02 February 2016
EMA/HMPC/759056/2015
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph *Valeriana officinalis* L., radix (EMA/HMPC/150848/2015)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Valeriana officinalis L.,* radix as released for public consultation on 22 July 2015 until 31 October 2015.

	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
AESGP	We are wondering why extensive corrections within the new draft of the HMPC monograph have become necessary. The existing monograph (2006) is based upon current scientific knowledge at that date and has been used in numerous applications so far. Adaptation to the new document would result in new evaluations leading to extensive modifications of the dossiers. Moreover, it is not quite clear to us why some herbal preparations are accepted as traditional use and others are not.	The information concerning herbal preparations of the former version of the AR and monograph were rather unspecific. According to the latest requirements concerning the declaration of herbal preparations which are covered by the monograph, the preparations should be given with their DER and extraction solvent. As to be seen from the market overview, some preparations fulfil the criteria of been on the market/in use for more then 30 years, while for other preparations and/or posology this was not proven/seen. Therefore these preparations could not (yet) been accepted for traditional use.

Specific comments on text

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2. Qualitative and quantitative composition	AESGP	We suggest adding the following herbal preparations under 'traditional use': • hydroalcoholic dry extract (60% V/V)	Not endorsed AESGP did not provide data such as DER, posology, indication etc. and prove of 30 years of usage (SPC or similar) for that preparation. Therefore the preparation

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Traditional use		Justification: This Valerian extract is traditionally used in a marketed French association of plants that used this kind of valerian dry extract (hydroalcoholic dry extract (60% V/V)) from 1980. So, this kind of extract should be considered as a “traditional” extract that can be added into the European monograph.	cannot be included into the monograph.
4.2. Posology and method of administration Well-established use	AESGP	<u>Dry extract</u> With regard to the dry extract (DER 3-7:1), extraction solvent: ethanol 40-70% (V/V), we suggest a range of 400-600 mg in order to achieve consistency. Information regarding posology is given as follows: Single dose: 450-600 mg dry extract; equivalent to 2 to 3 g of the herbal substance. However, given a DER native of 3-7:1 (average 5:1) 2 g of the herbal substance correspond to 400 mg of herbal preparation (not 450 mg, as declared). This should be corrected. <u>Posology in children</u> Posology *Adolescents, adults and elderly* *[..]* The use in children under 12 years of age is not recommended (see section 4.4 ‘Special warnings and precautions for use’).	Endorsed Not endorsed No adequate data. There are no clinical data regarding the treatment of children 6-11 years of age with Valeriana radix in the relevant indications.

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		Proposal for revision: Posology […] *Children between 6 and 12 years* For relief of mild nervous tension once daily. For relief of sleep disorders, a single dose half to one hour before bedtime. The use in children under 6 years of age is not recommended. Children between 6 and 12 years of age should be treated under medical supervision (see section 4.4 'Special warnings and precautions for use'). The ESCOP monograph on valerian root (ESCOP, 1997) allows the treatment of children between 3 and 12 years of age under medical supervision. As per ESCOP monograph the dosage is adjusted as proportion of body weight. Further details regarding our proposal to include children of this age group are given in our comment to section 4.4.	
4.2. Posology and method of administration Traditional use	AESGP	(b) powdered herbal substance The change of the following specification is not reproducible for us: HMPC Monograph Valerian Root 2006: 4.2/traditional use/ Posology/Oral use/Single dose: - 0.3 to 1 g dried valerian root	Endorsed A double check revealed that for the single dose 190 mg of the extract (DER 5.3-6.6:1, extraction solvent: methanol 45% (m/m)) the traditional criteria

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		(e.g. as powdered herbal substance) "For relief of mild symptoms of mental stress up to 3 times daily. To aid sleep, a single dose half to one hour before bedtime with an earlier dose during the evening if necessary." Draft HMPC Monograph Valerian Root 2015: 4.2/traditional use/ Posology/Oral use/Single dose: - 0.76 to 2 g ((b) powdered herbal substance)) up to 3 times daily The "single dose to aid sleep" is missing. The draft revised Assessment Report states under: 2.1.1 Information about products on the market in the EU/EEA Member States, Table 1, Active substance 1) Comminuted herbals substance: Preparation 6: Indication: Traditional herbal medicinal product for support of mental relaxation. pharmaceutical form: coated tablet strength: 190mg posology: 3 - 4 coated tablets daily 2.4 Overall conclusions on medicinal use, Table 3 Overview of evidence on period of medicinal use: Preparations 2 "dried herbal substance as powder": Indication a) relief of mild nervous tension and for the relief of difficulty in falling asleep Posology a) 3 x 2g daily 760 mg/day "760 mg"="0.76 g" originate from 4 coated tablets with 190 mg Valerian root powder a day. However, the traditional posology was noted with 3 - 4 coated tablets a day, therefore the daily dose is 570 mg – 760 mg. The traditional single dose could even be stated with 190 mg. Therefore there is no need to raise the formerly defined lower limit from "0.3 g" up to	of 30 years are not fulfilled. However for the same extract there is a tradition for the single dose of 450 mg. This was corrected in the monograph and AR, respectively.

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		"0.76". According to available information the lower limit of the single dose in traditional use should be furthermore "0.3 g Valerian Root Powder".	
4.4 Special warnings and precautions	AESGP	The use is not recommended in children below 12 years of age due to a lack of data on safety and efficacy. Proposal for revision: The use in children below 6 years of age is not recommended due to a lack of data on safety and efficacy. Children between 6 and 12 years of age should be treated under medical supervision. Draft HMPC assessment report on Valeriana officinalis (EMA/HMPC/150846/2015): *"In an open multicentre observational study n=918 children ≤12 years (n=720 ≥6 years; n=198 <6 years) have been treated with a combination product (coated tablets containing 160 mg valerian root dry extract (DER 4-5:1, extraction solvent: ethanol 70% (V/V) + 80 mg lemon balm dry extract (DER 4-6:1, extraction solvent: 30% ethanol (V/V)) for 4 weeks ±1 week. 80% of the children ≥6 years received the full adult dose without any tolerability problems. The study can be accepted to support the use of valerian root extract as a single active substance in children ≤12 years of age concerning tolerability regarding reduced doses of 2/3 of the adult dose. The indication of restlessness and sleeping problems covers developmental particularities in children, due to which data on*	Not endorsed For both studies mentioned a combination product (valerian root dry extract + lemon balm dry extract) was used. Such studies cannot be used to prove efficacy of the mono product. The intention of AESGP to broaden the use of the WEU extract of the Valerian root monograph to children from 6 to 11 years of age is based on two open observational studies in those children with combination products containing valerian root preparations and preparations of lemon balm, of which one study (Müller & Klement, 2006) was already mentioned in the draft. The observational study of Gromball *et al.* (2014) covers 152 children (complete data) with hyperactivity and concentration difficulties but not meeting ADHS criteria and has not necessarily relevance for the valerian root indication. Even when the symptoms resemble those mentioned as indication of the monograph the underlying condition is not necessarily a sleeping problem. Therefore and because of the combination product used the observational study does not enable the decision to broaden the scope of the

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		efficacy in children of the different age groups ≤12 years are necessary (Müller & Klement, 2006).” We would like to add the information that the indication of this study was restlessness and nervous sleep-induction disorders. In most patients the core symptoms dyssomnia and restlessness improved from moderate or severe to mild or absent. A total improvement defined as reduction in at least 1 or 2 points of the symptom score was achieved in 80.9% of the patients for the symptom dyssomnia and in 70.4% of the patients for restlessness. A subgroup analysis showed that both children below 6 years and children between 6 and 12 years profited from treatment In the prospective, multi-centre non-interventional study of Gromball *et al.* (2014) the efficacy of the combination preparation of 320 mg valerian root extract WS® 1014 (drug extract ratio 3-6:1, extraction solvent ethanol 62% (m/m)) and 80 mg of lemon balm extract WS® 1303 (drug/ extract ratio 4-6:1, extraction solvent ethanol 30% m/m)) was studied in 160 primary school children (6-11 years, average age 8.0 years) with hyperactivity and concentration difficulty not meeting the ADHS criteria. The children received the full adult dose of 640 mg of valerian root extract and 320 mg of lemon balm extract per day. All assessed symptoms, i.e. concentration deficits, hyperactivity and impulsiveness followed by impaired social behaviour as well as sleep disturbances with morning fatigue	monograph to children 6-11 years of age. The description of the study has been added to the AR.

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		improved markedly ($p < 0.0001$). The tolerability of the preparation was classified as very good by 96.9% of the paediatricians and 95.1% of the parents. Only two non-serious adverse events were noted whose causality to the intake of the study medication was assessed as unlikely. Regarding the assessment of efficacy there are of course limitations due to the design of both studies (open, post-marketing surveillance studies). In addition, as a combined preparation of valerian root and lemon balm extract was studied, the study indications do not exactly match the indication of valerian root as per HMPC herbal monograph. Nevertheless, the data from these studies support the plausibility of efficacy of valerian root in children together with the study of Hintelmann *et al.,* 2002 and the ESCOP monograph, which reflects the long-standing experience. In addition as acknowledged in the HMPC draft assessment report on Valeriana officinalis (EMA/HMPC/150846/2015) these studies demonstrate the good tolerability of daily doses of 640 mg valerian root dry extract (equal to average 2.9 g herbal substance) in children between 6 and 12 years of age. We therefore propose to enable treatment of children from this age group under medical supervision, which would ensure an appropriate diagnosis and the monitoring of efficacy of treatment in these patients.	
4.4 Special warnings and	AESGP	Combination with other sedatives requires medical diagnosis and supervision.	Not endorsed It was decided to delete the warning at all, since no

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precautions		We propose to maintain the wording: Combination with synthetic sedatives requires medical diagnosis and supervision or alternatively: Combination with sedatives on prescription requires medical supervision. In addition this information should remain in section 4.5 “Interactions”. The expression ”other sedatives” is rather comprehensive as it includes a broad spectrum of substances, ranging from e.g. OTC herbal medicines such as lemon balm leaf, passion flower herb and hops to synthetic medicines on prescription such as benzodiazepines and barbiturates. We understand that the intention of this warning is probably to avoid the concomitant use of Valerian root extract with GABA-ergic substances such as benzodiazepines and barbiturates in view of the theoretical potential for pharmacodynamic drug interactions suggested by preclinical in-vitro data on the mechanism of action of valerian root extracts in Xenopus oocytes (Trauner *et al*., 2008, Khom *et al.,* 2007) and the prolongation of the pentobarbital induced sleeping time by constituents of valerian root (e.g. Hendriks *et al*., 1985). However in the HMPC Draft assessment report on Valeriana officinalis (EMA/HMPC/150846/2015) the clinical relevance of these findings is rated as questionable. A recent review of Kelber *et al.,* 2014 concludes that there is recently no evidence for clinically relevant pharmacodynamic or pharmacokinetic interactions of Valerian root preparations. For the combination of valerian root with other herbal sedatives	non-clinical or clinical data supporting such a warning could be found.

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		there is so far no reason to suspect a clinically relevant pharmacodynamic interaction potential. The HMPC itself published a herbal monograph on the fixed combination of valerian root and hop strobile attesting its safe and effective use (EMA/HMPC/585558/2007 Corr.1). Also the German Advisory Board on Phytotherapy (Commission E) published several monographs on fixed herbal combinations containing valerian root: valerian root and hops; valerian root, hops and lemon balm; valerian root, hops and passionflower herb as well as passionflower herb, valerian root and lemon balm (Blumenthal *et al.,* 1998a-d). This is reflected in a number of authorised, i.e. sufficiently safe and effective herbal medicines containing these combinations in Germany and in the European Community that are available without prescription. It therefore does not appear justified to require the involvement of a physician in any case of combination of herbal sedatives with valerian root extract. According to regulatory guidance from the US FDA (Guidance for Industry (draft), February 2012) as well as from the EMA (Notice to applicants, SmPC guideline, 2009), the section 4.5 “Interactions” of the SmPC should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and in vivo pharmacokinetic studies of the medicinal product. In addition the inclusion of warnings with regard to interactions is considered appropriate in section 4.4 “Special Warnings and precautions for use” in	

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		case of major clinical importance. If it is considered necessary to provide information on the theoretically possible interaction with GABAergic substances (benzodiazepines and barbiturates) in spite of its questionable clinical relevance, it would better match the above guidelines to keep the information as in the previous version of the HMPC monograph on Valerian root EMEA/HMPC/340719/2005 in section 4.5 “Interactions” and with the limitation to “synthetic sedatives”. As these are medicines on prescription the information could alternatively refer to “sedatives on prescription”.	
5.3. Preclinical Safety Data	AESGP	We highly appreciate inclusion of results of the AMES tests on mutagenicity which did not give reasons for concerns. In this context we welcome the finalisation of the respective List Entry based on the monograph on Valerian root.	
	AESGP	Literature references (in bold = new references not mentioned in the HMPC list of references) Blumenthal M *et al*. (ed.). Fixed combination of Valerian root and Hops. In: The complete German commission E Monographs. Boston, USA: Integrative Medicine Communications; 1998a p. 303 Blumenthal M *et al*. (ed.). Fixed combination of Valerian root, Hops and Lemon Balm. In: The complete German commission E Monographs. Boston, USA: Integrative Medicine Communications; 1998b p. 304	

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		Blumenthal M *et al*. (ed.). Fixed combination of Valerian root, Hops and Passionflower herb. In: The complete German commission E Monographs. Boston, USA: Integrative Medicine Communications; 1998c p. 305 Blumenthal M *et al*. (ed.). Fixed combination of Passionflower herb, Valerian root and lemon balm. In: The complete German commission E Monographs. Boston, USA: Integrative Medicine Communications; 1998d p. 279 ESCOP (European Scientific Cooperative on Phytotherapy). ESCOP Monograph: Valerianae radix – Valerian root. European Scientific Cooperative on Phytotherapy, 2nd Edition, Supplement 2009 Gromball J, Beschorner F, Wantzen C, Paulsen U, Burkart M. Hyperactivity, concentration difficulties and impulsiveness improve during seven weeks' treatment with valerian root and lemon balm extracts in primary school children. Phytomedicine. 2014 Jul-Aug;21(8-9):1098-103 Hendriks H, Bos R, Woerdenbag HJ, Koster AS. Central nervous depressant activity of valerenic acid in the mouse. Planta Med. 1985, 51: 28-31 Hintelmann C. Einschlafstörungen bei Kindern unter 12 Jahren – Anwendungsbeobachtung mit hochdosiertem Baldrianextrakt. Schweiz Z Ganzheitsmedizin 2002, 14: 404-407 [German] Khom S, Baburin I, Timin E, Hohaus A, Trauner G, Kopp B *et al.* Valerenic acid potentiates and inhibits GABA(A) receptors:	

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		molecular mechanism and subunit specificity. Neuropharmacology. 2007, 53(1): 178-187 Kelber O, Nieber K, Kraft K. Valerian: no evidence for clinically relevant interactions. Evid Based Complement Alternat Med. 2014a, doi: 10.1155/2014/879396 Müller SF, Klement S: A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssominia in children. Phytomedicine 2006; 13(6): 383-387 Trauner G, Khom S, Baburin I, Benedek B, Hering S, Kopp B. Modulation of GABAA receptors by valerian extracts is related to the content of valerenic acid. Planta Med. 2008, 74(1): 19-24	