27 March 2018
EMA/HMPC/193919/2017
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Cimicifuga racemosa* (L.) Nutt., rhizoma (EMA/HMPC/48745/2017)

Final

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Cimicifuga racemosa* (L.) Nutt., rhizoma as released for public consultation on 04/08/2017 until 04/11/2017.

	Organisations and/or individuals
1	AESGP

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome

Deleted: ¶

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
4.2. Posology and method of administration (daily dose)	AESGP	**We propose to extend the posology for herbal preparations a) - c) with reference to the amount of herbal substance.** In the revised version of the monograph, the declaration changes from the fixed amount of the extracted drug to a defined amount of native dry extract. This corresponds to the actual situation of products approved in several European countries as well as in non-EU countries, and complies with the current EU requirements for declaration of herbal medicinal products (EMEA/HMPC/CHMP/CVMP/287539/05 Rev. 1). Nevertheless, there are also numerous cases within as well as outside the EU, where the daily dose is still set corresponding to the herbal substance, i.e. to 40 mg per day, based on the HMPC monograph EMA/HMPC/600717/2007 Corr. This dose is a commonly accepted daily dose, too, which still builds the fundament for established Marketing authorisations.	Not endorsed This was the wording of 4.2, original version: **Posology** *Female adults in the menopause* Daily dose (divided into 1 or 2 single doses): Dry extracts corresponding to 40 mg of the herbal substance. In the revised version, it was changed into: **Posology** *Female adults* Herbal Preparation A: Single dose: 2.8 mg Dosage frequency: 2 times daily

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		Due to the deviating contents of extractives in *Cimicifuga rhizome* a fixed amount of herbal substance is equal to a fixed amount of dry extract in single cases only. This is considered in the range of the DER. The consequence of a "redefinition" of the posology as proposed in the draft HMPC monograph would in practice have considerable consequences for the manufacturing process, and the complete quality documentation, too. The switch from the former declaration to the new description of the recommended daily dose in the chapter "posology" is appreciated but must be done under consideration of already existing long-standing marketing authorisations (MAs) within and outside the EU. One should be aware of the fact that the different declaration might lead to irritations. This can be avoided by a proposed extension of the posology wording by referring to the corresponding daily amount of herbal substance. *Cimicifuga* is an herbal drug with longstanding use. Accordingly, the history of the actually used dry extracts should not be ignored. The base for the above mentioned MAs are formerly accepted monographs, like Commission E [1], ESCOP [2] or previous versions of this HMPC, which defined the dosage only by reference to the amount of herbal substances (40 mg per day). Thus, it is important to keep this "bridge in the past". Within the Assessment Report (AR) on *Cimicifuga racemosa*, relevant clinical studies are mentioned with a dosage referring	Daily dose: 5.6 mg Herbal preparation B: Single dose: 6.5 mg Dosage frequency: 1 single daily dose Daily dose: 6.5 mg Herbal Preparation C: Single dose: 2.5 mg or 5.0 mg Dosage frequency: 1-2 times daily Daily dose: 5.0 mg" Since the posology refers to specific herbal preparations (dry extracts with defined DER), references to the corresponding amount of herbal substance have been deleted in the revised version of the EU herbal monograph. Historical data (e.g. Commission E, ESCOP) provide information regardless of the herbal preparation. Therefore, the posology in these documents usually refers to the amount of herbal substance. With establishment and revision of EU herbal monographs by the HMPC, the declaration changed from the fixed amount of the herbal substance to a defined amount of herbal preparation in compliance with current EU requirements.

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		to the amount of dry extract as well the corresponding amount of herbal substance (e.g. tables 1, and 6 AR). Especially available dose-response studies lay the focus on the amount of herbal substance. It is important that studies, in which the dosage refers only to the former specification, also remain usable, particularly for new MA applications. For a maximum gain of knowledge, all studies with *Cimicifuga racemosa* should be comparable with each other. Therefore, for example meta-analyses work with the amount of herbal substance instead of the amount of dry extract [3, 4]. The monograph itself mentions a preclinical *in vivo* study (chapter 5.3.) with no information about the amount of dry extract but the equivalent amount of herbal substance only. In summary, regarding the history of the herb, ongoing and future applications, comparability, and its relevance for the assessment, it is necessary to make a link between the old declaration (amount of herbal substance, daily dose 40 mg) and the new revised dosage recommendation (amount of dry extract). Therefore, we propose to extend the wording of the given chapter with the following specification as footnote: Herbal preparation a): Single dose: 2.8 mg Dosage frequency: 2 times daily Daily dose*: 5.6 mg	Information on posology at present is derived from clinical studies and supported by the marketing overviews. All data refer to specific herbal preparations. In terms of clinical efficacy it is important to refer to the herbal preparation which was used as study medication. Since the constituents relevant for the improvement of menopausal complaints are not known, the herbal preparation as a whole is the effective principle. The amount of herbal substance is not really meaningful without declaration of the preparation and could be misleading. This is exactly the problem with studies which lay the focus on the amount of herbal substance. Furthermore, in some publications the given information on dosage does not clearly indicate whether it refers to the amount of extract or drug. The declaration of a fixed amount of dry extract does not imply a “redefinition” of the posology. Quality standards do not change and the DER - given in a range - is further on taken into consideration. A reference to the corresponding amount of herbal substance will not be included in the revised monograph.

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		Herbal preparation b): Single dose: 6.5 mg Dosage frequency: 1 single daily dose Daily dose*: 6.5 mg Herbal preparation c): Single dose: 2.5 mg or 5.0 mg Dosage frequency: 1-2 times daily Daily dose*: 5.0 mg ** Daily dose: dry extracts corresponding to 40 mg of the herbal substance*	