16 September 2010
EMA/HMPC/127430/2010
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Leonurus cardiaca* L., herba

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

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Leonurus cardiaca* L., herba
Herbal preparation(s)	Comminuted herbal substance; tincture
Pharmaceutical forms	herbal tea; liquid preparations for oral use
Rapporteur	Konstantin Keller
Assessor(s)	Konstantin Keller

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Introduction

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

- Herbal substance(s)

Leonuri cardiacae herba, Motherwort Ph. Eur. 6.0: Whole or cut, dried flowering parts of *Leonurus cardiaca* L. Content: minimum 0.2% of flavonoids, expressed as hyperoside (Ph. Eur. 01/2008:1833 corrected 6.0).

Herba Leonuri cardiacae EB6: Dried above-earth parts of *Leonurus cardiaca* L. *var. villosus* (DESF.) BENTHAM, collected during the flowering season (July – September) (EB6). This variety is covered by the definition of the Ph. Eur.

Motherwort, *Leonuri cardiacae* herba (BHP 1974, 1990, 1994):
The dried aerial parts of *Leonurus cardiaca* L. collected when the plant is in flower. This definition is covered by the Ph. Eur.

- Herbal preparation(s)

powdered herbal substance (BHP 1994)

tincture 1:5, ethanol 70% V/V (Latvia, Mashkovskij 1972, Krylow 1993, Sokolov 1984)

tincture 1:5, ethanol 45% V/V (BHP 1974, Barnes 2007)

liquid extract 1:1, ethanol 25% V/V (Wichtl 2002, 2009, Bradley 1992, BHP 1974, Barnes 2007)

tincture 1:5, ethanol 34% V/V (Wichtl 2002, 2009)

tincture 1:5, ethanol 25% V/V (Bradley 1992)

dry extract 8-9:1, ethanol 40% m/m (Finzelberg 2000, Germany since 1993)

dry extract 7.5-8.8:1, ethanol 40% m/m (Germany since 1994)

- 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.

Other related herbal substances used in traditional medicine:

Leonurus japonicus HOUTT.:

Leonurus japonicus HOUTT., herba

Dried above-earth parts of *Leonurus japonicus* HOUTT. (chin. Yi Mu Cao) (Körfers 2009)

Fresh or dried above earth parts of *Leonurus heterophyllus* SWEET (= *L. japonicus* HOUTT.) (chin. yimucao) (Stöger 2009)

Dried above earth parts of *Leonurus japonicus* HOUTT., collected during flowering (BfArM)

Leonurus japonicus HOUTT., fructus

Dried fruits of *Leonurus japonicus* HOUTT. (chin.: Chong Wei Zi) (Körfers 2009)

Dried, ripe fruits of *Leonurus heterophyllus* SWEET (= *L. japonicus* HOUTT). (chin. chongweizi) (Stöger 2009)

Leonurus sibiricus L.

Leonus sibiricus L., semen(Korean: **충위자**, 익모초자)

Leonuri Semen is the seed of *Leonurus sibiricus* L. (Korean FDA).

1.1.1. Botanical and phytochemical characteristics

The genus *Leonurus* L. sensu stricto (*Lamiaceae*) comprises 24 species, divided in 3 sections and in 5 sub-sections. Section *Cardiochilium* (V.KRECZ. et KUPRIAN) KRESTOVSK, subsect. *heterophylli* (C.Y. WU et H.W. LI) KRESTOVSK; ser. *heterophylli* C.Y. WU et H.W. LI comprises *Leonurus japonicus* HOUTT. Subsect. *sibirici* KRESTOVSK comprises *Leonurus sibiricus* L. and section *Leonurus*, subssect. *Leonurus*, ser. *Leonurus* comprises *Leonurus cardiaca* L. and *Leonurus quinquelobatus* GILIB. (Kartnig 2006).

The taxonomy of *Leonurus* is still controversial and any allocation of bibliographic information to a defined species may be questioned under this aspect.

Although *L. sibiricus* is mentioned in the Korean Herbal Pharmacopoeia 2002 and some authors refer expressly to *L. sibiricus* L., it cannot be excluded that *L. japonicus* HOUTT. (syn *L. sibiricus* auct. non L.) has been used in the studies. Doubts may come from the fact that the authors usually refer to the traditional use in TCM, without addressing the fact that *L. japonicus* HOUTT. is used in TCM and not *L. sibiricus* L.

According to Bomme (2006) commercial seed material labelled as *L. sibiricus* represents in reality *L. japonicus* HOUTT. Individual plants of *L. japonicus* with small flowers that were collected in Siberia were falsely named *L. sibiricus* L.

Synonyms of *L. cardiaca* L:

Leonurus villosus DESF. et SPRENG. (Wichtl 2002, 2009)
Leonurus campestris ANDRZ. (Kartnig 2006)
Leonurus canescens DUMORT (Kartnig 2006)
Leonurus trilobatus (LAM.) DULAC (Kartnig 2006)
Cardiaca vulgaris MOENCH (Penso 1983)
Cardiaca trilobata LAM. (Kartnig 2006)
Cardiaca vulgaris MOENCH (Kartnig 2006)

Synonyms of *Leonurus cardiaca* L. var. villosus DESF:

Leonurus quinquelobatus GILIB. (Penso 1983)
Leonurus quinquelobatus DESF. (Penso 1983)

Synonyms of *Leonurus japonicus* HOUTT.:

Leonurus artemisia (LOUR.) S.Y. HU (Kartnig 2006)
Leonurus heterophyllus SWEET (Kartnig 2006, Harley 2001)
Leonurus sibiricus auct. non L. (Kartnig 2006, Harley 2001)
Leonurus sibiricus var. albiflora MIQUEL (Lin 2007)

Phytochemical characteristics of *L. cardiaca*, herba:

- Characteristic constituents are bitter tasting (Wichtl 2002, 2009) furanic diterpenens of the labdane type such as leocardin (Kartnig 2006) or leosibiricin (Knoess 1996):

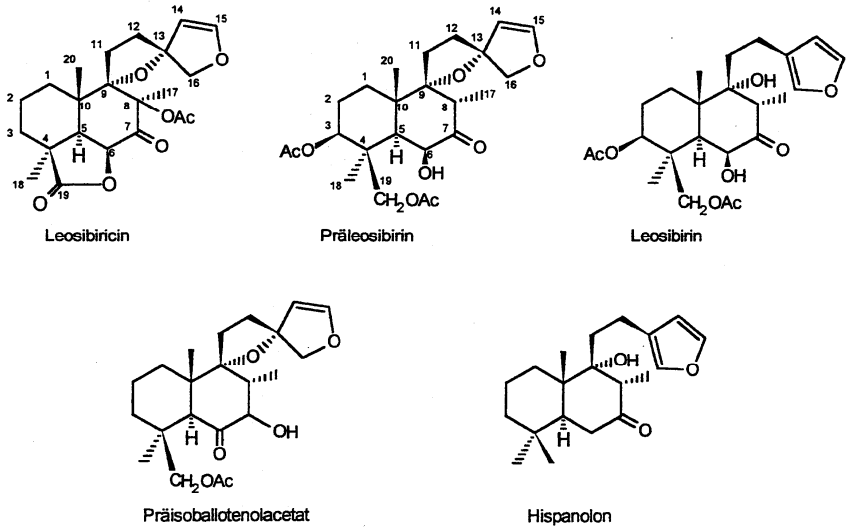
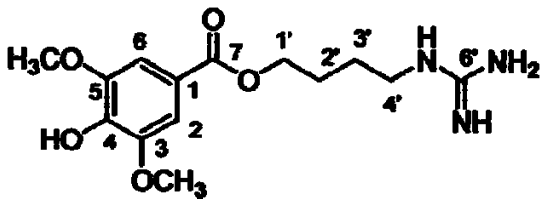


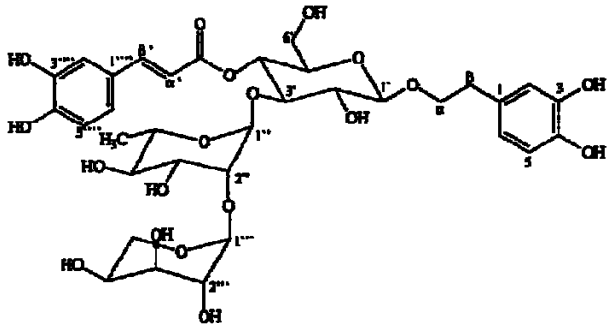
Abb. 11: FLD aus *L. cardiaca* L. - Leosibiricin (8ß-Acetoxy-9α,13R,15,16-diepoxy-7-ketolabda-14-en-19,6ß-olid), Präleosibirin (3,19-Diacetoxy-9α,13R,15,16-diepoxy-6-hydroxylabda-14-en-7-on), Leosibirin (3,19-Diacetoxy-15,16-epoxy-6,9-dihydroxylabda-13(16),14dien-7-on, Präisoballotenolacetat (19-Acetoxy-9α,13R,15,16-diepoxy-7-hydroxylabda-14-en-6-on und Hispanolon (15,16-Epoxy-9-hydroxylabda-13(16),14-dien-3-on).

- The main furanic labdane diterpene is leosibiricin that occurs mostly in flowers and young, fully developed leaves (2.6–3.2 mg/g fresh weight) (Knöss 1996, Knöss 1998). The fresh herb may contain up to 4 mg/g of furanic labdane diterpenes (Knöss 1998).
- Diterpenes of the clerodane type that had been found in investigations conducted by Brieskorn (1972, 1979) were neither found in the samples analysed by Knoess 1996 nor in other investigations, e.g. Agnihotri (2008), Cai (2006), Malakov (1985), Papanov (1997a, 1997b). A literature review covering investigations until 2006 stated that no other publications on the clerodane-type substance exist (Piozzi 2007).
- 0.35% stachydrine in the herb (Van Eijk 1952, Barnes 2007). Samples tested by HPTLC did contain 0.5–1.5% of stachydrine (Kuchta 2009).
- 0.0068% of leonurin (4'-guanidino-n-butyl-syringate) (Barnes 2007). The structure of leonurin has been confirmed by synthesis (Kishi 1968, Sugiura 1969).



Leonurin (Lin 2007)

- Approximately 1% of lavandulifolioside was isolated from *L. cardiaca* herb collected in Poland (Milkowska-Leyck 2002). Commercial samples did contain 0.2% (Ritter 2009).



Lavandulifolioside (Milkowska-Leyck 2002)

- The herb is reported to contain "small amounts" of essential oil (Kartnig 2006); Iridoids: ajugosid (= leonurid = 4-desoxyharpagid), ajugol, galiridosid, reptosid (no information on the concentration available) (Kartnig 2006), 0.26% ursolic acid , 0.1% caffeic acid-4-O-rutinosid, flavonoids deriving from quercetin, kaempferol, and apigenin, genkwanin and 5-9% of "tannins" of unknown structure. (Kartnig 1985, 2006, Kozlowa 1964, Schultz 1973, Tschesche 1980). A sample tested by Matkowski (2006) did contain 32.8 mg/g gallic acid equivalents (Folin Ciocalteu reagent).

  Samples from Lithuania did contain 0.01-0.02% of essential oil with germacrene D (26-32%), ß-caryophyllene (6-9%) and alpha-humulene (6-9%) as main constituents (Mockute 2006). Similar results were found when samples from northern Iran were studied (Morteza-Semnani 2008). During storage, ß-caryophyllene and alpha-humulene oxides are formed (Mockute 2005).

- Ali et al. (2007) isolated 25 mg of ursolic acid from 2 kg of *L. cardiaca* herb. Interestingly, the samples tested by Brieskorn (1952) did not contain any ursolic acid.

- Herbal material cultivated in Italy and in Poland did contain 0.032 and 0.28% sterols, mainly ß-sitosterol and stigmasterol (Senatore 1991).

- The presence of cardiac glycosides is controversial. Old studies (Schultz 1961a, 1961b) were not confirmed by other groups or more recent investigations (Reuter 1970). No glucosides were found (Romanowski 1960).

- 2.03 µg/g nickel and 0.6 µg/g chromium were found in the herb by atom absorption spectrometry. 65% of the Nickel and 51% of the chromium were extracted by tea infusion (Bloniarz 2008). A "high amount" of potassium nitrate was found (Kozlowa 1964). In herbal substance imported from Poland, 27.5 +/- 11.4 mg/kg x 10-3 of lead and 0.32 +/- 0.12 mg/kg x 10-3 of cadmium were found (Zitkevicius 2003). *L. cardiaca*, when grown on heavily polluted soil, did not accumulate heavy metals in a specific way. However, the extraction of Cd from the herb by preparation of an herbal tea was more efficient than for other herbs (Zheljazkov 2008).

- Water soluble extractives (BHP 1990, 1994): not less than 15%

Tincture (1:5), ethanol 70% V/V

By a photometric method (Folin-Ciocalteu reagent) a total amount of 227 mg “gallic acid equivalents” / ml were found. By HPLC analysis 46 µg/ml chlorogenic acid, 52 µg/ml rutosid, 17 µg/ml vitexin, 14 µg/ml isovitexin, 14 µg/ml hyperosid 8 µg/ml quercetin and 250 µg/ml ursolic acid were identified (Bernatoniene 2009).

The optimum extraction parameters for a tincture were investigated by Bernatoniene (2003, 2004). The yield of total flavonoids, calculated as quercetin was 0.0095%, 0.0193%, 0.0267%, 0.0269% and 0.0301% for ethanol 50, 60, 70, 80 and 90% V/V respectively. The dry residue increased from 2.4% (ethanol 50%), to 2.99% (ethanol 60%) to 3.97–4.00% (ethanol 70-96% V/V). Production of the tincture by maceration resulted in 2.56% dry residue and 0.0267% flavonoids, whereas percolation resulted in 3.97 % dry residue and 0.0326% flavonoids.

About 14.5% of lead and cadmium that were present in the herbal substance were transferred into a tincture prepared with ethanol 70% V/V (Zitkevicius 2003).

Other parts of *Leonurus cardiaca* L.

A lectin from *L. cardiaca* seeds agglutinates red blood cells with a CAD marker in a highly specific way. The lectin is proposed as a specific reagent for the elucidation of red blood cell polyagglutinability (Bird 1979, Leger 1996).

The seeds contain 34.5% fat. 11.7% of the fatty acids are laballenic acid (18:2delta5,6 allene), 0.7% 20:1delta9c acid and 0.2% phlomic acid (Aizetmüller 1998).

Other related herbal substances used in traditional medicine:

1. *Leonurus japonicus* HOUTT.:

Leonurus japonicus HOUTT., herba

Chinese Pharmacopoeia:

- water-extractable substances: > 15%
- Stachydrine: > 0.50%, calculated as
- Stachydrine hydrochloride (Stöger 2009)

The method of the Chinese Pharmacopoeia for determination of stachydrine was found “unreliable” by Bomme (2006) 0.2-1.1% of stachydrine was found by HPTLC (Kuchta 2009) 0.1-0.2% stachydrine was found in samples cultivated in China using ion-pair HPLC (Chao 2004).

L. japonicus HOUTT, herba that had been cultivated in Germany (Bomme 2003), did contain 0.5 – 1.5% (Bomme 2006), 0.5-1.0% (Heuberger 2008a) total flavonoids. Commercial samples did contain 0.1-0.5% of total flavonoids (Heuberger 2008a).

Minimum of 0.3% of flavonoids, calculated as hyperosid (BfArM).

The above earth parts of *L. japonicus* are reported to contain 0.01-0.05% leonurin, syringic acid, tiliroside, ajugoside and flavonoids. Blancafort 1977, Yeung 1977, Cong 2005, Qu 2006, Chao 2004) Kong (1976) isolated 50 mg leonurin from 1 kg of herb.

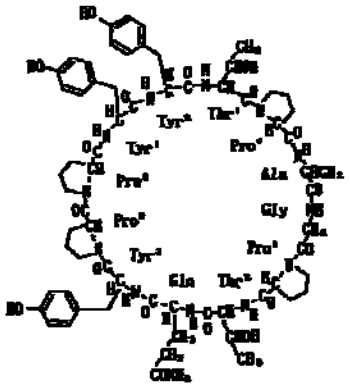
Diterpenes of the labdane-type, ß-sitosterol, stigmasterol, flavones (genkwanin) (Giang 2005a, 2005b, Hon 1991, Hon 1993, Widowitz 2009) ß-sitostenon (stigmast-4-en-3-one) (Horita 2002, Romero-González 2006).

A linear furanocoumarine-glucoside (nodakenin) has been found in the herb. No information on the quantity is available (Horstmann 1994).

Commercial samples of the herb originating from Asia complied with pharmacopoeial standards when tested for lead, cadmium, mercury and pesticides (Heuberger 2008b).

Leonurus japonicus HOUTT., fructus

The main Dragendorff-positive substance in the seeds is not leonurin or a similar alkaloid, but a cyclic petide: cycloleonurinin (Kinoshita 1991). A series of proline-rich cyclic nona-decapeptides (cycloleonuripetides A, B, C, D, E and F) has been isolated from the fruits (Morita 1996, 1997 a-c, 2006).



Cycloleonurinin (Kinoshita 1991)

2. *Leonurus sibiricus* L.

The main components of the essential oil from the herb were identified by GC-MS as trans-caryophyllene (33.43%), alpha-humulene (21.49%) and germacrene-D (24.95%) (Almeida 2005).

The herb contains furanic labdane diterpenes (Savona 1982, Satoh 2003).

The occurrence of leonurin, 4-guanidinobutanol-(1), arginin, and 4-guanidino-butyric-acid in the herb have been reported (Blancafort 1977, Reuter 1971). 0.124± 0.065% leonurin were found by HPLC in 34 samples of the herb collected throughout the regions of Korea (Sung 2001).

The seeds contain 28.5% fat. 18.1% of the fatty acids are laballenic acid (18:2delta-5,6allene), 1.3% 20:1delta9c acid and 0.3% phlomic acid (Aizetmüller 1998).

It seems that the different *Leonurus* species, except *L. marrubiastrum* L., present a similar phytochemical profile, especially when it comes to the presence of furanic diterpenes of the labdane-type. *L.marrubiastrum* L. is the only species where non-labdane furano diterpenes of the abietan-type were found. Genkwanin is proposed as a chemotaxonomic marker for the genus *Leonurus* (Malakov 1998, Piozzi 2007, Tasdemir 1998).

1.2. Information about products on the market in the Member States

France:

Combination products

Crataegi liquid extract 40 ml, Passiflorae tincture 10 ml, Valerianae tincture 15 ml, Avenae liquid extract 10 ml, Melissae liquid extract 10 ml, Leonuri cardiacae tincture 15 ml; oral use; in cases of palpitations: Adults 15 drops 3 times daily, in cases of sleep disorders: Adults 15 drops 2 times daily, Children over 6 years: 6 drops 2 times daily; traditionally used to reduce nervousness in adults, particularly in the case of exaggerated awareness of heartbeat (palpitations) after any heart disease has been shown to be absent; traditionally used to reduce nervousness in adults and children, notably in cases of disorders of sleep.

Germany:

Single ingredient products

Dry extract 8-9:1, ethanol 40% m/m, 17 years of use, oral liquid, 80 mg, 3 times per day, traditionally used to support the function of the cardiovascular system.

Dry extract 7.5-8.8:1, ethanol 40% m/m, 16 years of use, oral use, 200 mg, 3 times per day, traditionally used to support the function of the cardiovascular system.

Combination products

150 mg Leonuri herba, powder, 160 mg dry extract from Equiseti herba 6-9:1, ethanol 30% V/V, marketed for more than 34 years, oral use, 1 tablet 3 times per day, traditionally used to support the function of the cardiovascular system.

Four combinations with 4-5 active substances and three with more than five active substances, among them Crataegi fructus and Crataegi folium cum flore.

Hungary:

Combination products

1. Tea-mixture against arteriosclerosis: 20 g Ribis nigri folium, 20 g Crataegi summitas, 20 g Leonuri cardiacae herba, 20 g Plantaginis folium, 10 g Menthae piperitae folium, 10 g Visci albi stipes; 26 years of use, herbal tea, oral use, 3.5 g, 1-2 times per day; Prevention of the development of hypertension and arteriosclerosis, adjuvant therapy of mild cases of hypertension and arteriosclerosis, adjuvant therapy of senile cardiovascular complaints. It improves the efficacy of cardiac function, reduces the workload of the circulatory system by its mild diuretic effect.
2. Tea-mixture against arteriosclerosis in filters: 0.24 g Ribis nigri folium, 0.24 g Crataegi summitas, 0.24 g Leonuri cardiacae herba, 0.24 g Plantaginis folium, 0.12 g Menthae piperitae folium, 0.12 g Visci albi stipes) / 1 filter tasak (1.2 g teamixtures); 7 years of use; 2-3 filter sachet daily; 1-2 time per day; Prevention of the development of hypertension and arteriosclerosis, adjuvant therapy of mild cases of hypertension and arteriosclerosis, adjuvant therapy of senile cardiovascular complaints. It improves the efficacy of cardiac function, reduces the workload of the circulatory system by its mild diuretic effect.
3. Cardiac tranquillizer tea-mixture: 0.36 g *Crataegi folium cum flore,* 0.36 g *Leonuri cardiacae herba,* 0.36 g *Melissae herba,* 0.36 g *Visci albi stipes,* 0.06 g *Valerianae radix*/1 filter; 9 years of use; 1 filter sachet 3 times per day; For relieve cardiac complaints due to overload, exhaustion, nervousness and for relive of senile cardiovascular complaints. As adjuvant therapy of mild cases of hypertension and angina pectoris.

Latvia:

Single ingredient products

Comminuted herbal substance, in use for 38 years, herbal tea, oral use, infusion of 2 teaspoons comminuted herbal substance with 1 glass of boiling water, allow to infuse 20 minutes, 1/3 of glass 3 times per day, as a sedative in cases of hypersensitivity of central nervous system, treatment of heart and blood system neurosis, early stages of hypertension.

Tincture 1:5, ethanol 70% V/V, in use for 40 years, oral use, adults and adolescents: 30-50 drops, up to 4 times per day, for reduction of mild nervous tension, in cases of functional heart disorders; in cases of pre-hypertension, isolated clinical hypertension, borderline hypertension; treatment of

functional heart disorders (heart neurosis, manifested as palpitations, intermission, short term stitchy or long term pressure pain in heart) if there is no organic disease, but symptoms are caused by stress, anxiety, hypersensitivity of nervous system. Also used to reduce heart symptoms (for example, palpitations) caused by hyperthyreodism or hormonal changes during menopause.

Combination products

Eight combination products. Two contain vitamins and minerals; three combinations of Leonuri tinctura with Valerianae tinctura, Crataegi tinctura or fluid extract and Menthae piperitae tincture as heart function improving drops; two combinations of Leonuri herba with Valerianae radix, Lupuli flos, Mentha piperitae folium, Melissae folium as sedative; one combination of Leonuri herba with Crataegi inflorescentia, Crataegi fructus, Meliloti herba – as additional treatment of functional disorders of heart function and blood system.

Other products

According to the database of Latvian Food Centre: three food supplements containing a single ingredient; several combination products.

Lithuania:

Single ingredient products

Comminuted herbal substance, in use for 55 years, herbal tea, oral use, 4.5 g of herbal substance 1 - 3 times per day, to make an infusion, pour 150-200 ml of boiling water over 4.5 g of herbal substance. Steep for 10-15 minutes, 1-3 times daily, neuroregulatory related disorder of heart function (e. g. thyroid hyper function, climacteric period etc.), in absence of organic cardiovascular disease.

Tincture (1:5, extraction solvent ethanol 70% V/V), in use for 55 years, oral liquid, 30-50 drops in a half glass of water, 3-4 times per day, stress-, anxiety-, nervousness, thyroid hyper function or climacteric related heart dysfunction, in absence of organic cardiovascular disease, heart complaints.

Combination products

Combination products contain 3-5 active substances, among them preparations from Valerianae radix and Crataegi fructus.

Poland:

Single ingredient products

Leonuri herba, in use for 30 years, herbal tea, oral use, 1.5–2.5 g 2-3 times per day, sedative in nervous heart complaints.

Combination products

1. Leonuri herba + Melissae folium + Violae herba + Crataegi inflorescentia, 22 years of use, herbal tea, oral use, 3.6 g 4 times per day, nervous heart complaints.
2. Crataegi folium cum flore + Crataegi fructus + Leonuri cardiacae herba + Meliloti herba, 6 years of use, herbal tea, oral use, 1 g 1-2 times per day, nervous heart complaints (palpitations).
3. Lupuli strobulus + Melissae folium + Leonuri cardiacae herba + Lavandulae flos + Archangelicae radix + Rosae fructus, 19 years of use, herbal tea, oral use, 2 g 4 times per day, excessive nervous excitability.

4. Chamomillae anthodium + Melissae folium + Valerianae radix + Leonuri cardiacae herba + Crataegi inflorescentia + Lupuli strobuli, 15 years of use, herbal tea, oral use, 5 g 1-3 times per day, adjuvant in nervous tension; difficulty in falling asleep.
5. Solidaginis herba + Crataegi inflorescentia + Leonuri herba + Valerianae radix + Melissae folium + Polygoni avicularis herba + Lupuli strobuli, 15 years of use, herbal tea, oral use, 5 g 1-3 times per day, undue fatigue; supporting in initial phase of heart efficiency disorders.
6. Extractum compositum (1:3.5) ex: Leonuri herba, Lupuli strobilo, Melissae folio, Lavandulae flore; extraction solvent – ethanol 70%(v/v), 7 years of use, oral liquid, 7.5 ml 3 times per day, increased nervous tension; difficulty in falling asleep.
7. Melissae herbae intractum + Lupuli strobuli tinctura + Chamomillae anthodii tinctura + Leonuri herbae tinctura (extraction solvent – ethanol 70%(v/v)) + Crataegi inflorescentiae tinctura + Valerianae radicis tinctura, 14 years of use, oral liquid, 2.5 ml 1-3 times per day, adjuvant in nervous tension; difficulty in falling asleep.
8. Crataegi folium cum flore + Crataegi fructus + Leonuri cardiacae herba + Meliloti herba, 16 years of use, tablet, 2 tablets 2-3 times per day, adjuvant in initial phase of heart efficiency disorders (when usage of other drugs is not necessary, without symptoms of circulatory stasis); heart weakness in elder age.
9. Valerianae radix + Lupuli strobilus + Melissae folium + Leonuri herba, 18 years of use, tablet, 2 tablets 3 times per day, temporary mild nervous tension; temporary difficulty in falling asleep.

United Kingdom:

Motherwort is included in the General sales List. Nine products that contain motherwort are reported for the UK market (Barnes 2007). No further details on these products could be retrieved. None of these is authorised or registered (see section I).

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products authorised or registered
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Two combinations with 9-10 ingredients authorised in 1962; re-evaluation ongoing. At least one food supplement
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products authorised or registered. No information on other types of medicinal use.
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No traditional or other products marketed
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	No authorised or registered medicinal

					products; one food supplement (extract with water from flowers)
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered medicinal products; one food supplement
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products authorised or registered
France	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	One combination product authorised in 1953
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Two single ingredient products authorised in 1993 and 1994. Eight fixed combinations marketed since at least 1976
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal or other product marketed
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Three combination products marketed since 1994
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Three single ingredient and 8 combination products marketed (since 1970/1972). Additional single ingredient and combination products marketed as food supplements
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Lithuania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Single ingredient and combination products marketed since 1955
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products marketed
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal or other product marketed; L.

					cardica is classified as "medicinal herb" that needs a marketing authorisation / registration
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Single ingredient products marketed for more than 30 years; 9 combination products marketed for 6 to 22 years
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information received
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No data on marketed finished products available. Leonuri cardiacae herba is frequently mentioned in the lay herbal books/articles which show the traditional use of this herbal drug
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products authorised or registered
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products authorised or registered; herbal teas might be covered by former "exemptions" (no data available)

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'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.2. Search and assessment methodology

The term "*Leonurus*" has been searched on 28 December 2009 in following databases:

CC00 - CCMED copyright ZBMED
CDSR93 - Cochrane Library - CDSR copyright Cochrane
DAHTA - DAHTA-Datenbank copyright Bundesministerium für Gesundheit
AR96 - Deutsches Ärzteblatt copyright DAEB
GA03 - gms copyright gms

GM03 - gms Meetings copyright gms
HG05 - Hogrefe-Verlagsdatenbank und Volltexte copyright Hogrefe-Verlagsgruppe
KR03 - Karger-Verlagsdatenbank copyright Karger-Verlag
KL97 - Kluwer-Verlagsdatenbank copyright Kluwer Academic Publishers
KP05 - Krause & Pachernegg Verlagsdatenbank copyright KuP
CDAR94 - NHS-CRD-DARE copyright Cochrane
INAHTA - NHS-CRD-HTA copyright NHS CRD 2009
SM78 - SOMED copyright LOEGD 2002
SPPP - Springer-Verlagsdatenbank PrePrint copyright Springer-Verlag
SP97 - Springer-Verlagsdatenbank copyright Springer-Verlag
TVPP - Thieme-Verlagsdatenbank PrePrint copyright Thieme-Verlag
TV01 - Thieme-Verlagsdatenbank copyright Thieme-Verlag
CCTR93 - Cochrane Library - Central copyright Cochrane
ME60 - MEDLINE copyright NLM
ZT00 - AnimAlt-ZEBET copyright BfR (ZEBET) 2009
MK77 - MEDIKAT copyright ZB MED
ED93 - ETHMED copyright IDEM 2009
HN69 - HECLINET copyright IFG 2002
CV72 - CAB Abstracts copyright CAB
CB85 - AMED copyright THE BRITISH LIBRARY 2009
NHSEED - NHS-EED copyright NHS EED 2009
AZ72 - GLOBAL Health copyright CAB
IA70 - IPA copyright Thomson Reuters
BA26 - BIOSIS Previews copyright Thomson Reuters
EM74 - EMBASE copyright 2009 Elsevier B.V.
DH64 - Derwent Drug Backfile copyright Thomson Reuters
EA08 - EMBASE Alert copyright 2009 Elsevier B.V.
DD83 - Derwent Drug File copyright Thomson Reuters
II78 - ISTPB + ISTP/ISSHP copyright Thomson Reuters
IS74 - SciSearch copyright Thomson Reuters
T165 - XTOXLINE copyright NLM 2006
TB69 - TOXBIO copyright Thomson Reuters
AN83 - Adis Newsletters copyright Wolters Kluwer Health - Adis International

748 documents have been retrieved from this search. No further restrictions of search terms have been used.

The RTECS database was consulted for toxicological facts. No additional information was found.

Literature and data submitted by the company Valentis, Vilnius, and by AESGP were consulted. Articles and data that were found to be relevant for assessment are included in the list of references.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The continous medicinal use of Leonuri cardiaca herba in Europe is documented for several centuries: Mattiolius (1626), Lonicerus (1679), Schröder (1685), Benedum (2006), Wittstein (1882), Hoppe (1949), Hoppe (1957), Hoppe (1975), Weiss (2009).

The **comminuted herbal substance** and the **powder** are described in EB6 for more than 50 years (EB6). The comminuted herbal substance, "Herba Leonuri cardiacae conc.", has been continuously sold

for more than 30 years in Germany as a herbal tea delivered to pharmacies and drug stores (Caelo 1979, Caelo 1994, Caelo 1997, Caelo 2003, Caelo 2009). The use of the herbal substance in tea infusions in UK is documented by the BHP (1974), BHP (1990) and Bradley (1992). The comminuted herbal substance has been used an herbal tea in Poland for more than 30 years (see above) and in Lithuania for 55 years. A monograph from the Russian Pharmacopoeia 9th edition has been the basis for marketing of the comminuted herbal substance in Lithuania; since 2000 in the Drug Register of Latvia, however on the market since 1972 (Latvia).

A **tincture 1:5 with ethanol 70% V/V** has been on the market in Lithuania for 55 years and has been registered in 1994 (registration certificate 94/843/9 issued by the Ministry of Health). Before 1994, the liquid extract was distributed to Lithuania from manufacturers originating from the former UdSSR (Mashkovskij 1972, Krylow 1993, Sokolov 1984). According to a PSUR submitted by one company, more than 380.000 packages (30 ml or 50 ml) of the liquid extract have been distributed in both countries from 2003 to 2009.

Since 1993 in the Drug Register of Latvia, however on the market since 1970s when Motherwort tincture was included in the register of the former USSR and therefore was on the market in Latvia as its former part (Latvia).

A **liquid extract 1:1, ethanol 25% V/V** has been in continuous use for more than 30 years (Wichtl 2002, 2009, Bradley 1992, BHP 1974).

The limited information on a medicinal use of the **powdered herbal substance** makes it difficult to establish a plausible traditional use. Although the powder is mentioned in EB6, limited evidence of medicinal use as a single ingredient product could be found. The powdered herbal substance is included in BHP (1994). However, a fixed combination with two ingredients has been marketed in Germany for more than 34 years (see II.1.2.). As the combination of only two very distinct ingredients, 150 mg Leonuri herba, powder, 160 mg dry extract from Equiseti herba 6-9:1, ethanol 30% V/V, could be considered as a "comparable product" and reference, the inclusion of the powder into the monograph seems to be acceptable.

A **tincture 1:5, ethanol 45% V/V** has been mentioned in BHP (1974) and in Barnes (2007), but no additional information of use could be retrieved.

No information on more than 30 years of traditional use has been found for the following preparations that were found in literature and data submitted by AESGP:

- Tincture 1:5, ethanol 34% V/V (Wichtl 2002, 2009)
- Tincture 1:5, ethanol 25% V/V (Bradley 1992)
- Dry extract 8-9:1, ethanol 40% m/m (Finzelberg 2000, Germany since 1993)
- Dry extract 7.5-8.8:1, ethanol 40% m/m (Germany since 1994)

It might be questioned if the reported figures relating to the drug-extract-ratio of dry extracts represent real differences.

2.2. Information on traditional/current indications and specified substances/preparations

Indications reported:

(comminuted) herbal substance:

- reported to have cardiac activity, especially in neurosis (Hoppe 1957),
- used as a sedative in neurogenic and functional heart complaints (Hoppe 1957),

- nervous cardiac complaints, feeling of anxiety, cardiac palpitations, vegetative "heart neurosis" (Schulze 1944),
- trembling and palpitations of the heart (Mattiolius 1626),
- relieves cardiac pain (Lonicerus 1679),
- improves cardiac blood flow (Lonicerus 1679),
- cardiac irregularities (Lonicerus 1679),
- angina pectoris (Lonicerus 1679),
- cardiac complaints, esp. in children (Schröder 1685),
- nervous cardiac disorders (Wichtl 2002, 2009, Kommission E 1986, Thomson 1978),
- traditionally used to support cardiovascular function (Kommission E from Wichtl 2002, 2009),
- sedative in nervous heart complaints (Poland),
- nervous cardiac disorders (Weiß 1938),
- sedative, vegetative neurosis, vegetative-functional heart complaints, vegetative dystonia (Weiß 1944, Weiss 1974, Weiss 1980, Weiss 1997, Weiss 2009),
- functional heart complaints (Kraft 2009),
- heart disorders caused by anxiety and stress (no difference to *L. japonicus* HOUTT.) (Balch 2002),
- sedative, cardiotonic, hypotensive (Bradley 1992),
- neuropathic cardiac disorders, cardiac complaints of nervous origin (Bradley 1992),
- palpitation of the heart arising from hysteric cause (Steinmetz 1954),
- sedative, antispasmodic, cardiac debility, simple tachycardia, effort syndrome, amenorrhoea, specifically for cardiac symptoms associated with neurosis (Barnes 2007),
- originally used in cardiovascular neurosis, angina pectoris, hypertonia, since the beginning of the 20th century as a sedative, e.g. in nervous conditions, psychasthenia, neurasthenia with insomnia, stress, hyperreactivity, vegetative-vascular dystonia, nervous symptoms in the premenopausal and postmenopausal period. Claimed to be 2-3 time more active than Valerian (Sokolov 1984),
- nervous symptoms, cardiovascular neurosis, early stages of hypertension (Mashkovskij 1972, Krylow 1993),
- neuroregulatory related disorder of heart function (e. g. thyroid hyperfunction, climacteric period etc.), in absence of organic cardiovascular disease (Lithuania),
- treatment of heart and blood system neurosis, early stages of hypertension (Latvia),
- as a sedative in cases of hypersensitivity of central nervous system (Latvia),
- traditionally as a sedative (Wichtl 2002, 2009),
- hysterical complaints (Steinmetz 1954),
- relieves nervous irritability, calming action (Steinmetz 1954),
- used in many traditions in trouble with concentrating, non-organic sleep problems, heart palpitations (Abascal 2004),
- climacteric disorders (Hoppe 1957),
- traditionally in climacteric complaints, (Wichtl 2002, 2009),
- to facilitate menstruation, "emenagogum", (Hoppe 1957),
- traditionally in amenorrhoe (Wichtl 2002, 2009),
- used in many traditions in "uterine weekness" (Abascal 2004),
- premenstrual syndrome (no difference to *L. japonicus* HOUTT.) (Balch 2002),
- India: in Unani medicine ("Baranjaasif", name also used for *Artemisia vulgaris* L. and *Achillea millefolium* L.) in absent or painful menstruation, premenstrual tension, menopausal flushes (Khare 2007),
- spasms (Mattiolius 1626),
- paralysis of the limbs (Mattiolius 1626),
- historically (!) for the treatment of wounds, to expell phlegm from the lungs, to support gastric function (Wittstein 1882),
- pain of the stomach, pain caused by gall-stones (Steinmetz 1954),

- adjuvant in hyperactivity of the thyroid (Wichtl 2002, 2009), (Kommission E 1986),
- tachycardia associated with hyperthyreosis (Weiss 1974, Weiss 1980), but: "*L. cardiaca* has no thyreostatic acitivity" (Weiss 1997).

Uses in US eclectic medicine:
Infusions in hysterical affections, sleeplessness, delirium, uterine pain and –disorders (Hatfield 1886).

Tincture (1:5), ethanol 70 % V/V

- Stress-, anxiety-, nervousness, thyroid hyperfunction or climacteric related heart dysfunction, in absence of organic cardiovascular disease heart complaints (Lithuania)
- Reduction of mild nervous tension, in cases of functional heart disorders; in cases of pre-hypertension, isolated clinical hypertension, borderline hypertension; treatment of functional heart disorders (heart neurosis, manifested as palpitations, intermission, short term stitchy or long term pressure pain in heart) if there is no organic disease, but symptoms are caused by stress, anxiety, hypersensitivity of nervous system. Also used to reduce heart symptoms (for example, palpitations) caused by hyperthyreodism or hormonal changes during menopause (Latvia)

Liquid extract 1:1, ethanol 25 % V/V

- sedative, cardiotonic, hypotensive (Bradley 1992)
- sedative, antispasmodic; cardiac symptoms associated with neurosis (BHP 1974)
- neuropathic cardiac disorders, cardiac complaints of nervous origin (Bradley 1992)
- sedative, antispasmodic,; cardiac debility, simple tachycardia, effort syndrome, amenorrhoea, specifically for cardiac symptoms associated with neurosis (Barnes 2007)

Tincture 1:5, ethanol 45 % V/V

- sedative, antispasmodic; cardiac symptoms associated with neurosis (BHP 1974)
- sedative, antispasmodic; cardiac debility, simple tachycardia, effort syndrome, amenorrhoea, specifically for cardiac symptoms associated with neurosis (Barnes 2007)

Tincture 1:5, ethanol 25 % V/V

- sedative, cardiotonic, hypotensive (Bradley 1992)
- neuropathic cardiac disorders, cardiac complaints of nervous origin (Bradley 1992)

Traditional uses of other *Leonurus* species:

***Leonurus japonicus* HOUTT., herb:**

- The first reported use “to expel dead fetus and retained placenta” is described in the first official Chines Pharmacopoeoa Tang Peng Ts’ao (659 A.D.) (Blancafort 1977).
- Current TCM: Menstrual disorders, painful menstruation, amenorrhoea, prolonged menorrhoea, edema with reduced elimination of urine, oedema in acute nephritis (Stöger 2009). Most frequently used as an emenagogue in form of a decoction. In eastern parts of China to promote uterine recovery after delivery (Kong 1976, Bensky 2004).
- Premenstrual syndrome, heart disorders caused by anxiety and stress (no difference to *L. cardiaca* L.) (Balch 2002).
- In a retrospective study in Taiwan, *L. japonicus*, herba was the most commonly prescribed herbal substance for the treatment of symptoms related to menopause. The study investigated records of 3432 that were treated in the time period between January 2003 and December 2006 (Chen 2010).
- Posology:

Single dose
9-30 g (Stöger 2009)

9-15 g (large doses up to 30 g) (Bensky 2004)

10-20 g as a decoction, 2-3 doses per day (Kong 1974)

***Leonurus japonicus* HOUTT., fruit:**

- Current TCM: To activate blood circulation and regulate menstruation, to subdue hyperactivity of the liver and to clear the eye from opacity. Used in menstrual disorders, amenorrhea, hysmenorrhea, inflammation of the eye with formation of corneal opacity; dizziness and headache (Pharm. Commission Chin. 1996).
- Menstrual disorders, amenorrhoea, painful menstruation, inflammation of eye, corneal opacity, dizziness, pain and sensation of tension (Stöger 2009, Jia 2006).
- Posology:

Single dose
4.5-9 g (Pharm. Commission Chin. 1996, Stöger 2009)
3-9 g (Bensky 2004)

The daily dose should not exceed 15 g for because of possible toxicity (Bensky 2004).

***Leonurus sibiricus* L., herb (see general comment in 1.1.1.)**

Used in Korean traditional medicine for the treatment of uterine leiomyoma (Bajracharya 2009).

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

Posology (oral use)

As an herbal tea:

- single dose 1.5 g (EB6)
- single dose 1.5 g, daily dose 4.5 g (Wichtl 2002, 2009; Kommission E 1986)
- single dose 1.5 – 2.5 g, 2-3 times per day (Poland)
- single dose 3 g, for a decoction, 2-3 times per day (Weiß 1938)
- single dose 2 g, twice a day (Weiss 1944, Weiss 1974, Weiss 1980, Weiss 1997, Weiss 2009)
- single dose 1 g, 2-3 times per day as an adjuvant in hyperthyreosis (Weiss 1997, Weiss 2009)
- single dose 4.5 g, 1-3 times per day (Lithuania)
- single dose 2-4 g, three times daily (Bradley 1992, Barnes 2007)
- 15 g/200 ml boiling water, take 1/3 of the tea preparation twice a day; if CNS suppression occurs, doses are either reduced or treatment is interrupted for 5-7 days (Sokolov 1984). This recommendation would correspond to a single dose of 5 g, twice a day.
- 15 g/200 ml boiling water, 1 table-spoon 3-5 times per day (Mashkovskij 1972). Presuming that a table spoon would correspond to 10–15 ml this would correspond to a single dose of 0.75–1.13 g, 3-5 times daily.
- 2 teaspoons comminuted herbal substance with 1 glass of boiling water, allow infusing 20 minutes, 1/3 of glass 3 times per day (Latvia). Presuming that a teaspoon would correspond to 1–1.5 g, a single dose would correspond to approx. 0.7–1 g, 3 times a day.
- single dose 1 tea spoon (1-1.5 g) of comminuted herbal substance for tea infusions, twice a day (Thomson 1978).
- single dose: 2 teaspoons (2-3 g) comminuted herbal substance for tea infusions, twice a day (Kraft 2009)
- single dose 2-4 g, three times per day (BHP 1974)

The majority of posologies proposed by authors would be covered by a single dose of 1.5 to 4.5 g, and a daily dose of 3 to 10 g.

Powdered herbal substance:

The posology of the powder as part of the comparable fixed combination is 150 mg, 1-3 times per day. No specific actions are expected from the Equisetum extract in the relevant indication. The posology is plausible when compared with the posology of tinctures.

Tincture 1:5, ethanol 70% V/V:

- single dose 30-50 drops, 3-4 times per day (Sokolov 1984, Mashkovskij 1972)
- single dose 30-50 drops, up to 4 times per day (Latvia)
- single dose 30-50 drops in a half glass of water, 3-4 times per day (Lithuania)
- According to DAB 7, 1 drop of ethanol 70% corresponds to 18 mg, 55 drops=1 g
- single dose approx. 0.5–1.0 g, 3-4 times per day

Liquid extract 1:1, ethanol 25% V/V:

single dose 2-4 ml, 3 times daily (BHP 1974, Bradley 1992, Barnes 2007, Wichtl 2002, 2009)

Tincture 1:5, ethanol 45% V/V:

single dose 2-6 ml, 3 times per day (BHP 1974, Barnes 2007)

Posologies of preparations without traditional use over at least 30 years:

- tincture 1:5, ethanol 34% V/V single dose 2-6 ml, three times daily (Wichtl 2002, 2009)
- tincture 1:5, ethanol 25% V/V single dose 4-10 ml three times daily (Bradley 1992)

Duration of use:

- Long-term use (minimum 2 months) is required to obtain effects (Weiß 1938, Weiß 1944, Weiss 1974)
- Long-term use is recommended (Kraft 2009)

3. Non-Clinical Data

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

In vitro experiments

Action on free radicals / antioxidant action
A radical scavenging action in ABTS (2.2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) and DPPH (2.2-diphenyl-1-picrylhydrazyl) radicals has been found with the tincture 1:5, ethanol 70% V/V. After 10 minutes 88% (ABTS) and 85% (DPPH) of the effect of the comparator Trolox was found (Bernatoniene 2009).
According to Masteikova (2008) the antioxidant activity of *L. cardiaca* tincture, as compared to a tincture from hawthorn fruits, does not correlate with the total phenol content and is mainly related to the presence of rutoside (55 µg/ml). An antioxidant effect in vitro was found with an extract prepared with methanol 60% from the herb, which was extracted first with chloroform (Matkowski 2006).

Antimicrobial activity

A dry extract of the herb with chloroform inhibited the growth of *St. aureus* in the agar diffusion test and in the serial dilution test (MIC 500 µg/ml) (Sattar 1995).

The chloroform-soluble fraction of an extract prepared with methanol showed activity against a multi-drug resistant strain of *P. falciparum* (IC_{50} 3.1 µg/ml; comparator artemisinin: IC_{50} 0.0027 µg/ml). No relevant activity was found against Trypanosoma cruzi, T. brucei rhodesiense and L. donovani (Tasdemir 2005).

Antiviral activity

Aqueous extracts from *L. cardiaca* herb inhibited almost completely tick-borne encephalitis virus in vitro in SPEV (porcine embryo kidney) cell cultures. I.p. injection in infected (LD_{50} dose of the virus) mice induced 34% protection when given 7 days prior to infection (Fokina 1991).

Antiinflammatory action

Ali et al (2007) investigated a potential anti-inflammatory action of ursolic acid isolated from *L. cardiaca*. In a "respiratory burst model" an inhibition of superoxide production by human neutrophils was observed (IC_{50} ursolic acid 140.76 µg/mL, comparing to Indomethacin 246.35 µg/ml and ASA 70.45 µg/mL).

Cardiovascular action

A purified extract with water from *L. cardiacae* herba was investigated in the isolated rabbit heart *in vitro*. 0.1 to 3.0 mg/ml of the extract were applied intracoronarily. The extract reduced significantly and in a dose-dependent way left ventricular pressure by 15 +/- 5mm Hg and heart rate by 14 +/- 1 bpm, enhanced relative coronary flow by 10 +/- 5% and atrioventricular conduction time by 5 +/- 1 ms. The ventricular propagation velocity was not affected. At 1 mg/ml, activation-recovery-intervals and QTc were prolonged (QTc from 0.24 to 0.26 s) while dispersion was reduced by 23 +/- 18% .The authors conclude that the extract exerts calciumantogonistic effects and class III like antiarrhytmic effects. Other, non aqueous extracts were not effective or toxic (Kuchta 2008, Dhein 2007).

The extract was subject of a patent application in 2005. According to the application, the extract is prepared by purifying a lyophylized extract with water with lipophilic organic solvents, redissolving the water soluble part in water, precipitating the solution with methanol and using the supernatant fluid. This purified extract may be further purified by elimination of potassium (Dhein 2005, Ritter 2009). The refined extract contained approximately 6% stachydrine, 0.1% rutosid, 0.2% verbascosid, 0.3% lavandulifolioside (Kuchta 2009, Ritter 2009). Furanic diterpenes that were toxic to the isolated heart preparation and resulted in cardiac arrest were eliminated by prior extraction with dichloromethane (Ritter 2009). The refined extract was applied intracoronarily in isolated rabbit hearts perfused according to the Langendorff technique. Mapping experiments with 256 electrodes on the heart surface showed a reduction of left ventricular pressure and an increase of relative coronary flow at concentrations of 1.0 and 2.0 mg/ml. Furthermore, the PQ-interval was prolonged and both the basic cycle length and the activation recovery interval increased. In addition, voltage-clamp measurements were performed on the following cell models in order to characterise the electrophysiological profile of the extract: neonatal rat ventricular cardiomyocytes to investigate the effect on I (Na) and I (Ca.L), sinoatrial node cells and ventricular myocytes isolated from adult guinea pigs to test effects on I (f) and action potential (AP) duration, as well as HERG-transfected HEK 293 cells to analyse the influence on the I (K.r). In these voltage clamp experiments the purified exerted a calcium-antagonistic activity by I (Ca.L) blockade, reduced the repolarising current I (K.r), and prolonged the AP-duration, while I (Na) was not affected. Although the extract displayed only weak effects on the I (f) amplitude and voltage dependence, it significantly prolonged the activation time constant of I (f). Thus, the purified extract acts on multiple electrophysiological targets, specifically I (Ca.L), I (K.r), and I (f), observed both at whole organ and single cell level. The actions correspond to class III antiarrhytmic drugs,

however a proarrhytmogenic activity and a potential to induce torsade de points was not observed, even at 2 mg/ml. In summary, a bradycardic action of "multi-ion channel blocker type" could be confirmed (Ritter 2009).

Up to 10^{-3} g/ml of dry extracts of the herb prepared with methanol 50% and chloroform did not have any relaxant effect on KCl-induced contractions in rabbit aorta strips in vitro (Rauwald 1994). Lack of Ca-antagonistic activity and even a slight increase in contraction is reported by Rauwald (1991).

Other actions on isolated organs
Isolated small intestine of guinea pigs: Ashes/minerals from *L. cardiaca* herb resulted in a strong increase of the tonus, whereas a decoction or an ethanolic extract (see sedative action) resulted in a week increase of tonus (Erspamer 1947).
Isolated small intestine of dogs: A decoction resulted in an increase of tonus that returned slowly back to normal, an ethanolic extract resulted in an increase that was hardly reversible, whereas the ashes induced an immediate increase in tonus easily reversible (Espamer 1947).
Isolated uterus of guinea pigs: 0.2 ml/8 ml of a 10% decoction; an ethanolic extract corresponding to 0.4 g herb/8ml and ashes corresponding to 0.4 g herb/8 ml resulted in a clear increase of the tonus (Erspamer 1947).
Espamer (1947) concludes that *L. cardiaca* herb has a minor, mostly excitant action on the small intestine and uterus that is, in part, associated with the minerals present in the herb.

In vivo experiments

Analgesic action
10 mg/kg of non-specified furanic labdane diterpenes are reported to have reduced abdominal contractions in mice that were induced by injection of acetic acid by 80-95%. The observed inhibition by ASS or paracetamol was 35%. No further details are presented (Brand 1999).

An aqueous and an ethanolic extract are reported to have analgetic effects in the hot plate test in mice. No further details are given (Szocs 1999).

Cardiovascular action
The aerial parts of plant material collected in Poland were extracted first with chloroform and then with methanol. The dry extract with methanol was further fractionated into ethyl ether, ethyl acetate and n-butanol. From the n-butanol fraction lavandulifolioside was isolated. In the Langendorff-heart from rats the n-butanol fraction (50 – 2000 µg) significantly reduced the heart rate from 183 (control) to 94 min^{-1}. 200–2000 µg lavandulifolioside reduced the heart rate from 231 to 164 min^{-1}. The extract fraction (50-2000 µg) and lavandulifolioside (200-2000 µg) resulted in a significant reduction in the coronary outflow. A significant prolongation of the P-Q, QRS and QT-intervals is reported with 100 – 2000 µg of the extract fraction and 200 µg of the isolated substance. 50 mg/kg b.w. i.v. (1/20 LD_{50}) of lavandulifolioside did not have any influence on the pulse rate or the blood pressure of normotensive rats, whereas 77 mg/kg b.w. i.v. produced a significant decrease in systolic and diastolic blood pressure (Milkowska-Leyck 2002).

Injection of 0.02–2.5 mg/frog stachydrine isolated from *L. cardiaca*, is reported to reduce the systolic heart rate. The effect is proposed for biological standardisation of *Leonurus cardiaca* – preparations (Rodina 1968).

In a dog, i.v. injection of an ethanolic extract (corresponding to 0.5–8 g herb/animal), a decoction (corresponding to 0.1-0.5 g of herb) or of minerals/ashes (corresponding to 2 g of herb) from *L. cardiaca* (see sedative action) resulted in a small, short term reduction of blood pressure and in a slight, short term increase of respiratory frequency. A week negative inotropic and negative chronotropic action in the isolated frog heart is associated with the minerals present in water extracts (Erspamer 1948).

Sedative action

Erspamer (1948) investigated potential sedative actions of *L. cardiacae* herba in frogs and mice. A comparison between the effects of a 5% decoction (delivering 27-32% extractibles), an extract with ethanol 95% (7.6-9.3% extractibles) and ashes prepared from the dry residue of the decoction (12.7-13.2% of the herbal substance) were performed. The dry residue of extracts was used in experiments. In frogs, a reduction or disappearance of the rightening reflex after injection in the dorsal lymph sack was observed. With doses corresponding to 0.1 g herb (decoct), 0.25 g herb (extract with ethanol) and 0.2 g herb (ashes) a partial or complete paralysis was found. Comparing to infusions from Valeriana officinalis root, the decoct from L. cardiaca was 2-3 times more effective. The author concludes that the decoction is 2-3 times more active than the ethanolic extract and that the minerals contribute to the effect of the decoction. In mice, the influence of the decoction or extract with ethanol on the spontaneous motility was assessed. After injection of ethanolic extract corresponding to 1-2.5 g of herb/mouse, a reduction in motility was observed. 5 g/mouse resulted in death of some animals after 3 or 9 h). The decoction given in doses corresponding to 0.2–0.6 g/mouse (injection) or 0.5 to 1.5 g/mouse (p.o.) resulted in a reduction of motility. The effect was dose dependent and lasted for 2 to 10 hours. After injection of a dose corresponding to 0.6 g/mouse 2/3 animals died after 30-55 min; a dose of 1g/mouse killed all animals within 15 min. No lethal effects were seen after p.o. dosing. The author concludes that the injection of the decoction is 3-4 times more efficient than the oral dose and the relation between the minimal effective and minimal lethal dose after injection is 1:2. The injection of the ethanolic extract is 6 times less effective than the decoction; the relation between the minimal effective dose and the minimal lethal dose is 1:5. Minerals/ashes are supposed to contribute to the effect after injection, but they cannot explain the full effect of the decoction. Although the author concludes that *L. cardiaca* has a weak sedative action, the models used and the limited number of test animals without any statistical evaluation cannot confirm this type of action from a modern perspective.

0.5-1.5 ml of the tincture were administered s.c. in rabbits with electrodes installed in their posterior extremity. A "sedative action" was investigated by the d.c. amperage necessary to provoke a flexor contraction of the muscle of the posterior extremity of the animals prior and after injection.
1 ml/ animal s.c. resulted in a higher amperage necessary to induce contraction (Polyakov 1962). No conclusions on sedative actions can be drawn from this model.

800 and 1600 mg/kg b.w., intragastrically of lavandulifolioside did not influence the locomotor activity in mice. 800 mg/kg b.w. of a n-butanol fraction of an extract prepared with methanol (see cardiovascular actions) reduced the locomotor activity significantly by 65% (Milkowska-Leyck 2002).

0.5 ml/mouse i.p. of an extract of the aerial parts of *Leonurus cardiaca* L. var. villosus DESF. with water (10%) is reported to reduce the motor acitivity by 50% after 3h. The extract antagonized the hypermotility induced by s.c. methyl phenidate (20 mg/kg b.w.), prolonged the ether-anaesthesia and reduced the convulsant effect of pentetrazol. No details are given (Racz 1989).

3.5 ml/kg b.w., p.o. of an extract with ethanol (concentration not given) slightly prolonged the hexobarbital sleeping time in female NMRI mice. 1.75 ml/kg b.w. had no significant effect (Weischer 1994).

Studies on related herbal substances/preparations

***Leonurus japonicus* HOUTT., herba**

Antioxidant action

An extract with acetone-water 7:3 V/V was active in the DPPH (2.2-diphenyl-1-picrylhydrazyl) free radical scavenging assay (IC_{50} 76 µg/ml). The activity was mainly associated with gallic acid, kaempferol, quercetin, and myricetin that were isolated from the extract (Qu 2006).

Antiinflammatory actions
The activity prostaglandin E 9-ketoreductase from swine kidney was increased in vitro by addition of an aqueous extract from the herb. According to the authors, this may imply an increase in PGF 2 alpha and, consequently, an inhibition of oxytocinase activity in human serum during pregnancy. The finding, together with the induction of uterine contractions may explain the traditional use as abortive medication (Hsieh 1985).

Haematological actions
2 mg/10 ml of a dry extract prepared with methanol inhibited the platelet-activating factor (PAF) receptor binding in rabbit platelets by 51%. For an extract from Ginkgo leaves (positive control), an 80% inhibition was observed (Kang 2005).

Pre-incubation of human umbilical vein cells with 50 mg/ml of a lyophilised extract inhibited the tissue factor expression induced by thrombin. The effect was time- and concentration-dependent (Yin 2008).

Leonurin isolated from the herb, inhibited rabbit platelet aggregation induced by thrombine (IC_{50} 97.22 µM), arachidonic acid (IC_{50} 31.03 µM) and collagen (IC50 44.48 µM) in vitro (Lin 2007).

A furanic diterpene, prehispanolone, isolated from the herb inhibited the binding of [3H]-PAF to rabbit platelets (IC_{50}= 14.1 +/- 7.9 µM It also inhibited platelet aggregation induced by 2 nM PAF in a concentration-dependent manner, with an IC_{50} of 28.4 +/- 7.3 µM. Positive controls, among them ginkgolides (BN5221) showed IC_{50} values of 4.8 resp. 3.3 µM. Aggregation induced by thrombin, ADP and collagen were not inhibited by 50µM prehispanolone. The tetrahydrofuran ring is essential for activity. In acidic conditions, prehispanolone is readily transformed into inactive hispanolone (Lee 1991).

Actions on the endocrine system
Prolonged administration of the herb in pigs and rats is reported to decrease the level of estrogene in the urine and in the serum with no change in the menstrual cycle (Chen 1982).

No estrogenic or antiestrogenic activity was observed with a dry extract prepared from the herb with ethanol 95% in a recombinant yeast system featuring both a human estrogene receptor expression plasmid and a reporter plasmid (Kim 2008).

Cardiovascular actions
An extract of the herb with acetone 70% has shown anti-arrhythmic activity in vitro in digoxin-induced arrhythmia using papillary muscle of guinea-pig. By activity guided fractionation, stigmast-4-en-3-one (beta-sitostenone) was isolated as active constituent. The structure was confirmed by synthesis. The ED_{50} of anti-arrhythmic activity of beta-sitostenone was 35 µg/ml (Horita 2002).

Pretreatment with 400 mg/kg b.w./day with a dry extract prepared with water (approx. 5:1) that did contain stachydrine, quercetin and kaempferol as main constituents did not influence the survival rate of rats with a myocardial infarction caused by ligation of the coronary artery. An antioxidant effect is attributed to the presence of flavonoids (Sun 2005).
Pretreatment over two weeks with 400 mg/kg b.w./day with a dry extract prepared with water (approx. 5:1) that did contain stachydrine, quercetin and kaempferol as main constituents reduced significantly the volume of cerebral infarction induced in rats by middle cerebral artery occlusion. A neurological deficit score was reduced, although no significant effect is described. The pretreatment antagonized significantly the drop in antioxidant capacity of the rat serum after induction of the cerebral infarction. DNA oxidative damage was significantly reduced (Loh 2009).

In anesthetised rats with myocardial ischemia induced by ligature of the coronary artery, i.v. injection of an extract (no details given) significantly reduced plasma fibrinogen, lowered platelet aggregation rate induced by ADP and collagen (Yin 2003).

Actions on smooth muscle
Leonurin from *L. japonicus* stimulated in vitro the contraction of uterine smooth muscle from mice, pretreated with oestrogen. Significant effects on frequency and amplitude are reported for 40 µg /ml and 90 µg/ml. In smooth muscle from portal veins from rats, a dose dependent reduction of the amplitude by 32–640 µM leonurin was observed. The effect was comparable to 0.003–0.03 µM nifedipine. A significant increase in frequency was only observed at the highest concentration of 640 µM leonurin, whereas nifedipine produced significant effects over the total dose range (Chen 2000).

Leonurin (0.4 µg/ml) isolated from the herb, induced regular contractions of large amplitude in uterine preparations from rats. Actively contracting uterine preparations from estrous rats responded by an increased rate of contraction (Yeung 1977).

Leonurin induced concentration-dependent and endothelium-independent relaxation of phenylephrine pretreated rat aorta rings (IC_{50} 86 µM). It caused a concentration dependent inhibition of vascular contractile responses to KCl (IC_{50} 96 µM) and relaxed aortic contraction caused by prostaglandin F2-alpha. All effects were reversible and did not affect the resting tension. Similar effects were observed with 0.03–3.0 µM nifedipine (Chen 2001).
An extract prepared with water (0.3 mg/ml) stimulated slightly contractions of the the isolated rat aorta with endothelium. Contractions induced by 3–10 µM phenylephrine were markedly enhanced by the extract in a dose-depend, reversible way. A maximum effect was seen with 1-3 mg/ml. The effect was not observed in rat aorta without endothelium. An extract with acetone 70% was active, whereas extracts with methanol 70% or ethanol 70% were not. By comparison to the effects of a NO synthase inhibitor (L-NAME = L-Nitro-Ariginine-Methyl-Ester) the authors conclude that the extract may have a similar mode of action (Pang 2001).

Antiproliferative action
The effects of a freeze-dried extract with water of the dried, above earth parts of *L. japonicus* were investigated. Results were expressed in equivalents of herbal starting material. An inhibition of proliferation in vitro, after 48h hours incubation with the extract, is reported for the following tumor cell lines (IC_{50} expressed as raw herbal material): C-33A human cervix carcinoma (8 mg/ml), A-549 human lung carcinoma (20 mg/ml), MCF7 human breast adenocarcinoma (40 mg/ml), MDA-MB-453 human breast carcinoma (25 mg/ml), DU 145 human prostate carcinoma (20 mg/ml), LN CaP human prostate carcinoma (20 mg/ml), TsuPr1 human prostate carcinoma (12.5 mg/ml). An apoptotic mechanism involving mitochondrial depolarization, cytochrome-c release and caspase 3 activation is proposed (Chinwala 2003).

Cytotoxicity of a dry extract from the aerial parts with 70% ethanol (approx. 28:1) was analyzed with MTT assay on ER negative MDA-MB-231 and ER positive MCF-7 human breast cancer cell lines. The extract caused cell death in a dose-dependent and time-dependent fashion in both ER positive (IC_{50} 96.2 µg/ml) and negative (IC_{50} 89.1 µg/ml) breast cancer cells. Morphology, Hoechst 33342 staining and flow cytometry evidence all indicated the cell death is not in an apoptotic nature. Furthermore, low concentrations of the extract caused cell cycle arrest at G2/M phase (Tao 2009).

Anticonvulsive action
The essential oil from *L. japonicus* from Brazil, up to 700 mg/kg b.w i.p., was not effective in preventing pentylenetetrazol-induced convulsions in mice (Coelho de Souza 1998).

Actions on the uterus
Leonurin isolated from the herb increased the frequency and amplitude of contractions in uterine strips from proestrous rats or ovarectomised rats pretreated with estradiol. In a concentration range of 0.2-1.0 µg/ml a dose-dependent, reversible effect was found (Kong 1976).
In myometrium samples of patients undergoing total hysterectomy, an increase in frequency and amplitude in uterine contractions was recorded in vitro after adding a dry extract prepared with

methanol from the herb to the organ bath. 4 samples from patients well beyond menopause did not react (Kong 1974).

Other actions
Leonurin, isolated from the herb, inhibited in vitro rabbit muscle creatine kinase activity in concentration- and time-dependent manners (at 0.75 and 1.51 mmol from 12 to 72 h). Similar effects are described for guanidin-HCl. Leonurin first acts as a non-competitive inhibitor and then as an irreversible inhibitor (Wang 2004).

Protective effects of synthetic leonurin against doxycycline (DOX)-induced cardiomyopathy in H9c2 cells were investigated. Pretreatment of isolated cells with 1-100 µM leonurin, 2 h before DOX treatment could reduce DOX-induced (2 µM) apoptotic death of H9c2 cell, reduce MDA formation and intracellular Ca2+ overload. The authors conclude that leonurin reduced DOX-induced apoptosis in H9c2 cell by increasing anti-oxidant, anti-apoptotic ability and protecting mitochondrial function (Xin 2009).

***Leonurus japonicus* HOUTT., fructus**

Cycloleonurinin isolated from the fruits did not present any activity on the isolated guinea pig ileum, the isolated rat aorta (up to 3 x 10^{-5} M), or on the blood pressure in urethane anesthetized rats (5 mg/kg b.w. i.v.) (Kinoshita 1991).

Cycloleonurinin inhibited the mitogen (concanavalin A) induced response of human peripheral-blood lymphocytes (IC_{50} 28 ng/ml). The effect was comparable to cyclosporin A (IC_{50} 3 ng/ml) (Morita 1997a).
Cycloleonuripeptide B and C showed growth inhibition in p-388 lymphocytic leukemia cells (IC_{50} 6.0 µg/ml, 3.7 µg/ml) (Morita 1996).

A heat-stable antimicrobial protein, designated LJAMP2, was isolated. LJAMP2 exhibited a molecular mass of 6.2 kDa. In vitro bioassays showed that LJAMP2 inhibits the growth of a variety of microbes, including filamentous fungi, bacteria and yeast. The growth of three phytopathogenic fungi, *Alternaria brassicae*, *Botrytis maydis*, and *Rhizoctonia cerealis*, were inhibited at 7.5 µM of LJAMP2, whereas *Bacillus subtilis* was about 15 µM. The IC_{50} of LJAMP2 for *Aspergillus niger*, *B. maydis*, *Fusarium oxysporum*, *Penicillium digitatum* and *Saccharomyces cerevisiae* are 5.5, 6.1, 9.3, 40.0, and 76.0 µM, respectively (Yang 2006).

***Leonurus sibiricus* L. (see comment in 1.1.1.):**

Antioxidant activity
The aqueous extract of *Leonurus sibiricus* L., herba was examined for its reducing power, scavenging ability toward superoxide and hydroxyl radicals, and their inhibitory effect on lipid peroxidation. The extract was found to be active on scavenging of superoxide radicals. The level of hydroxyl radical scavenging activity tended to be lower than that for superoxide radicals. Inhibitory effects on lipid peroxidation were examined using a rabbit erythrocyte-ghost system (Nam 2004).

Inhibition of the cytochromes
Lyophilised extracts with water from "Leonuri herba" commonly used in Korea (species not specified; *L. sibiricus* L. or *L. japonicus* HOUTT.), were tested for inhibition of several cytochrome P450 (CYP) isoforms and microsomal NADPH-CYP reductase. The abilities of 1-1000 µg/ml to inhibit phenacetin O-deethylation (CYP1A2), tolbutamide 4-methylhydroxylation (CYP2C9), S-mephenytoin 4′-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), chlorzoxazone 6-hydroxylation (CYP2E1), midazolam 1-hydroxylation (CYP3A4) and NADPH-CYP reductase were tested using human liver microsomes. The following IC_{50} (µg/ml) were found (comparator quercetin µM/ml):

CYP 1A2 830.9 (1.25), CYP 2C9 698.8 (19.2), CYP 2C19 342.1 (>30), CYP 2D6 >1000 (>30), CYP 2E1 >1000 (>30), CYP 3A4 712.9 (>30), NADH-CYP reductase >1000 (0.88) (Liu 2006).

The MeOH extract, CH_2Cl_2 fraction, EtOAc fraction, n-BuOH fraction and H_2O fraction of *Leonurus sibiricus* herb showed significant inhibitory effects on Cyp 1A1/2, 2B1/2, 2E1. The IC_{50} values of these extracts were found to be below 50 µg/ml (Jeong 2002).

Antimicrobial action:
An in vitro antimicrobial action against *St. aureus*, *S. epidermis*, *Strepotococcus pyogenes*, *E. coli*, *Vibrio colerae*, *Shigella dysenteriae*, and *S. boydii* has been found for CCl_4 and chloroform extracts of the aerial parts. The zone of inhibition of 500 µg/disc of extract has been similar to 30 µg/disc of kanamycin. No or a minor inhibition was observed with extracts prepared with methanol or acetone (Ahmed 2006).
A methanolic extract from *L. sibiricus* herb from Brazil presented in vitro an inhibition of *B. subtilis*. No inhibitory effect was observed in *St. aureus*, *St. epidermidis, E. coli, Micrococcus luteus, C. albicans, S. cerevisiae* (Coelho de Souza 2004).
Dry extracts prepared by stepwise extraction with ethanol 96% and ethanol 70% were reported to have a significant antifungal activity in vitro (< 2 µg/spot) Heinrich (1991).
An extract with ethanol 70% was reported to be active in vitro against *C. albicans, St aureus* and *Ps. aeruginosa* (Wadt 1996).

Cytotoxic actions:
A lyophilised water extract from *L. sibiricus* L., herba, (0.1 mg/mL) did not have any significant effect on the growth of human myometrial or leiomyomal cells in vitro. The study could not confirm prior results reported by Baek (2006) (Bajracharya 2009).
Furanic diterpenes, isolated from the herb, showed weak cytotoxic activity against L1210 leukaemia cells in vitro (IC_{50} 50-60 µg/ml) (Satoh 2003).

Action on endogenous mediators (NO, TNF-alpha, Interleukines)
0.01–1 g/kg of a lyophilized extract with water (approx 10-20:1, contradictory information provided) from the herb was investigated in mouse peritoneal macrophages in vitro. The concentration range was chosen to reflect the traditional dose of *L. sibiricus* herb in man (0.1 g/kg). The test solution of extract contained less then 10 pg/mL endotoxin, so that endotoxin related effects were excluded. Whereas the extract had no direct effect on the NO production there was a marked increased action when combined with recombinant interferon–gamma. The effect could be antagonized by pretreatment with pyrrolidine dithiocarbamate (PDTC), an inhibitor of nuclear factor kappa-B. PDTC antagonized the increase of TNF-alpha production in peritoneal macrophages stimulated with recombinant interferon-gamma (An 2008).

The anti-inflammatory effect of a lyophilised extract prepared with water on the secretion of tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 and IL-8 was investigated in a human mast cell line (HMC-1). Incubation of HMC-1 cells with phorbol 12-myristate 13-acetate (PMA) plus calcium ionophore A23187 and 0.1 and 1 mg/ml extract inhibited significantly the production of TNF-alpha, IL-6, and IL-8 by 57%, 78.2% and 84.8% respectively (at 1 mg/ml). The extract had no cytotoxic effects on HMC-1 cell viability. Stimulation with PMA plus A23187 induced NF-kappaB activation in HMC-1 cells, was inhibited by 1 mg/ml extract (Shin 2009).

Sedative action:
200 mg/kg and 400 mg/kg, i.p., of a dry extract (approx. 10:1) prepared with methanol 90% are reported to reduce the onset of sleep and to prolong the sleeping ime in pentobarbital induced sleep in mice. The same doses of the extract caused a significant decrease of scores in different exploratory behaviour tests (open field test, hole cross test, hole board test) in mice (Ahmed 2005).

Antiinflammatory action

250 and 500 mg/kg i.p. of a dry extract from the herb prepared with methanol showed a significant analgesic effect in acetic acid-induced writhing in mice. The writhing count was reduced by 44.15 rsp. 69.68%. 25 mg/kg b.w. i.p. of Diclofenac resulted in a 74.67% reduction. 200 and 400 mg/kg, p.o. showed a significant anti-inflammatory activity against carrageenin induced paw oedema in rats. The maximum inhibition after 3h was 27% resp. 40%, comparing to 42% inhibition by 100 mg/kg b.w. p.o. phenylbutazone (Islam 2005).

Anticancer action

Feeding 5-7 month old and 8-12 months old C3H/He mice with 0.5% of a dry extract prepared with methanol 60% in drinking water over 20 days significantly reduced the number and size of hyperplastic alveolar nodules in the mammary glands in both age groups. No influence on estrous cycle, plasma prolactin, anterior pituitary, adrenals or ovaries was found (Nagasawa 1990a).

Permanent feeding of multiparous GR/A mice with 0.5% of an dry extract prepared with methanol 60% in drinking water over several litters enhanced the development of both pregnancy-dependent mammary tumours (PDMT) and mammary cancers originated from PDMT: 1st litter 31.3% (extract) vs. 11.9% (water), 2nd litter 74.1% vs. 34.1%, 3rd litter 86.7% vs. 95.0%. By contrast, the treatment markedly suppressed the development of mammary cancers that originated from hyperplastic alveolar nodules (HAN) associated with the decreased formation of HAN. The incidence of uterine adenomyosis was also inhibited in mice given motherwort (7.1% vs. 41.7%). The cause of discrepancy of the effects of motherwort on mammary cancers due to their origins could not be explained (Nagasawa 1990b). Administration of the extract could counteract the reduced lactation caused by PDMT (measured by the pub growth rate and weight) without any influence on the prolactin level. Mammary DNA and RNA contents were increased in PDMT-positive mice. The authors conclude that the restoration of lactation is principally attributed to its stimulation of mammary gland epithelial cell function and not by an endocrine mechanism (Nagasawa 1991).

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

No studies have been performed. In absence of constituents with known therapeutic activity, kinetic studies are not required.

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

***L. cardiaca* L. var. *villosus* DESF., herba**

Extract with water (1ml=1 g dry material): LD_{50} i.p., mouse, 10,800 mg/kg b.w. (Racz 1989).

***L. cardiaca*, herba:**

N-butanol fraction from an extract with methanol from *L. cardiaca*, herba (see cardiovascular effects): LD50 i.v. 400 mg/kg b.w.; p.o.>2000 mg/kg b.w. (Milkowska-Leyck 2002).

Related herbal substances and isolated constituents

Acute / subchronic toxicity

The toxicity of the dried herb of *L. sibiricus* L. on Sprague Dawley male and female rats was evaluated through 90-day sub-chronic studies. The rats were fed powdered herb at the rate of 0.5 (low dose), 5 (medium dose) and 25 (high dose) g/kg body weight. Minor treatment-related effects were observed for body weights, organ weights and the lipid profile parameters and these did not appear to be of toxicological significance. Signs of renal and liver toxicity were evident in the medium and high dose groups when plasma creatinine and liver enzymes (ALT, AST) were found to be significantly higher

when compared with the control and the low dose groups. A decrease of alkaline phosphatase (ALP) was observed in the medium and in the high dose groups. The haematology study revealed a statistically significant mild anaemia in rats from the medium and high dose groups as indicated by decreases in haemoglobin, red blood cell count and packed cell volume (haematocrit value). Administration of the herb at medium and high dose was also found to cause adverse effects in histopathological structure of the liver (mild-severe degeneration biliary hyperplasia, megalocytosis, lymphocytic infiltration, degeneration of hepatocytes) and kidney (renal nephrosis) of both male and female rats. The low dose group showed no significant differences compared to the control. According to the authors, a dose of 0.5 g/kg bw is considered safe (Pin 2009).

Extract from *L. japonicus herb* (not specified), LD_{50}, i.v., mice: 30-60 g/kg b.w. (Chinwala 2003).

Adult male rats fed on a diet with 50% *L. japonicus herb* for 80 days showed no toxic effects or change in fertility (Kong 1976, Chinwala 2003).

Total alkaloids from *L. japonicus herb* (not specified), i.v., mice, 572 mg/kg b.w. (Chinwala 2003).

Lavandulifolioside isolated from *L. cardiaca*: LD50 i.v. approx. 1000 mg/kg b.w., p.o. > 2000 mg/kg b.w. (Milkowska-Leyck 2002).

No adverse effects in rats after 2 *mg/rat leonurin i.p. for 4 days (Kong 1976, Chinwala 2003).*

30 mg/kg b.w. per day of leonurin, s.c., in rabbits over 2 weeks did not affect food intake, faecal and urinary excretions and body weight (Chinwala 2003).

Leonurin of synthetic origin is reported to be non-toxic up to 4g/kg b.w. in rats. No details are given (Chan 1983).

Toxicity on reproduction
A fed containing 50% of powdered *L. japonicus herb* did not affect fertility in male rats (Chinwala 2003).

The milk production in rats fed a diet with 1% of the herb, starting on day 18 of gestation, was significantly increased on day 8, 13 and 18 of lactation by 15.22, 19.11 and 19.25% as compared to non-supplemented controls. The pup weight on day 15 and 22 was increased by 9.99 and 9.01% respectively. The daily weight gain on days 8-14, 15-21 and 1-21 was increased by 19.44%, 6.78% and 11.11% (Shi 2007).

Rats given 0.5 mg/ml leonurin of synthetic origin as the only water source over 3 generations and cross-bred with treated mates showed no sign of aberration in gross morphology, growth rate, sex ratio, liter size and pup weight. No further details are given (Chan 1983).

3.4. Overall conclusions on non-clinical data

Pharmacodynamic studies on Asian and European *Leonurus* species follow the different traditional uses: sedative and cardiovascular effects for *L. cardiaca* were investigated in Europe whereas effects of *L. japonicus* on reproductive organs and haematological parameters were focused in Asia. There is some overlap between the effects of both species, although it remains an open question if the different studies reflect a different pharmacological profile or simply a different area of interest.

From a perspective of safety the bradycardic actions, renal and liver toxicity and the activity on the uterus deserve attention. Water soluble components exert in vitro in relatively high doses of 1-2 mg/ml a negative inotropic and bradycardiac action. The relevance of these findings for the oral use of the tincture or herbal tea is highly questionable. The finding that, even at that high concentrations, no potential for induction of torsade-de-points is present, adds to the safety of traditional preparations.

The finding of renal and liver toxicity in animals after prolonged feeding of high doses of *L. sibiricus* powder is not considered relevant for the use of the herbal tea or the tincture under the conditions proposed in the monograph. The maximum dose for preparation of an herbal tea is 10 g/day, representing an additional safety margin of 2.5 (50 kg person) compared to the dose of powder that is considered safe in the feeding experiment. The maximum daily doses of the liquid extract 1:1 (12 ml) would result in a safety margin of 2 and of the powder (450 mg) in a safety factor of > 50. In addition to that, the duration of use under OTC conditions is limited to 4 weeks vs. 90 days in the feeding study. As clerodane-type furanic diterpenes that were found in Teucrium and that are known for hepatoxicity are absent from *Leonurus*, the reason for the effects remain unknown. It may deserve additional studies and calculations if the furanic part of the labdane-type diterpenes present in *Leonurus* represent some structural alerts that need to be investigated further.

Although no studies have been performed with *L. cardiaca* on toxicity in reproduction, the data on leonurin (present in *L. cardiaca*) and the studies in Asian *Leonurus* species point to a risk and confirm the contraindication in pregnancy that is widely and consistently found in several handbooks.

No studies on genotoxicity and carcinogenicity have been found.

The data on sedative actions, although limited, contribute to the plausibility of the traditional use of *L. cardiaca* in the indication covered by the monograph.

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

According to Ovanesov (2005) enhanced anxiety state is accompanied by a limitation of the color-discrimination function of the retina in young humans. Chronic administration of tofisopam (grandaxin) or tinctura leonuri is reported to have decreased anxiety and significantly improved the colour discrimination function of retina with respect to all four colours studied. The author suggests that this improvement may be related to an action upon the GABAergic processes both in the retina and in the related cerebral structures. No details are presented.

After repeated administration of melatonin (0.75 mg at night, 10 days) a significant decrease in the thresholds of retinal brightness sensitivity and an improved emotional state in anxious young subjects have been observed. Similar, but less pronounced effects were observed after the treatment with *Leonurus cardiaca* tincture. The authors suggest that there might be a relation between the limitation of anxiety and the improvement of visual function (sensitivity). No details are presented (Ovanesov 2006).

Other Leonurus species:

***L. japonicus* HOUTT.:**

Haematological parameters
The results of a clinical study, involving 105 men with "blood hyperviscosity" (hypertension 60, atherothrombotic brain infarction 21, brain atherosclerosis 9, diabetes 3) are reported. The patients did receive 10 ml of a preparation consisting of a decoction of the herb (5 g/ml) in 250 ml 5% glucose i.v. per day for 15 days. No details on the preparation are available. Improvement of symptoms such as vertigo, headache, insomnia, numbness in limbs, ability to stand on one leg with closing eyes, is

reported for the majority of patients. Platelet aggregation that was investigated in 65 patients was significantly reduced (Zou 1989).

52 Patients with thrombocytopenic purpurea were treated by TCM "Huo Xue Hua Yu" medications, i.e., agents that are traditional associated with “activated blood flow and elimination of blood stasis”, among them *Leonurus japonicus*. An overall response rate of 88%, with platelet and megakaryocyte recovery is reported. The elevated PAIgG and the platelet count felt to normal levels in the majority of cases. No detailed information could be found (Deng 1993).

Uterotonic activity
The effect of an infusion of the herb was investigated in 141 fertile women. A single dose of 150 ml of a decoction prepared from 30 g of herb was administered orally. Intra-uterine pressure was measured by a catheter filled with sterile saline-citrate solution. The base line was established through a recording of 30-90 min before dosing. After dosing, pressure was monitored for another 1-2 hours. 121 cases were fit for evaluation. Of these, an effect was seen in 50 cases (success rate 41%). Two additional cases presented an increase in contraction frequency without increased pressure. The pressure increase corresponded to 150% to 300% of the base line pressure. Control with water resulted in a 2.7% increase, control with 0.2 mg, i.m. Ergonovine resulted in a comparable increase of intrauterine pressure. As the success rate of Ergonovine injection was 61%, p.o. application of the decoction had a relative potency of 91%. Abdominal pain (4.1%) and increased diuresis (48%) were observed. No influence on blood pressure or heart rate was seen. The uterotonic effect was independent from the stage of menstrual cycle, age, parity, uterine position in situ, blood pressure and pulse rate. The authors associated the effect to leonurin (Chan 1983).

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

No clinical studies have been performed. In absence of constituents with known therapeutic activity, pharmakokinetic studies are not required.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No information on dose-response studies was found.

4.2.2. Clinical studies (case studies and clinical trials)

Fifty male and female patients with arterial hypertension stage 1 (n=22; bp 140-159/90-99) or stage 2 (n=28; bp 160-179;100-109) that presented symptoms of anxiety and sleep disorders were treated for 28 days with 2 x 600 mg of an extract from L. cardiaca, herba, prepared with soybean oil (DER 1:10 m/V). The extract contained 0.3 mg total iridoids/dose. A significant decrease in BP, as compared to baseline values, was observed (Stage 1: SBP 144.5 ->129.4 mm Hg; DBP 96.1 -> 85.9 mm Hg, stage 2: 153.3 -> 141.6 mm Hg, DBP 102.7 -> 91.9 mm Hg). Symptom scores relating to anxiety, emotional liability, and sleeping improved significantly, as compared to baseline. No significant effect on heart rate was observed (Shikov 2010 a, Shikov 2010 b).

Due to the short duration of the study and due to the absence of a control group, no conclusion on efficacy can be drawn from this study. However, the results add to the plausibility of the traditional use.

Studies with combination products

Fifty male alcohol abusers (mean age 45.6 years) with sleep disturbances were enrolled in a cross-over, placebo controlled study with a fixed combination product. On 2 consecutive nights, the volunteers were given tablets containing 170 mg *valerian (Valeriana officinalis) root, 50 mg hop cones, 50 mg balm (Melissa officinalis) leaves and 50 mg moth*erwort (*Leonurus officinalis* [sic]) herb, or the placebo, which contained 5 mg valerian root. Treatments were taken orally 1 hour before bed. The following morning a questionnaire was completed by the volunteers, concerning sleep quality, dream recall, frequency of night awakenings, and fatigue and sleepiness in the morning. Statistical analysis using the Wilcoxon matched-pairs signed-ranks test (using each subject as his own control) was performed on the resulting data. The combination showed significant improvement in sleep quality, a reduced feeling of sleepiness the next day, a decrease in the recall of bad dreams and a notable decrease in night awakenings. No conclusion with respect to any contribution of *L. cardiaca* to this effect can be drawn (Widy-Tyszkiewicz 1997).

Studies with preparations from* L. japonicus*, herba

85 patients with acute cerebral ischemic infarction were randomized to receive either 10 ml of a "*Leonurus* injection" plus 500 ml 0.9% NaCl solution i.v. drip q.d. for 15 days or 20 ml of a "Salvia miltiorrhiza injection" plus 500 ml 0.9% NaCl solution i.v. drip q.d. for 15 days. No details on the extract are given. As compared to the start of the study, there was a significant difference favouring the *Leonurus* preparation in the curative rate (neurological deficit status; 70% improvement vs. 31%). The *Leonurus* preparation reduced serum lipids, fibrinogen and had an anticoagulant action (Xu 2002).

An injection prepared from *L. japonicus* herb (no details on the extract) was tested for preventing postpartum haemorrhage after caesarean section in a prospective, randomized and single blinded multi-centre study. 440 women underwent caesarean section (CS) indicated by obstetric factors were enrolled from 15 teaching hospitals in China and assigned into three groups: group of motherwort: 147 cases were administered by motherwort 40 mg uterine injection during CS and 20 mg intramuscular injection per 12 hours 3 times after CS; group of motherwort+oxytocin: 144 cases were administered by motherwort 40 mg and oxytocin 10 U uterine injection during CS and motherwort 20 mg intramuscular injection per 12 hours 3 times after CS and group of oxytocin: 149 cases were administered by oxytocin 10 U uterine injection and oxytocin 10 U+5% glucose 500 ml intravenously injection during operation and oxytocin 10 U intramuscular injection per 12 hours 3 times after CS. The following clinical parameter was collected and analyzed: (1) The amount of blood loss during operation, at 2, 6, 12, 24, 48 hours after operation. (2) The total amount of blood loss in 24 hours after CS and the incidence of postpartum haemorrhage. (3) The change of level of haemoglobin (Hb) and counting of red blood cell (RBC) from prepartum to postpartum. (4) Adverse reaction. The mean amount of blood loss during operation were (368+/-258) ml in group of motherwort, (255+/-114) ml in group of motherwort+oxytocin and (269+/-141) ml in group of oxytocin, which exhibited significant difference among three groups (P<0.01). No significant differences in the amount of blood loss among three groups were observed at 2, 6, 12, 24, 48 hours after CS. The amount of blood loss of postpartum at 24 hours were (480+/-276) ml in group of motherwort, (361+/-179) ml in group of motherwort+oxytocin, (381+/-179) ml in group of oxytocin, which showed significant difference among 3 groups (P<0.01). The incidence of postpartum hemorrhage was 32.0% (47/147) in group of motherwort, 11.1% (16/144) in group of motherwort+oxytocin, and 18.8% in (28/149) in group of oxytocin. The lowest rate of postpartum blood loss in group of motherwort+oxytocin and the highest rate in group of motherwort differed significantly (P<0.01). The decreased level of RBC and Hb were shown that RBC (0.3+/-0.5)x10(12)/L and Hb (9+/-13) g/L in group of motherwort, RBC (0.2+/-0.4)x10(12)/L and Hb (6+/-10) g/L in group of motherwort+oxytocin and RBC (0.2+/-0.4)x10(12)/L and Hb (7+/-30) g/L in group of oxytocin respectively. The value of RBC and Hb in group of oxytocin and motherwort+oxytocin showed significant difference (P<0.05). Two cases with allergic reactions were

observed. The authors conclude that combined use of motherwort injection and oxytocin to prevent postpartum haemorrhagia during or after caesarean section is safe and effective (Lin 2009).

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

No clinical studies of good quality have been found. The statement in a very old textbook (Schröder 1685) that preparations from *L. cardiaca* are "especially useful for the treatment of cardiac complaints in children" is not substantiated by new studies, although the use of a combination product in France that has been in use since 1953 points to the same direction.
A collection of case reports has been published by Orlandi (1950): 11 children were treated with a dry extract prepared with water incorporated in granules. 6 g of granules per day, containing 0.03 g of dry extract, were administered in three single doses. No further details on the extract are given. One infant (15 months) presented complex symptoms associated with rachitis and central seizures among them restlessness, irritability, and spasms. After treatment with *Leonurus* extract for one week, a general improvement of the nervous symptoms is reported. Ten children (2.5 to 9 years) presenting heterogeneous symptoms such as heart palpitations, extrasystolic tachycardia, vasomotoric complaints, irritability, sleep disorders, nervousness, anxiety. Treatment for 5 days to 1 month resulted in an improvement of nervous symptoms and heart palpitations. The author concludes that the extract has a sedative action in children. In view of the small number of cases, the heterogeneity of conditions and the limited availability of information on medication and other interventions applied no conclusion on the safety and efficacy of *L. cardiaca* in the paediatric population can be drawn.

4.3. Overall conclusions on clinical pharmacology and efficacy

The summary statement by Benedum (2006) that "traditionally the effects of the drug on palpitations, anxiety attacks, cardiac asthenia, labile pulse, and altogether on nervous cardialgia are excellently substantiated" cannot be fully endorsed. No studies on efficacy have been retrieved from literature searches. The use as an adjuvant in hyperthyreosis (Kommission E 1986, Wichtl 2002, 2009) is not supported by any clinical data. Initiation of treatment for any type of thyroid disorder should be considered only under the supervision of an experienced medical doctor (American Botanical Council 2008). In absence of clinical studies, an indication in the area of well-established use is not possible. Taking into account the continuous, long standing use of the comminuted herbal substance, the powder, the tinctures and the liquid extract in symptoms of nervous tension the traditional use in this indication is plausible. Cardiac complaints are consistently and widely mentioned in the literature and such use may even be reflected by the plant's name. Although the indication is covered by the broader term, nervous cardiac complaints such as palpitations were included under the condition that initial diagnosis by a doctor has ruled out any serious condition such as arrhythmia, hyperthyreosis, organic heart diseases, etc.

As other specific expressions of symptoms of nervous tension such as hyperthyroidism, or other indications such as anxiety may indicate a serious condition and require intervention by a medical doctor for diagnosis, treatment and follow-up, such a differentiation is not appropriate, although a traditional use could be extracted from literature.

5. Clinical Safety/Pharmacovigilance

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

No clinical studies with single ingredient products were found.

5.2. Patient exposure

The herbal substance has been continuously distributed in the EU for more than 30 years, it is present in official pharmacopoeias for more than 50 years and the continuous use of the herbal tea is documented for nearly 400 years (see above).

98.000 packages of 25 ml tincture have been sold in Lithuania in 2008. More than 350.000 packages were distributed from 2003 until March 2009 (Valentis 2009).

5.3. Adverse events and serious adverse events and deaths

Unknown (Krylow 1993).

A 94 year old woman was admitted at hospital for heart failure and bradyarrhytmia. She had been treated before over three days with spironolactone and a combination product that contains *L. cardiaca* herb. ECG showed complete AV block, prolonged QTC, and late ventricular premature beats. As the authors suspected a wrong OTC use of cardiac glycosides, digoxin plasma level was assessed (0.73 µg/l). The authors assume that glycosides present in *L. cardiaca* may have cross-reacted with the assay. Electrophysiological tests showed nodal and intrahissian conduction disturbances that persisted after the use of the combination was stopped. The authors conclude that the combination product may have contributed to the cardiac disorders observed in the patient (Remblier 1999). No similar cases have been reported to the French Agency; PSURS from 2002 and 2008 did not present any special side effects.

The following information on adverse events is labelled for a tincture marketed in Lithuania and Latvia: Very rarely hypersensitivity may occur; gastro-intestinal disorders (nausea, diarrhoea, stomach pain may occur. No reports on AE were received in the period of PSUR (2003-2009) (Valentis 2009).

No case reports of allergic reactions, including contact allergy, were found in literature. The occurrence of gastric complaints may be associated with the tannins or the bitter taste of the herbal preparations. As such a "class labelling" is absent in monographs *on* Centaurii herba, or Hamamelidis cortex, the inclusion of an ADR is in absence of any case reports not appropriate.

5.4. Laboratory findings

None reported.

5.5. Safety in special populations and situations

Potential for interactions:

None documented (Barnes 2007).

Abebe (2002) has claimed that *Leonurus cardiaca* L would contain "coumarin" and might interfer with NSAIDs with respect to decrease in blood coagulation/increased bleeding. Appropriate precautionary mesures when taken with NSAIDs or in coagulation disorders are recommended. However, coumarin does not interfer directly with blood-coagulation and neither coumarin nor dicoumarole-like structures have been reported as constituents of *L. cardiaca* herb. The article by Zou (1989) used for this claim referred to a different species (*L. heterophyllus* = *L. japonicus*) and a different class of substances (prehispanolone = labdane-diterpene). The statement from Yarnell (2009) "claiming that, because one coumarin-derived family of molecules is anticoagulant, all coumarins are anticoagulant is bad science" can be supported, although the authors classify prehispanolone as a "coumarin".
Miller (1998) and Harkness (2003) have reported that motherwort would contain cardiac glycosides and significant interactions may occur. Although the presence of glycosides with "cardiac action" was

reported in old literature, no digitalis like cardiac glycosides has been found. The recommendation to avoid taking motherwort for this reason has no scientific basis.
Potentiates the effects of hypnotics and analgetics (Krylow 1993). For studies on effects on the cytochrome-system see the section on *Leonurus sibirus L.* in chapter 3.1.

Overdose:

A dose of 3000 mg of solid extract per day, taken in capsule or tablet form, is likely to cause diarrhoea, stomach irritation, or uterine bleeding (Balch 2002). This statement seems to refer to an earlier statement from Van Hellemont (1986) that a dose in excess of 3.0 grams of a powdered extract may cause diarrhoea, uterine bleeding, and stomach irritation. No details on the extract are recorded.

Pregnancy/Lactation:

Because of the traditional use for uterine stimulation, motherwort should not be used by pregnant women (Balch 2002).
Contraindicated in pregnancy (Bradley 1992).
Not to be used during pregnancy; emenagogue / uterine stimulant (McGuffin 1997).
The use during pregnancy and lactation should be avoided (Barnes 2007).

Other Leonurus species:

Pregnancy/Lactation:

L. japonicus Houtt., herba:

L. japonicus Houtt., herba is contraindicated during pregnancy (Stöger 2009) for uterotonic effect (see 4.1.1.)

Precautions for use:

L. japonicus Houtt., fructus:

To be used with special care in patients with wide pupils (Stöger 2009).

Overdose:

L. japonicus Houtt., fructus:

After ingestions of 20-30 g toxic reactions may appear in 4-10 hours. Symptoms include generalised weakness, paralysis of lower limbs, numb, painful sensation of the whole body, an oppressive sensation in the chest and sweating (Bensky 2004).

5.6. Overall conclusions on clinical safety

Preparations of *L. cardiaca* are safe under the conditions of use included in the monograph. Preclinical data, a clinical study with *L. sibiricus* and consistent information from handbooks are the basis for establishing a contra-indication in pregnancy.
The adverse events mentioned for the tincture seem to be of a hypothetical nature. No case reports have been found.
The duration of use should be limited to 4 weeks because of the clinical condition that would need a medical diagnosis after that period of time and because of inconclusive signals for risks at higher doses/prolonged use from animal experiments. Information with respect to interaction with sedatives has not been included, although it is reported in a general way without any case reports.
The potential for interaction with substances such as warfarin deserves careful consideration. Warnings that can be found in handbooks are based on the wrong assumption that *L. cardiaca* may contain relevant amounts of "coumarins" with an anti-coagulant effect. However, relatively high dosages of

preparations of Asian *L. japonicus* are reported to have influenced blood aggregation. As no case reports were found for *L. cardiaca* preparations and the posologies included in the monograph, no warning is included.

6. Overall conclusions

In absence of clinical studies, an indication in the area of well-established use is not substantiated.

Taking into account the pharmacological data and the continuous, long standing use of the herbal substance and preparations thereof in symptoms of nervous tension the traditional use in this indication is plausible. There is no need to consult a physician for diagnosis of this condition or for follow up within the period of time foreseen in the monograph.

The indication may cover gynaecological, cardiovascular or gastro-intestinal symptoms of nervous tension. The indication "nervous tension" has been accepted for Valerianae radix (WEU). The term, although used here in a traditional context, seems to be more appropriate than the indication "symptoms of mental stress" that has been used e.g. for Passiflorae herba, Melissae folium and others. It reflects better the endogenous causes traditionally attributed to Leonuri cardiacae herba (vegetative dystonia, neurosis) rather than exogenous "stressors". Leonuri cardiacae herba is often compared by authors with Valerianae radix and Melissae folium and combinations often contain preparations of these substances.

Cardiac complaints are consistently and widely mentioned in the literature and such use may even be reflected by the plant's name. Although the indication is already covered by the broader term, nervous cardiac complaints were included under the condition that initial diagnosis by a doctor has ruled out any serious condition such as arrhythmia, hyperthyreosis, organic heart diseases, etc.

As other specific expressions of symptoms of nervous tension such as hyperthyreosis, or other indications such as anxiety may indicate a serious condition and require intervention by a medical doctor for diagnosis, treatment and follow-up, such a differentiation is not appropriate, although a traditional use could be extracted from literature.

In absence of adequate data on genotoxicity, a list entry cannot be proposed.

Annex

List of references