities: The information regarding herbal tea combinations in the therapeutic area 'urinary tract disorders' was gathered from EU member states. No additional data were submitted by interested parties during the call for scientific data.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

No product could be retrieved with *Herniariae herba* as the only active ingredient.

Information on relevant combination medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

| Active substance | Indication | Pharmaceutical form Strength Posology Duration of use | Regulatory Status (date, Member State) |
|---|---|---|---|
| Tea bags containing: Herniariae herba 1 g Graminis rhizoma 0.25 g Equiseti herba 0.15 g Sambuci flos 0.1 g | Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract. | 2-4 times per day 1 tea bag as infusion | Spain 1926 |
| 1 tea bag contains Betulae folium 450 mg Uvae ursi folium 450 mg Menthae piperitae herba 225 mg Ononidis radix 150 mg Petroselini radix 150 mg Herniariae herba 75 mg | Inflammatory diseases of urinary tract. The infusion has diuretic, antiseptic and anti-inflammatory effects and relaxes smooth muscle spasms. | Pour one cup (1/4 l) of boiling water over 1 tea bag and leave to infuse 5-10 minutes in a covered cup. The infusion must not boil. Drink warm and unsweetened 3 to 5 times a day. Adding a pinch of sodium bicarbonate (baking soda) is recommended for enhancing the effects of the drink. Always prepare fresh infusion just before using. | Slovakia since 1998 |

| Active substance | Indication | Pharmaceutical form Strength Posology Duration of use | Regulatory Status (date, Member State) |
|--|--|--|--|
| Betulae folium 25 parts Herniariae herba 25 parts Equiseti herba 37.5 parts Callunae herba 10 parts, impregnated with 2.5 parts sodium carbonate | Support of renal function, flushing of the urinary tract, supportive in inflammations of the urinary tract | 1 table spoon (ca. 4 g) as infusion. 3 times daily | AT, WEU 1957 |
| Betulae folium 450 mg Uvae ursi folium 450 mg (Menthae piperitae herba 225 mg) Ononidis radix 150 mg Petroselinii radix 150 mg Herniariae herba 75 mg | An adjuvant for treatment of symptoms of mild lower urinary tract infections such as burning sensation during urination and frequent urination | 1 tea bag (1.5 g)/250 ml of boiling water as a herbal infusion 3–5 times daily | CZ In medicinal use since 1995 THMP since 2011 (evidence of 30 years of medicinal use by references) |

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on other products marketed in the EU/EEA (where relevant)

Not applicable

2.1.2. Information on products on the market outside the EU/EEA

Not applicable

2.2. Information on documented medicinal use and historical data from literature

Herniariae herba is in medicinal use in combinations at least since the beginning of the 20th century (see Table 1). The documented use of Herniariae herba as mono preparation from books dates back since 1976.

Table 2: Overview of historical data on Herniariae herba as single active ingredient

| Herbal preparation | Documented Use / Traditional Use | Pharmaceutical form Strength Posology Duration of use | Reference |
|-----------------------------|----------------------------------|--|--------------------------|
| Comminuted herbal substance | As a diuretic tea | Single dose 2-3 g Daily dose 10 g As decoction | Issekutz & Issekutz 1979 |
| Comminuted herbal | Chronic cystitis, | Single dose 1.5 -3 g | List & Hörhammer |

| Herbal preparation | Documented Use / Traditional Use | Pharmaceutical form Strength Posology Duration of use | Reference |
|--------------------|-----------------------------------|--|-----------|
| substance | urethritis, spasms in the bladder | Daily dose 10 g As decoction | 1976 |

2.3. Overall conclusions on medicinal use

The traditional medicinal use of *Herniariae herba* is documented for at least 30 years, 15 of them in the EU. The indication is consistently related to urinary tract disorders. Therefore the indication in the EU herbal monograph should be in line with other herbal substances in the same therapeutic area. Single and daily dose are evident from literature sources.

Table 3: Overview of evidence on period of medicinal use of *Herniariae herba* as single active ingredient.

| Herbal preparation Pharmaceutical form | Indication | Strength Posology | Period of medicinal use |
|---|---|---|---|
| Comminuted herbal substance as herbal tea for 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. | Single dose 1.5-3 g Daily dose up to 10 g Dosage frequency: 3-5 times daily as an herbal infusion or herbal decoction | Issekutz & Issekutz 1979 List & Hörhammer 1976 |

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Antimicrobial activity

Wojnicz *et al.* (2012) prepared a dry extract of a decoction of 20 g *Herniaria glabra* in 180 ml of water. The extract was dissolved in water to obtain concentrations ranging from 0.125 to 20.0 mg/ml. The extract showed a significant growth-inhibiting effect on uropathogenic *E. coli*. The surface hydrophobicity of autoaggregating *E. coli* strain was changed. At a concentration of 0.125 mg /ml a statistically significant biofilm reduction was noticed after 4, 5 and 6 days of bacterial incubation.

Studies related to kidney stones

Atmani *et al.* (2004a, 2003) administered a dried aqueous extract of *Herniaria hirsuta* (dry extract of a decoction, no further details available) to normal and calcium oxalate nephrolithiasic rats during 3 weeks. 50 mg of the extract were given daily. Water intake and urinary volume increased in nephrolithiasic rats, but their urinary pH decreased especially in the third week of treatment. Urinary oxalate increased significantly during the second week for untreated rats and remained constant in rats treated with *Herniaria* decoction. However, urinary calcium decreased significantly in week 2 in untreated rats and remained constant in treated rats. Qualitative analysis of crystalluria showed that

untreated rats excreted large CaOx monohydrate and few dihydrate crystals while treated animals excreted mostly small CaOx dihydrate crystals. The examination of kidney sections revealed that CaOx deposition was limited in treated rats when compared to untreated ones.

In another experiment Atmani *et al.* (2004b) demonstrated that this aqueous extract inhibited in a dose dependent manner the adhesion of calcium oxalate monohydrate crystals to Madin Darby canine kidney cells. Moreover the extract displaced a significant portion of prebound crystals without apparent effects on the cell function.

Atmani & Khan (2000) observed that in human urine samples *H. hirsuta* (dry extract, extraction solvent water, DER not specified, 0.0625-1 mg/ml) promoted the nucleation of calcium oxalate crystals, increased their number but decreased their size.

Grases *et al.* (1995) assumed that the antilithiasic effect of *Herniaria hirsuta* in rats can only be observed when a high protein diet is administered. In rats receiving standard diet *Herniaria* infusion increased the urine volume.

Meiouet *et al.* (2011) studied the ability of a *Herniaria* extract to dissolve *in vitro* cystine stones which represent 1% of urinary calculi in adults and 10% in children. The extract was an infusion of 2 g *Herniaria hirsuta* in 100 ml water / NaCl solution (9%). After 8 weeks the stones were completely dissolved while in the control group only about 20% disappeared.

Table 4: Overview of the main non-clinical data/conclusions

| Herbal preparation tested | Strength Dosage Route of administration | Experimental model In vivo/ In vitro | Reference Year of publication | Main non-clinical conclusions |
|--|--|---|---|--|
| Dried decoction of 20 g herbal substance in 180 ml distilled water | 0.125 – 20 mg dried extract / ml | <i>In vitro</i> <i>E. coli</i> | Wojnicz <i>et al.</i> 2012 | Antibiofilm activity Growth inhibition |
| Infusion of 2 g herbal substance in 100 ml water / NaCl solution (9%) | | <i>In vitro</i> Cystine stones from patients | Meiouet <i>et al.</i> 2011 | Cystine stones were completely dissolved after 8 weeks in the infusion |
| Dry extract of a decoction of <i>H. hirsuta</i> (no further details available) | 50 mg extract daily Oral | <i>In vivo</i> Rats Induction of calcium oxalate nephrolithiasis by ethylene glycol | Atmani <i>et al.</i> 2004a, 2003 | Increase in urinary volume Reduction of calcium oxalate deposition |
| Dry extract of a decoction of <i>H. hirsuta</i> (no further details available) | No information available | <i>In vitro</i> Madin Darby canine kidney cells | Atmani <i>et al.</i> 2004b | Inhibition of adhesion of calcium oxalate crystals to cells |
| Extracts of powdered <i>H. hirsuta</i> | 0.0625-1 mg/ml | <i>In vitro</i> Induced calcium oxalate crystallisation in human urine samples | Atmani <i>et al.</i> 2000 | <i>H. hirsuta</i> promoted the nucleation of crystals of smaller size. |
| Infusion of <i>H. hirsuta</i> 4 g/litre | Oral, water supply replaced by infusion for 7 days | <i>In vivo</i> Rats receiving different diets | Grases <i>et al.</i> 1995 | Antilithiasic effect correlated with high protein diet |

3.1.2. Secondary pharmacodynamics

Chekroune & Benamara (2017) investigated whether gallstones from an Algerian female patient can be dissolved *ex vivo* by different herbal agents. An infusion of *Herniaria hirsuta* (20 g in 1 litre water, infusion time 15 minutes) reached similar gallstone dissolving capacity as chenodesoxycholic acid.

Van Dooren *et al.* (2015) investigated the efficacy of an infusion of *Herniaria hirsuta* against cholelithiasis in dogs. Infusion: 80 g *Herniaria hirsuta* (collected in Morocco) with 4 litres of boiling water (equal to 3 g per 150 ml). The infusion yielded in 15 g of lyophilisate equivalent to a DER of 5.3:1. The infusion contained 4.51% total flavonoids and 12.74% total saponins. Dogs were divided into 3 groups i.e. control dogs (CG), dogs treated with ursodeoxycholic acid (UDCA) (2×7.35 mg/kg body weight/day) and dogs treated with the standardized infusion (HG) (2×48.5 mg/kg body weight/day). Dogs were fed a fatty diet during 120 days after which a diet without additional fat was introduced till day 180. Treatment started 30 days after introduction of the fatty diet and lasted till the end of the experiment. The experiments showed a minor difference for bile cholesterol between the control group and treated dogs after 30 days of treatment with the infusion, and the difference was more pronounced after 90 days of treatment. Even 30 days after discontinuation of the cholesterol-rich diet a significant difference remained between the groups. There was no statistically significant difference in blood cholesterol.

Rovčanin *et al.* (2015) studied the antibacterial effect of an aqueous and an ethanolic (ethanol 70%) extract of *Herniaria hirsuta* on multiple antibiotic resistant *E. coli*. The extracts were prepared by extracting 100 g plant material with 100 ml extraction solvent. *E. coli* was contained in urine samples of patients with the diagnosis of nosocomial urinary sepsis. The results are compared to standard strain *E. coli* ATCC 25922. Both extracts exhibited antibacterial activity with a more pronounced effect of the ethanolic extract.

Skariyachan *et al.* (2014) identified Herniarin as potential lead structure against virulent gene products of *Vibrio cholera* towards Trimethoprim using *in silico* screening.

Rhiouani *et al.* (1999, 2001) observed that the saponins of *Herniaria glabra* (200 mg / kg BW over 1 month) were able to significantly lower the blood pressure in spontaneously hypertensive rats.

3.1.3. Safety pharmacology

No data available for *H. glabra*, *H. hirsuta* and *H. incana*.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Only few non-clinical data related to the herbal preparation are published. In principle the results support the traditional medicinal use of *Herniariae herba* in urinary tract disorders. However, the relevance of the data of animal studies remains unclear because of missing data on the actual posology. The data from *in vitro* experiments are of less importance as data on absorption and metabolisation in humans are completely missing.

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

No data available.

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

3.3.1. Single dose toxicity

Rhiouani *et al.* (2008) administered a dried aqueous extract of *Herniaria glabra* leaves (50 g herbal substance decocted with 500 ml water, dry extract yield 15% equivalent to a DER of 6.6:1) in doses between 2.5 and 14.5 g /kg BW by gavage to mice. The NOAEL level was determined with 5 g/kg BW. Main behavioural signs of toxicity were atypical locomotion, anorexia, asthenia, ataxia, piloerection and urination. The LD50 was calculated to be 8.5 g/kg BW. The authors conclude that there is a low acute toxicity of this extract.

Comment: The signs of toxicity were observed at dosages which were outside the relevant dosage range for such a test design (5 g/kg BW). Therefore the interpretation of low acute toxicity by the authors can be followed.

3.3.2. Repeat dose toxicity

Rhiouani *et al.* (2008) administered a dried aqueous extract of *Herniaria glabra* leaves (50 g herbal substance decocted with 500 ml water, dry extract yield 15% equivalent to a DER of 6.6:1) in doses of 1, 2 and 4 g/kg BW by gavage to rats for 90 days. Treated rats showed a significant decrease in body weight gain compared to the untreated animals. At the highest dose, the *Herniaria* extract caused a significant increase in erythrocytes, leukocytes (WBC), platelets, and eosinophils, but it had no effect on the differential WBC counts (lymphocytes, monocytes, neutrophils and basophils). Only at the highest dose, the extract caused a significant increase in serum levels of the liver enzymes, alanine aminotransferase and aspartate aminotransferase, as well as serum creatinine, indicating toxic effect of the high dose of the extract on the liver and kidney. The organ toxicity was confirmed by histopathological examination, which showed centrilobular sinusoidal congestion, disruption of the central vein and hepatocellular necrosis in the liver, and interstitial and intraglomerular congestion, tubular atrophy, and inflammation in the kidney. However, due to the lack of mortality or clinically significant changes in the biological (except for hypoglycemia) and hematological parameters in rats after 90 days of daily dosing, the authors concluded that the *Herniaria* extract does not appear to have significant toxicity (except at high doses).

Comment: The signs of toxicity were observed at dosages which were outside the relevant dosage range for such a test design according to CPMP/SWP/1042/99 Rev.1 corr. (2 g/kg BW). Therefore the interpretation of low repeated dose toxicity by the authors can be followed.

3.3.3. Genotoxicity

Van Dooren *et al.* (2015) published an AMES test of an infusion of 80 g *Herniaria hirsuta* (collected in Morocco) with 4 litres of boiling water (equal to 3 g per 150 ml). The infusion yielded in 15 g of lyophilisate equivalent to a DER of 5.3:1. The test was performed according to the OECD guideline (plate incorporation method) with the *Salmonella typhimurium* test strains TA 1535, TA 100, TA 98, TA 1537 and TA 102. The extract was tested in concentrations from 0.015 mg up to 5 mg per plate with and without metabolic activation. Each concentration was tested in triplicate. For none of the tested strains a dose-response relationship was observed. In addition, for none of the strains there was a doubling of the amount of revertants in comparison with the negative control.

Assessor's comment:

The AMES test was basically performed according to the OECD-Guideline concerning Salmonella typhimurium strains (TA1535, TA100, TA98, TA1537 and TA102, with and without metabolic

activation). According to the authors the test revealed no mutagenic effects under the circumstances of the test. However, a pre-incubation test was not performed. Usually for strains with a high spontaneous revision rate (such as TA 102) the two fold rule does not apply, instead the 1.5-fold is applied in such cases. Taking that into consideration for TA102 positive results are seen. Therefore this AMES test is considered inadequate and it cannot be rated as sufficient for the establishment of a list entry.

3.3.4. Carcinogenicity

No data available. No constituents with concern known.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

Data on studies to the single dose and repeat dose toxicity of an aqueous extract do not reveal any concern.

Data regarding genotoxicity are incomplete. Due to limitations of the test design of the published AMES test no list entry can be proposed.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional use.

Specific data on pharmacokinetics and interactions are not available.

Data on studies to the single dose and repeat dose toxicity of an aqueous extract do not reveal any concern.

Data regarding genotoxicity are incomplete. Due to limitations of the test design of the published AMES test no list entry can be proposed.

Tests on reproductive toxicity and carcinogenicity have not been performed.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Oral administration of aqueous extracts of *Herniariae herba* can be regarded as safe at traditionally used doses with the exception of patients with severe renal or cardiac disease e.g. renal and heart failure.

4. Clinical Data

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.2. Clinical efficacy

No data available.

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

As no data are available no conclusions can be drawn.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

No data available.

5.2. Patient exposure

No data available.

5.3. Adverse events, serious adverse events and deaths

No data available.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

No data available.

As no data on the safe use in the paediatric population are available the use in children and adolescents below 18 years of age is not recommended.

5.5.2. Contraindications

No data available.

For safety reasons the use is contraindicated in case of hypersensitivity to the active substance and in conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease).

5.5.3. Special Warnings and precautions for use

No data available.

For safety reasons patients should consult a doctor or a qualified health care practitioner if urinary tract complaints worsen or symptoms such as fever, dysuria, spasm, or blood in the urine occur during the use of medicinal product.

5.5.4. Drug interactions and other forms of interaction

None reported.

5.5.5. Fertility, pregnancy and lactation

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

No fertility data available.

5.5.6. Overdose

No case of overdose has been reported.

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

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

There are no literature reports on possible side effects of the medicinal use of aqueous extracts of *Herniariae herba*.

Based on the traditional medicinal use it can be concluded that the use is safe for adults and elderly. Due to the lack of data the use cannot be recommended for children and adolescents below 18 years of age.

6. Overall conclusions (benefit-risk assessment)

The review of literature provides evidence that *Herniariae herba* is in traditional medicinal use since at least 30 years with 15 years within the EU. All requirements for traditional use according to Dir. 2001/83 as amended are fulfilled (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, plausibility and safety). There are no data on clinical efficacy available. Therefore well-established use cannot be considered.

There are no literature reports on possible side effects of the medicinal use of aqueous extracts of *Herniariae herba*. Data regarding genotoxicity are incomplete. Tests on reproductive toxicity and carcinogenicity have not been performed. There are no safety concerns regarding the use of herbal infusions or decoctions of *Herniariae herba* in the proposed posology of 1.5-3 g as single dose and a maximum daily dose of 10 g. However, as there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Oral administration of aqueous extracts of *Herniariae herba* can be regarded as safe at traditionally used doses with the exception of patients with severe renal or cardiac disease e.g. renal and heart failure.

The indication is consistently related to urinary tract disorders. Therefore, the indication in the EU herbal monograph should be in line with other herbal substances in the same therapeutic area: Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

The therapeutic area is 'urinary tract and genital disorders'.

As no risks are known the benefit-risk balance is considered positive.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC.

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

Annex

List of references