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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Leonurus cardiaca* L., herba

Rapporteur(s)	I Chinou
Peer-reviewer	W Knoess

HMPC decision on review of monograph on *Leonurus cardiaca* L., herba adopted on 16 September 2010	30 January 2018
Call for scientific data (start and end date)	From 31 March.2018 to 30 June 2018
Agreed by Working Party on European Union monographs and list (MLWP)	September 2018
Adoption by Committee on Herbal Medicinal Products (HMPC)	16 January 2019

Review of new data on *Leonurus cardiaca* L., herba

Periodic review (from 2010 to 2018)

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases): The EudraVigilance database was search on 2018-12-18 using the search terms “Leonuri herba”, “Leonuri tincture”, “*Leonurus cardiaca* extract” and “*Leonurus cardiaca* tincture”.

☒ Scientific/Medical/Toxicological databases Scopus – key *Leonurus cardiac* L. (Lamiaceae) motherwort; search date: 02/01/2019

☒ Other: Library of the National and Kapodistrian University of Athens (Lab of Pharmacognosy and Chemistry of Natural Products)

Regulatory practice

☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)

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☒ New market overview (including pharmacovigilance actions taken in member states)

☐ Referral

☒ Ph.Eur. monograph

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☐ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

Availability of new information (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒
Other	Yes	No
	☐	☒

Summary and conclusions on the review

During the review 74 new references not yet available during the first assessment were identified; 24 of them were considered relevant for the assessment.

No reference was provided by Interested Parties during the Call for data.

No reference justifies a revision of the monograph.

No revision is considered required because the 24 relevant references include only results on chemistry of secondary metabolites of *Leonurus cardiac*a with further phytochemical and botanical comparison with *Leonurus japonicus*, *Leonurus sibiricus* and *Leonurus glaucescens* together with some non-clinical studies (*in vitro* and *in vivo*) related mainly to the antibacterial (against *S. aureus*) action, anti-inflammatory, analgesic and antioxidant activities.

There is one reference with a clinical study on a soybean oil extract of *Leonurus cardiaca* aerial parts (1:10, w/v), which is not among herbal preparations included in the current monograph (powder, comminuted substance and hydroalcoholic extracts) based on existing bibliographic and European market overview data. Taking into account that the composition and therapeutic use of the existing preparations in the EU herbal monograph are different from that of the oil extract, data found in literature on such particular extract could not be further used and extrapolated to powder and/or water and alcohol-water extracts. The data about the oil extract is not considered in this review.

No new safety concerns related to the use of *Leonurus cardiaca* were found. No new medicinal products containing Leonuri cardiaca herba as the single active substance, fulfilling the requirements of traditional use or WEU, were reported by EU member states or by Interested Parties during the call for data.

References

a) References relevant for the assessment:

Alonso Llorente A., Nogués Esteve M. Therapeutic potential of motherwort (*Leonurus cardiaca* L.). *Revista Fitoterap* 2015, 15(2):101-107

Bernatoniene J., Kopustinskiene D.M., Jakstas V., Majiene D., Baniene R., Kuršvietiene L., *et al*. The effect of *Leonurus cardiaca* herb extract and some of its flavonoids on mitochondrial oxidative phosphorylation in the heart. *Planta Medica* 2014, 80(7):525-532

Cao T.T., Chen H.H., Dong Z., Xu Y.W., Zhao P., Guo W., *et al*. Stachydrine protects against pressure overload-induced cardiac hypertrophy by suppressing autophagy. *Cell Physiol Biochem* 2017, 42:103-114

Cheng H., Bo Y., Shen W., Tan J., Jia Z., Xu C., *et al*. Leonurine ameliorates kidney fibrosis via suppressing TGF-beta and NF-kappa B signaling pathway in UUO mice. *Int Immunopharmacol* 2015, 25:406-415

Flemmig J., Noetzel I., Arnhold J., Rauwald H.W. *Leonurus cardiaca* L. herb extracts and their constituents promote lactoperoxidase activity. *J Funct Foods* 2015, 17:328-339

Goetz P. *Leonurus cardiaca* L. (Lamiaceae), agripaume. *Phytothérapie* 2013, 11(3):188–191

Kuchta K., Ortwein J., Çali A., Volk R.B., Rauwald H.W. Identification of cardioactive *Leonurus* and *Leonotis* drugs by quantitative HPLC determination and HPTLC detection of phenolic marker constituents. *Nat Prod Commun* 2016, 11(8):1129-1133

Li X., Wang B., Li Y., Wang L., Zhao X., Zhou X. *et al*. The Th1/Th2/Th17/Treg paradigm induced by stachydrine hydrochloride reduces uterine bleeding in RU486-induced abortion mice. *J Ethnopharmacol* 2013, 145:241-253

Liu X.H., Pan L.L., Chen P.F., Zhu Y.Z. Leonurine improves ischemia-induced myocardial injury through antioxidative activity. *Phytomed* 2010, 17:753-759

Liu X., Pan L., Gong Q., Zhu Y. Leonurine (SCM-198) improves cardiac recovery in rat during chronic infarction. *Eur J Pharmacol*, 2010, 649:236-241

Mamedov, N., Mamadalieva, N. Medicinal plants from countries of former USSR used for treatment of depression (Book Chapter) in *Herbal Medicine in Depression: Traditional Medicine to Innovative Drug Delivery* 1, Ed by Grosso C. Springer Intern Publ Switzerland, 2016, pages 183-258

Matławska, I., Wojtyniak K., Szymański M. *Leonurus cardiaca* L. (Motherwort): A review of its phytochemistry and pharmacology. *Phytother Res* 2013, 27(8):1115-1120

Micota B., Sadowska B., Podsedek A., Redzynia M., Rózalska B. *Leonurus cardiaca* L. herb - a derived extract and an ursolic acid as the factors affecting the adhesion capacity of *Staphylococcus aureus* in the context of infective endocarditis. *Acta Biochim Polon* 2014, 61(2):385-388

Micota B., Sadowska B., Podsędek A., Paszkiewicz M., Sosnowska D., Różalska, B. Is it true that plant-derived polyphenols are always beneficial for the human? *In vitro* study on *Leonurus cardiaca* extract properties in the context of the pathogenesis of *Staphylococcus aureus* infections. *J Med Microbiol* 2016, 65(10):1171-1181

Rauwald H.W., Savtschenko A., Merten A., Rusch C., Appel K., Kuchta K. $GABA_A$ Receptor binding assays of standardized *Leonurus cardiaca* and *Leonurus japonicus* Extracts as well as their isolated constituents. *Planta Medica* 2015, 81(12-13):1103-1110

Sadowska B., Micota B., Rozalski M., Redzynia M., Rozalski, M. The immunomodulatory potential of *Leonurus cardiaca* extract in relation to endothelial cells and platelets. *Inn Immun* 2017, 23(3):285-295

Shikov A.N., Pozharitskaya O.N., Makarov V.G., Demchenko D.V., Shikh E.V. Effect of *Leonurus cardiaca* oil extract in patients with arterial hypertension accompanied by anxiety and sleep disorders. *Phytother Res* 2011, 25(4):540-543

Shikov A.N., Tsitsilin A.N., Pozharitskaya O.N., Makarov V.G., Heinrich M. Traditional and current food use of wild plants listed in the Russian Pharmacopoeia. *Front Pharm*acol 2017, 8:841

Simion I.M., Casoni D., Sârbu C. Characterization and classification of medicinal plants according to their antioxidant profile estimated by thin layer chromatography assisted by chemometric expertise. *J Liq Chrom Relat Technol* 2018, 41(6):342-348

Song X., Wang T., Zhang Z., Jiang H., Wang W., Cao Y. Leonurine Exerts Anti-Inflammatory Effect by Regulating Inflammatory Signaling Pathways and Cytokines in LPS-Induced Mouse Mastitis. *Inflammation* 2014, 38(1):79-88

Wang D., Wang J., Liu Y., Zhao Z., Liu Q. Roles of Chinese herbal medicines in ischemic heart diseases (IHD) by regulating oxidative stress. *Int J Cardiol* 2016, 220:314-319

Wu H., Dai A., Chen X., Yang X., Li X., Huang C., *et al*. Leonurine ameliorates the inflammatory responses in lipopolysaccharide-induced endometritis. *Int Immunopharm* 2018, 61:156-161

Zhang R.H., Liu Z.K., Yang D.S., Zhang X.J., Sun H.D., Xiao W.L. Phytochemistry and pharmacology of the genus *Leonurus*: The herb to benefit the mothers and more. *Phytochemistry*, 2018, 147:167-183

Zhao L., Wu D., Sang M., Xu Y., Liu Z., Wu Q. Stachydrine ameliorates isoproterenol-induced cardiac hypertrophy and fibrosis by suppressing inflammation and oxidative stress through inhibiting NF-kappaB and JAK/STAT signaling pathways in rats. *Int. Immunopharmacol*, 2017, 48:102-109

b) References that justify the need for the revision of the monograph:

None

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

The HMPC agreed not to revise the monograph, assessment report and list of references on Leonuri cardiacae herba by majority.

The following members did not agree with the decision of the HMPC and were of the position that there are new data/findings of relevance for the content of the monograph and a revision is needed: A Le, AP Martins, L Anderson, H Pinto Ferreira.

H Pinto Ferreira: *I have concerns related with the revision of the monograph Leonorus cardiaca. In order to prevent the wrong use of the product in situations that can risk the health and even the life of the consumer, special warnings related to the use for indication 2 should have been included. In this sense the safety of the product is not completely fulfilled. Also the indication 2 is not in line with the Article 16a, 1a, of the Directive 2001/83/EC.*