European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON
'COMMUNITY HERBAL MONOGRAPH ON *VALERIANA OFFICINALIS* L., RADIX'
EMEA/HMPC/340719/2005

Artikel I. Table 1: Organisations that commented on the document as released for consultation in September 2005 until 31 January 2006

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	British Herbal Medicine Association (BHMA)
3.	Bio-health Ltd, United Kingdom
4.	Biohorma BV, The Netherlands
5.	European Herbal Practitioners Association (EHPA)
6.	European Federation of Association of Health Product Manufacturers (EHPM)
7.	Society for Medicinal Plant Research (GA)
8.	Kooperation Phytopharmaka, Germany
9.	Medical Products Agency, Sweden
10.	The European Scientific Cooperative on Phytotherapy (ESCOP)
11.	The Herbal Forum, United Kingdom
12.	Irish Medicines Board
13.	The Medicines Evaluation Board of the Netherlands
14.	Medicines and Healthcare products Regulatory Agency, United Kingdom
15.	National Agency for Medicines, Finland
16.	Laboratorium Farmaceutyczne Labofarm, Poland
17.	Institute for Pharmacology and Toxicology, University Muenster, Germany
18.	University of Ljubljana, Slovenia

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Table 2: Discussion of comments

General comment	Comment and rationale	Rapporteur's response
Supporting literature	Data regarding combination products	For the assessment of the efficacy of the monographs on one herbal substance data regarding combination products can only be taken into account if the concomitant ingredients do not contribute relevantly to the efficacy of the combination. Monographs for single herbal substances should not give recommendations for combination possibilities.
Comments and references	References to comments are missing.	Comments should be substantiated by evidence if the commentator wants them to be accepted.
Monograph title	▪ It was suggested to add the following and alternative way (used by the European Pharmacopoeia) of expressing the plant name and part used: "Valerianae radix". ▪ In accordance with the terminology used in the European Pharmacopoeia, the interested party suggests to use the correct Latin expression in brackets: Valerianae radix	The title was changed into `*Valeriana officinalis* L., radix´, which is in line with guidance in the `Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use´ (EMEA/HMPC/182352/2005 Revision 2) and the respective document for traditional use (EMEA/HMPC/182320/2005 Revision 2).
Template	▪ It was suggested to correct the reference to "Article 10(1)(a)(ii)" into Article "10a" of Directive 2001/83/EC as amended.	Corrected in the new version, see `Template for a Community herbal monograph´ (EMEA/HMPC/107436/2005 Revision 2).

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2. Qualitative and quantitative composition	▪ Many herbal preparations can figure in both the well-established and traditional use areas. Whether the use is well-established or traditional depends on individual data on indication, strength (including drug-extract-ratio) and posology. For this reason we propose, for example, extracts prepared with water, ethanol/water or methanol/water to be included into both areas. ▪ Well-established use: Preparations produced with methanol as a solvent represent in some EU countries half of the market (e.g. Germany). An important part of available clinical data is based on these preparations. For this reason, the commentator proposes that under "Valerian root preparations" figure: "Extracts prepared with water, ethanol/water (ethanol max. 70 % V/V) *or methanol/water (methanol max 45 %)*". ▪ Traditional use: We suggest adding under "Herbal preparations" (traditional use): *"Extracts prepared with water, ethanol/water (ethanol max. 70 % V/V) or methanol/water (methanol max. 45 %)"* These preparations are used in some EU countries based on long tradition and experience of over 30 years. For this precise reason, in Germany for example, these are included in the list according to section 109a of the German Medicines Law (no. 146, 147, 158, 160, 431). Compared to the well-established preparations based on water, ethanol/water or methanol/water, the traditionally used preparations have a different dose, i.e. the drug equivalent is much lower. Aqueous extracts are comparable to herbal teas, since they represent a "dried" herbal tea preparation. The annotator points out that the traditionally used herbal preparation "*tincture*" is missing. To take again the German example, Valerian tinctures are part of German Pharmacopoeias since the early 20th century, e.g. from the years 1910 (DAB 5), 1943/1944 (ErgB DAB 6), 1968 (DAB 7). Valerian tincture is also included in the German "Standardzulassungen" according to § 36 of the German Medicines Law (AMG).	Well established/Traditional use: For the purpose of a clear differentiation the HMPC has decided to list different herbal preparations into the well-established or the traditional part of the monograph but not in both of them. In general, only the preparation, but not the daily dose, is decisive. For this reason, extracts with ethanol/water have been included in the well-established part since the scientific body of evidence supports only these under WEU. Aqueous preparations have been included in the traditional part (see assessment report). Extracts with methanol: The 'available clinical data' cited for extracts with methanol are not documented in a comprehensible manner. Indeed, only a single preclinical trial with an aqueous-methanolic extract was identified (Mueller et al., 2002). Clinical data are not available at all, bridging-studies showing equivalent effects of aqueous-methanolic and aqueous-ethanolic extracts have not been performed. According to the draft 'Guideline on the assessment of clinical safety and efficacy in monographs for well-established and monographs/lists for traditional herbal medicinal products' (EMEA/HMPC/104613/2005) herbal preparations can be considered as sufficiently identical only if no relevant differences in the manufacturing process exist. In the case of aqueous-methanolic extracts such relevant differences must be assumed. For this reason, additional data demonstrating equivalent analytical composition or identical pharmacodynamic effects compared to aqueous-ethanolic extracts are necessary to justify 'well-established use' for these preparations. In conclusion, a 'well-established' status for extracts with methanol/water as extraction solvent is not justified. Concerning traditional use, inclusion of aqueous-methanolic extracts in the the mentioned German list cannot be accepted as proof of 'tradition' over 30 years. The German health authority could not identify a product containing an methanol/water extract of valerian root as single active ingredient which has been marketed over 30 years and thus would fulfil the condition for 'traditional use'.

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2. Qualitative and quantitative composition Continuation		In addition, no such products were reported from other Member States. For this reason also a 'traditional' status could not be recognized for extracts with methanol/water. § 109a AMG (German Medicines law): The criteria that have been used for the selection of preparations to be included in the list according to section 109a of the German Medicines Law are not sufficient for the inclusion into the EU Traditional Database, since requirements for the proof of tradition accepted in this context are different from those laid down in Directive 2004/24/EC. Herbal teas: The HMPC decided to shift aqueous extracts from well-established to traditional use because of a lack of evidence of clinical efficacy for these preparations (July 2006). The same applies to herbal teas. In this context, we follow the approach of the annotator that aqueous extracts and herbal teas are comparable. In general, preparations have to be listed either in the 'well-established use' part or in the 'traditional use' part of a monograph and inclusion in both parts is impossible. Because of the exceptional case of the well-known traditional use of valerian tincture, the HMPC decided to allow valerian tincture to be mentioned in the 'traditional' part of the monograph with a specific dosage.
		Extracts are included under well-established use if clinical data supporting the efficacy are available. All other extracts can be included in the traditional use chapter, if proof of 15/15 years of tradition is provided. Tinctures are covered by the Ph. Eur. monograph on "Extracts" (see above).
	▪ Well-established use In the draft, water and water/ethanol-mixtures up to maximal 70 % ethanol (V/V) are mentioned. As in the German market there is a considerable number of extracts produced with methanol, the solvent ethanol should be replaced by "hydroalcohol" or mixtures of methanol-/ethanol-water. ▪ Traditional use In this paragraph aqueous extracts should be listed as traditionally used preparations, since such extracts represent a dried form of a tea.	Well-established use: See above. Traditional use: See above.

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2. Qualitative and quantitative composition Continuation	▪ We propose that the following should be added under "Herbal preparations": "Extracts prepared with water, ethanol/water (ethanol max. 70% v/v), methanol max. 50% v/v), Tinctures (1:5, ethanol max. 70% v/v)".	See above.
	▪ *We note that the herbal preparation for traditional use (qualitative and quantitive composition) is limited to dried valerian root, fresh plant juice and valerian root oil. On the other hand, the well-established use preparation is an extract prepared with water, ethanol/water or a tincture (1:5 70%). This raises the following questions and comments:* 1. Why is the tincture form apparently limited to well-established use? Valerian tincture has long (over 50 years at least) been a traditional mode of presentation of valerian in the UK and Ireland. For this reason, surely this tincture form should surely also be available under "traditional use". 2. Will the tincture and extract form of presentation be limited in general in all forthcoming monographs to well-established use? We argue against this as for at least the last 50 years tinctures have been the preferred method of presentation in the UK and Ireland of many non-licensed over-the-counter herbal remedies so that this presentation has as much right to be deemed "traditional use" as "well- established use". 3. We are surprised to see Valerian root oil available for internal use under the traditional use presentation as essential oils are rather powerful for self prescribing internally. On the other hand, the tea has an unpleasant taste and odour and therefore is not as popular as the tincture form. For this reason, as observed above, valerian tincture has had a long-standing traditional use.	See above. 1. The monograph on valerian root specifically deals with the characteristics and particularities of this herbal substance and does not represent general HMPC decisions which are conferrable to other herbal substances. 2. Valerian root contains 0.3 – 0.8 % essential oil. The recommended single dose of 15 mg oil corresponds to the content in 3 g of the fresh drug; an increased risk is not presumed. In addition, the LD50 of essential oil of valerian root, 1,500 mg in rats weighing 100 g was found to be the highest of 27 essential oils tested, including for example, peppermint and anise oils (von Skremlik, 1959).

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2. Qualitative and quantitative composition Continuation	▪ We would question the rationale behind the determination to make valerian root preparations where extracts and tinctures are involved as being preparations suitable only for well-established use. What is the scientific logic for this decision as we cannot see any logical reason that preparations of valerian root, i.e. extracts or tinctures, could not be produced and marketed under traditional use? Clearly, the tinctures or extracts are representative of the whole material (dried valerian root) in ratios of 3:1, 4:1, 5:1, but this does not, in any way, impart an additional dimension to the product, apart from the extract drug ratio that allows a higher dose in a smaller tablet or capsule. Apart from this factor, we do not accept that the extract or tincture is superior in effect to the whole dried valerian root. In fact, one could argue that as valerian's therapeutic activity is NOT due to a single known active, the extractive process of water and ethanol, active compounds may be de-natured during the process and, therefore, not available as active compounds in the final product. We therefore contend that this is not justified, that dried valerian root cannot be considered for well-established use and similarly the reverse also applies. We would suggest that extracts and tinctures should be allowed, under the traditional use regulation scheme.	According to Article 16a(1) of Directive 2001/83/EC, preparations that are suitable for an authorisation according to Article 6 (e.g. 'well-established' preparations) cannot be registered as 'traditional' preparations. The question whether extracts or tinctures are superior to the whole dried root cannot be answered due to lack of data. For the same reason the unsubstantiated statement that the whole drug is supposed to be as least as effective as the investigated extracts must be rejected. To our knowledge not a single preclinical or clinical trial with the dried root powder has been published, this means that the level of evidence is very low (level IV) and not compatible with the 'well-established' indication for valerian root, in particular the 'sleep disorders' indication.
	▪ The commentator suggests for valerian root (well-established and traditional use) to add: "tincture, extract prepared with water, ethanol/water (ethanol max. 70 % V/V)" Furthermore, the traditionally used herbal preparation "tincture" is missing. Valerian tinctures are part of several pharmacopoeias. A draft monograph on valerian tincture has been published in Pharmeuropa 2005;17(3):1899. Furthermore many preparations are used in Europe based on tradition and long-term experience for more than 30 years and are included in the list according to German Medicines Law (section 109a; no. 146, 147, 158, 160, 431).	See above.

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2. Qualitative and quantitative composition Continuation	▪ Well-established use Under "valerian root preparations", we propose: "Extract prepared with water, ethanol/water (ethanol max. 70 % V/V) or methanol/water (methanol max 45 %)". Reasons: A large part of the European market is covered by preparations produced with methanol as a solvent. ▪ Traditional use We suggest to add under "Herbal preparations": "Extract prepared with water, ethanol/water (ethanol max. 70 % V/V) or methanol/water (methanol max. 45 %)" These preparations are used in Europe based on tradition and long-term experience for more than 30 years. For this reason they are included in the list according to section 109a of the German Medicines Law (no. 146, 147, 158, 160, 431). Compared to the well-established preparations based on water, ethanol/water or methanol/water, the traditionally used preparations have a different dose, i.e. the drug equivalent is much lower. Furthermore, the traditionally used herbal preparation "tincture" is missing. Valerian tinctures are part of pharmacopoeias since the early 20th century, e.g. in Germany. Valerian tincture is also included in the German "Standardzulassungen" according to section 36 of the German Medicines Law (AMG). A draft monograph on Valerian tincture has been published in Pharmeuropa 2005;17(3):1899	Well-established use See above. ▪ Traditional use See above. "Standardzulassungen" according to section 36 of the German Medicines Law (AMG) cover preparations with proven efficacy.
	▪ Under 'Traditional Use', should be included: - Extract prepared with water, ethanol/water (ethanol max. 70 % V/V) Tinctures (1:5, ethanol max. 70 % V/V)	See above.
	▪ Both extracts and tinctures, as proposed for well-established use, should be included under traditional use.	See above.

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2. Qualitative and quantitative composition Continuation	▪ Rationale for the range of solvent concentration of the extracts prepared with ethanol accepted under well established use.	According to the decision that aqueous extracts including herbal tea were shifted to the traditional part of the monograph, the extraction solvent concentration for ethanol/water extracts had to be specified with a lower limit on the well-established side. The chosen range of ethanol concentrations reflects the solvent concentrations of the most commonly accepted extracts authorized under well-established use on the European market.
4.1. Therapeutic indication	▪ The following publications have not been included in the Assessment Report. Abstracts have been attached for information: Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. *Sleep Med.* 2000;1(2):91-99. Coxeter PD, Schluter PJ, Eastwood HL, Nikles CJ, Glasziou PP Valerian does not appear to reduce symptoms for patients with chronic insomnia in general practice using a series of randomised n-of-1 trials. *Complement Ther Med.* 2003;11(4):215-22. Jacobs BP, Bent S, Tice JA, Blackwell T, Cummings SR An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Medicine (Baltimore).* 2005; 84 (4):197-207.	The trials by Coxeter, Jacobs and Gurley have been included in the new version of the assessment report. The publication by Stevinson and Ernst is a review without presenting new data, the rapporteur´s assessment is included in the assessment report and list of references.
	▪ Proposals for 'Well-established medicinal use': *(Summary of comment)* - Insomnia indication Of the seven studies presented only one study demonstrated any statistically significant difference versus placebo. On the face of it these data do not support the efficacy of valerian at the doses used in the studies. The data do not support the proposed posology. The data are inadequate to demonstrate well-established medicinal use for this indication.	Indication: "relief of sleep disorders" The comment that 'of the seven studies presented only one study demonstrated any statistically significant difference versus placebo' is misleading. Several relevant studies are disregarded in this statement, e.g. the trial by Ziegler (2002) which demonstrated therapeutic equivalence of valerian root 2.7 g/d vs. Oxazepam 10 mg/d, accompanied by better tolerability of valerian root, in a confirmatory trial. The general conclusion, that the data 'do not support the proposed posology' and 'are inadequate to demonstrate well-established use for this indication' is not substantiated by arguments; for this reason it cannot be further discussed.

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4.1. Therapeutic indication Continuation	- Anxiety indication The evidence to support this indication is based on two pharmacodynamic studies and one clinical study. The evidence to support the well-established medicinal use of valerian for the indication "relief of mild nervous tension and difficulty in falling asleep" is lacking. The evidence for this indication is based on the results of one small study the results of which are of unknown clinical significance.	Indication: "relief of mild nervous tension" It is correct that the grade of evidence for 'relief of mild nervous tension' is much lower than that for "relief of sleep disorders" and does not exceed level III. However, well-established use is not restricted to indications proven by placebo-controlled trials. According to the 'Guideline on the assessment of clinical safety and efficacy in the preparation of Community herbal monographs for well-established and of Community herbal monographs/entries to the Community list for traditional herbal medicinal products/substances/preparations' (EMEA/HMPC/104613/05), not only controlled trials but also other clinical trials, cohort or longitudinal studies, observational (non-interventional) studies, case-control-studies, other collections of single cases allowing a scientific evaluation, scientifically documented medical experience, for example scientific literature and expertise from scientific medical associations have to be taken in consideration for evaluation of clinical evidence. The recommended low-level indication which merely supports a relief of mild symptoms adequately reflects the low level of clinical evidence.
	- It is entirely unknown how the proposed posology for this indication has been arrived at. - Overall conclusions Due to the lack of at least 10 years of data demonstrating efficacy of valerian, well-established medicinal use cannot be accepted for either indication. The evidence does not support the position of valerian as having well-established medicinal use and recognised efficacy as required by Article 10a of Directive 2001/83/EC. The commentator suggests for the Well-established use: Notwithstanding the lack of evidence of efficacy: The term 'mild nervous tension' is not a recognised clinical term. Mild anxiety should be used. And for Traditional use: The following alternative wording is suggested: 'Traditional herbal medicinal product for the relief of mild anxiety and to aid natural sleep exclusively based on long-standing use.'	Posology: The daily dose (3 x 90 mg extract corresponding to approximately 3 x 400 – 500 mg of the drug) chosen in the trial of Kamm-Kohl is unusually low. It is distinctly lower than the dose range in all other clinical trials and that is recommended in the Commission E and ESCOP monographs as well as in the HMPWP Core Data (EMEA/HMPWP/14/99). It can be assumed that clinical experience is mainly based on these recommendations. Since there is no information available on optimal dosing in the 'mild nervous tension indication' and no relevant toxicities are known for the higher dose, it was decided to adopt the well-tried dosing regimen of the above-mentioned monographs. The statement regarding the 'lack of at least 10 years of data demonstrating efficacy of valerian' cannot be commented due to missing substantiation. The term 'mild anxiety' is not rated to be adequate for 'well-established' and/or 'traditional' use because of the low level of evidence achieved in this field. For this reason the HMPC decided to adopt the rapporteur's proposal with minor changes. Furthermore, diagnosis and treatment of anxiety require the supervision of a medical practitioner; the indication is thus not suitable for a 'traditional use' registration.

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4.1. Therapeutic indication Continuation		'Well-established' and 'traditional' indications for preparations of the same drug should generally have different wordings to reflect the different levels of evidence. Since even the 'well-established' claim for the day-time use of valerian root is low-level, a formulation for the 'traditional' claim cannot be found without leaving the field of medical terminology as found in dictionaries. 'Mental relaxation' was provisionally chosen as an attempt to reflect the genuine traditional use of valerian root which is not only found in strictly medical applications but commonly also in the field of food supplements. A clear separation of traditional use in these two areas is not always possible due to different regulation of herbal products in the Member States in the past. The proposals of several institutions to improve this formulation were appreciated and the following rewording for the 'traditional' claim - which excludes the need for involving a medical practitioner- was agreed by decision of the HMPC (July 2006) : "Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use."
	▪ We propose that the following should be used under Traditional Use, as an alternative to the proposed wording: "Traditional herbal medicinal product for the relief of tenseness and mild anxiety, and to aid natural sleep exclusively based on long-standing use."	See above.
	▪ We should also like to comment on the therapeutic indications, in particular, the traditional claim "for support or mental relaxation". This DOES NOT, as far as we are aware, represent an adverse condition or a medical term that we can locate in any medical dictionary and therefore consider this statement to be one that should be more clearly defined as 'nervous anxiety' or 'nervous tension'.	See above.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.1. Therapeutic indication Continuation	▪ There is insufficient evidence to support a well-established use indication. The data provided do not in our view fulfill the requirements for well-established use in accordance with Annex 1 of 2001/83/EC as amended. ▪ The indication should be amended as follows: Traditional herbal medicinal product for the relief of temporary mild nervous tension and temporary difficulty in falling asleep support of mental relaxation and to aid natural sleep exclusively based on long standing use. ▪ *We note the suggested therapeutic indication for traditional use is "for support of mental relaxation and to aid natural sleep exclusively based on long-standing use". We make the following comments:* *1.* The meaning of the phrase "exclusively based on long-standing use" is unclear. We believe that the word *"exclusively*" will probably not be understood as meant here - i.e. *"entirely based on"*. Moreover *"exclusively based on long-standing use"* could easily be misinterpreted as a direction to the patient to take the medicine over a long period of time to achieve any effect. We suggest some other phrase is used such as *"the basis of this medicine is traditional use"*. *2.* As far as we are aware, the phrase "*support of mental relaxation*" is not a recognised medical indication. Surely this should be a *bone-fide* medical indication as we are dealing with a medicine even if it is in the traditional use category. If this non-medical terminology is widely used in describing the indications of traditional use products, we are concerned that it may cause confusion and introduce lack of precision in self-prescribing these over-the counter products.	The statement regarding 'insufficient evidence to support a well-established use indication' cannot be commented due to missing clarification of the dissenting opinion. See above. 1. The formulation 'Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.' derives from Directive 2001/83/EC Art. 16g 2(a). 2. See above.
	▪ The wording "according to ICD-10, F51.0" should be deleted from the therapeutic indication. The information could be given in the assessment report instead. "Mild and nervous tension" is not an established condition. An indication according to ICD should be used instead.	We follow the proposal to exclude the wording "according to ICD-10, F51.0"; this change was included in the final monograph version. Regarding the comment on the mild nervous tension indication, see above.

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4.1. Therapeutic indication Continuation	▪ This includes a Traditional Use indication "for support of mental relaxation and to aid natural sleep" which are not exclusively medicinal indications and may be made as claims on botanical food supplements. We propose its replacement by "for relief of the stresses and strains of everyday life, mild anxiety and to aid an inability to sleep"	See above.
	▪ We note that under section 4.1, the therapeutic indications mentioned for traditional medicinal product use are *"for support of mental relaxation and to aid natural sleep"*. In our opinion this indication can be considered as a "health claim" as defined under proposed EU Regulation on Nutrition and Health Claims made on foods rather than as a therapeutic indication with reference to EU Medicinal legislation (Directive 2001/83/EC): It does not refer to an indication for the treatment or prevention of a disease, nor can it be considered as a reference to restoring, correcting or modifying a physiological function by exerting a pharmacological, immunological or metabolic action as interpreted by the European Court of Justice in its extensive case law. On the contrary, this statement clearly refers to health and support of the normal physiology of an individual. This is also coherent with the fact that existing member state legislation authorizes the use of Valeriana Radix in foods and food supplements at a dosage above the proposed monograph dose of 0,3 to 1 g dried valerian root up to maximum of 4 dosages a day: this is notably the case in Belgium which authorizes the use of this substance in foods up to a dose of 3,6 g of dried valerian root per day. We therefore can not agree that such an indication be considered as a therapeutic indication for Valeriana Radix and recommend that the Committee reconsiders this indication in accordance with the medicines definition. We therefore urge the Committee to carefully consider existing and forthcoming food legislation in order to avoid creating potential conflicts between the medicinal and food areas.	See above. The proposed reformulation fulfils the demand of 'restoring a physiological function' in our view and allows a demarcation between a medicinal product and a food with 'health claim'.

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4.1. Therapeutic indication Continuation	▪ The traditional indication in the latest revision is not acceptable ("stresses and strains of everyday life" –too broad). Proposal: "Traditional herbal medicinal product for the relief of mild restlessness and to aid natural sleep exclusively based on long-standing use"	'Mild anxiety' or 'mild restlessness' are not acceptable for traditional use (medical differential diagnosis). It was agreed (HPMC July 2006) to diminish the traditional use wording by: "Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use."
4.2. Posology and method of administration	▪ Duration of use. Available documentation is clearly insufficient to support a recommendation to continue use of valerian for 2-4 weeks. It should be stated that no specific data is available.	Gradual onset of effects is a common observation for herbal medicines. Increase of efficacy over 2 – 4 or 6 weeks has been observed with valerian root in two controlled clinical trials and in a drug-monitoring trial (Ziegler , 2002, Vorbach, 1996, Hintelmann, 2002), and no pronounced acute effects were observed in the pharmacological studies. Against this background it does not seem to be useful to recommend valerian root for short-term treatment. Although actually no experience on long-term intake is available, the data of the cited studies should be rated as sufficient for the recommendation of 2 – 4 weeks intake, the more so as they confirm the common clinical experience. In addition, a consensus exists that long-term studies should be avoided with hypnotic drugs, since these would - at least for chemical substances - carry a hazard for the patients due to the dependency risks for most drugs (Angst et al., 1995). Concerning traditional use the recommendation regarding a use of 2 – 4 weeks is not included, because there is no traditional plausibility on it. Special warnings have been adapted accordingly.

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4.2. Posology and method of administration Continuation	▪ Well-established use: We suggest including extracts prepared with methanol as follows: "… extracts with water, ethanol/water (ethanol max. 70 % V/V) or methanol/water (methanol max 45 %) equivalent to 2 to 3 g of the drug." Reasons: This is in line with extracts widely used in the European market. ▪ Traditional use: For herbal preparations, we propose the following wording: Single dose: 0.3 to 1.5 g dried Valerian root (…) extracts with water, ethanol/water (ethanol max. 70 % V/V) or methanol/water (methanol max 45 %) as well as tincture, equivalent to 0.3 to 1.5 g of the drug … This is in line with marketing authorisations according to section 109a of the German Medicines Law. Such extracts are known for more than 30 years in the European Union and should therefore be considered as traditional with the dosage equivalent of 0,3 to 1,5 g dried Valerian root. ▪ In accordance with the ESCOP monograph, we suggest to add to both areas: "Children from 3 to 12 years under medical supervision only: proportion of adult dose according to body-weight, as non-alcoholic preparations."	Well-established use: See above (chapter "2. Qualitative and quantitative composition"). Traditional use: See above (chapter 2. Qualitative and quantitative composition) The dose range for traditional use was discussed in the HMPC; it was decided to choose the range given in the British Herbal Pharmacopoeia. For extracts with methanol/water no 'tradition' is proven and no 'traditional' dosing recommendation is available, as outlined above. Registrations according to § 109a of German Medicines Law are not decisive for the rating as 'traditional' in the sense of Directive 2004/24/EC. The herbal preparation tincture has been shifted to the traditional use because tincture has been traditionally used in drop amounts (see lower dosage in BP) and would have to be taken in much greater amounts if kept under well-established use (specific decision for valerian root). Children The proposal to include a recommendation for treatment of children is not supported by scientific references or other justifications. The proposed dosing schedule is not substantiated. Only one drug monitoring trial in children has been published (Hintelmann, 2002). These data are judged too scanty to justify a general recommendation. The application for use of medicinal products containing valerian root in children below the age of 12 years should be justified by specific clinical experience. In all other cases the lack of experience should be addressed as a relative contraindication in the SPC as proposed, see also below.

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4.2 Posology and method of administration Continuation	▪ As a general comment, the rationale for the different posologies for well-established vs, traditional use needs to be clarified.	Posology While the posology for 'well-established' preparations is confirmed by results of clinical trials in the "relief of sleep disorders" indication, posology for 'traditional' preparations can only be derived from the traditional dosing recommendations. For valerian root oil and expressed juice from fresh plant the single dose recommendations of the corresponding marketed preparations were adopted. Regarding the dose recommendation for dried valerian root, the HMPC decided to refer to the British Pharmacopoeia.
	Well-established use The term 'mild nervous tension' is not a recognised clinical term. Mild anxiety should be used.	Well-established use 'Mild nervous tension': see response above (chapter 4.1 Therapeutic indications).
	This product should only be given to adults (over the age of 18 years).	No reason is given why the product should be given only to adults. We do not agree since no specific risks are known that prohibit intake by adolescents.
	The statement under duration of use is not supported by the literature. Suggest replacing the word 'intake' with 'continued use'	Duration of use: see above. "Intake" has been replaced with "continued use" in the final monograph.
	Traditional use Suggest changing 'For support of sleep' to 'To aid sleep' Suggest replacing the word 'intake' with 'continued use'	Traditional use The proposed changes concerning the indication have already been included in the published draft. 'Continued use' is no longer addressed in the traditional part.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.2 Posology and method of administration Continuation	▪ Well-established use As stated above we suggest to include extracts prepared with methanol as follows: "… extracts with water, ethanol/water (ethanol max. 70 % V/V) *or methanol/water (methanol max 45 %) equivalent to 2 to 3 g of the drug"*. In some EU countries, such extracts are widely used and supported by clinical data. The given single dose for the <u>tincture</u> in the field of well-established use is misleading, because tincture dosages have never been given as drug equivalents. Therefore, the single dose should be stated as previously in the existing core-SPC of Valerianae radix, i.e. "*1 to 3 ml of tincture*". ▪ Traditional use For herbal preparations, we propose the following wording: Single dose: *- 0.3 to 1.5 g dried Valerian root (…)* *- extracts with water, ethanol/water (ethanol max. 70 % V/V) or methanol/water (methanol max 45 %) equivalent to 0.3 to 1.5 g of the drug* - … This is in line, for example, with marketing authorisations according to section 109a of the German Medicines Law. Such extracts are known for more than 30 years in the European Union and should therefore be considered as traditional with the dosage equivalent of 0,3 to 1,5 g dried Valerian root. The single dose for the herbal preparation "tincture" has to be included accordingly. The proposal is: *"0,2 - 1,0 g (15 – 60 drops) tincture"* This proposal is justified on the above-mentioned pharmacopoeias describing traditional Valerian tincture.	Well-established use Regarding aqueous-methanolic extracts see above (chapter 2. Qualitative and quantitative composition). Tincture dosage: Due to lack of clinical data the proposed dosage cannot be rated as 'well-established'. As described above, the HMPC decided (July 2006) to include tinctures under traditional use with a specific dose recommendation, in view of the very common use and due to further discussion. Traditional use See above. Tincture single dose: Since dose recommendations for valerian root tincture vary greatly between the pharmacopoeias (single dose: approx. 0.2 – 8 ml) it was decided in HMPC (July 2006) to introduce a traditional dosage for valerian tincture corresponding to 0.3 – 1.0 g of herbal substance.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.2 Posology and method of administration Continuation	▪ Under duration of use we suggest to add in both columns: "In principle, there is no restriction in the duration of treatment with valerian root." ▪ In 4.4. Special warnings and precautions for use it is stated that "*because there is no experience available, use of this product is not recommended in children below the age of 12 years.*" We would like to point out that in the monograph for Valeriana in ESCOP includes indications for children. Therefore, we propose to delete the sentence of section 4.4 and to include under section 4.2 Posology and method of administration "*…Children from 3 to 12 years (under medical supervision): proportion of adult dose according to bodyweight, as tea infusion or dry extract*."	Duration of use: Data on long-term use and optimal duration of treatment with valerian root are not available; for this reason we do not support to include the proposed text on treatment duration. Treatment of children below the age of 12 years: see above.
	▪ The commentator suggests the following wording for the herbal drug (Traditional use): Single dose: - 0.3 to 1.5 g dried Valerian root - extracts with water, ethanol/water (ethanol max. 70 % V/V) as well as tincture, equivalent to 0.3 to 1.5 g of the drug.	See above.
	▪ To support the use of Valerian root in children from 3 to 12 years, the following study is presented: Müller SF et al. (2006).	Müller SF et al. (2006) Phytomedicine (article in press): n = 918 Children ≤12 years (n = 719 ≥ 6 years) have been treated with a combination product (valerian root + lemon balm containing 75% of the monographconform single dose of valerian root for 4 weeks ±1 week. 80% of the children ≥ 6 years received the full adult dose without any tolerability problems. The study could be accepted to support the use of valerian root as single herbal substance in children ≤ 12 years of age concerning tolerability regarding reduced doses of 2/3 of the adult dose, but the indication of restlessness and sleeping problems covers developmental particularities, due to which data on efficacy in children of the different age groups ≤ 12 years are necessary. In addition, traditional use in children cannot be accepted, because the described developmental particularities need differential diagnosis.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.2 Posology and method of administration Continuation	▪ We propose that the following posology should be used under Traditional Use "Single dose: - 0.3 to 1 g dried Valerian root (e.g. as powdered drug, herbal extract, herbal tincture or as herbal tea, according to British Herbal Pharmacopoeia, 1976) - 15 ml of fresh plant juice - 15 mg of Valerian root oil For tenseness or mild anxiety 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. Maximum daily dose: 4 single doses"	See above. For proposal on rewording of the posology in traditional use, see the final monograph.
	▪ Traditional Use The proposed duration of use should be consistent with the recommendations of the European Commission Guideline on Summary of Products Characteristics for Benzodiazepines as Anxiolytics of Hypnotics. The following sentence should be deleted and replaced with appropriate instructions: To achieve optimal efficacy, continued use over 2 – 4 weeks is recommended.	The cited recommendations for benzodiazepines are not appropriate for valerian root since it is an OTC medication, no dependencies have been reported in contrast to benzodiazepines, and also typical side effects of benzodiazepines do not occur during valerian intake. Also optimal duration of treatment with valerian root has not been established, so there is no justification for recommending a specific duration of intake.
	▪ There is a gap between the dosage ranges given for Well-established & Traditional Valerian products. We propose allowing the dosage range of 0.3g-1.5g dried Valerian root for Traditional products to reduce this gap. Traditional use should also allow: - Extract prepared with water, ethanol/water (ethanol max. 70 % V/V) - Tinctures (1:5, ethanol max. 70 % V/V) equivalent to 0.3 to 1.5 g of the drug. The wording on dosages should be changed to reflect the indication proposed above: "For relief of the stresses and strains of everyday life or mild anxiety up to 3 times daily" "To aid an inability to sleep a single dose half to one hour before bedtime with an earlier dose during the evening if necessary."	See above. For proposal on rewording of the posology in traditional use, see the final monograph.
	▪ Two commentators suggest to add in section 4.3 Contraindication "*Children under 3 years of age*"	The reason for this contraindication is not given, so it cannot be commented.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.2 Posology and method of administration Continuation	▪ This should be amended to read patients who are know to be allergic to valerian or *any of the other ingredients* in this preparation should not use this preparation. ▪ <u>Well-established use:</u> The age for children should be below the age of 18 years. This should appear in contraindications (well-established use).	Inclusion of this text is refused, because statements concerning excipients are not subject of the monograph for the herbal substance. These statements should be introduced into the SPC of the relevant product. Well-established use: Treatment < 18 years: see response above.
4.4 Special warnings and precautions for use	▪ It is stated that "*because there is no experience available, use of this product is not recommended in children below the age of 12 years."* We would like to point out that in the monograph for Valeriana in ESCOP includes indications for children. Therefore, we propose to delete the sentence of section 4.4 and to include under section 4.2 Posology and method of administration "*…Children from 3 to 12 years (under medical supervision): proportion of adult dose according to bodyweight, as tea infusion or dry extract*."	See above (chapter 4.2 Posology and method of administration).
	▪ The indication for children from 3 to 12 is included in the ESCOP monograph for Valerianae radix. The commentator would like to be in line with this monograph and therefore proposes to as well as for the well-established as for the traditional use: <u>Leave out</u> the sentence "because there is no experience available, use of this product is not recommended in children below the age of 12 years: <u>Include</u> the use for children from 3 – 12	See above (chapter 4.2 Posology and method of administration).
	<u>Well-established use:</u> ▪ Suggest changing 'of intake' to 'continued use'. ▪ The age for children should be below the age of 18 years. This should appear in contraindications.	The text of published draft has already been corrected to 'continued use'. Treatment < 18 years: see response above (chapter 4.2 Posology and method of administration).

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.5 Interaction with other medicinal products	a) Co-medication with other sedatives ▪ We would disagree with the following section: *"An additive effect of barbiturates is possible and could result in excessive sedation. Co-medication with barbiturates is therefore not recommended. Since additive effects with other sedatives cannot be excluded, co-medication is not recommended as a general precaution"*. First we would like to remark that barbiturates are no longer of high relevance thus the two first sentence should be removed. The last sentence seems to contradict the well-established and/or traditional use of plausible combinations of different plant extracts used as sedatives. For clarification purposes, the mentioned sentences should be replaced by: "Co-medication with synthetic sedatives is not recommended". In addition, a statement such as "Combinations of Valerian root preparations with other sedative plant extracts are considered rational" should be added. This proposal is based on the practice of drug regularory authorities' positive assessment of such rational combinations. *Instead of "Clinically relevant interaction with drugs metabolised by the CYP 2D6 or CYP 3A4 pathway is unlikely" the sentence should read "Clinically relevant interaction with drugs metabolised by the CYP 2D6, CYP 3A4/5, CYP 1A2 or CYP 2E1 pathway is unlikely"*. [Donovan et al. 2004, Gurley et al 2005]	We agree to the removal of the two first sentences and rephrasing of the third sentence "Combination with synthetic sedatives requires medical diagnosis and supervision." (WEU). For THMPs see the final monograph (chapter 4.5). Since the monograph focuses on monotherapy, a positive comment on combination with other plant extracts is not indicated. We agree to correct the text on CYP interactions taking into account the proposal (inclusion of information on CYP 1A2, 2E1 and 4A4/5), see text in the final monograph (rephrased proposal included).
	▪ Two commentators suggest that instead of "Clinically relevant interaction with drugs metabolised by the CYP 2D6 or CYP 3A4 pathway is unlikely" the sentence should read, "Clinically relevant interaction with drugs metabolised by the CYP 2D6, CYP 3A4/5, CYP 1A2 or CYP 2E1 pathway is unlikely".	See above.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.5 Interaction with other medicinal products Continuation	▪ Suggest changing the wording of the second sentence as shown (changes underlined): ~~Valerian root probably has no c~~Clinically relevant interaction with ~~effects on the disposition of medications~~ drugs metabolised primarily by ~~dependent on~~ the CYP 2DG or CYP 3A4 pathway~~.~~ is unlikely.	See above.
	▪ Remove the paragraph referring to concomitant use with barbiturates for both Well established and Traditional Use sections.	Rephrased in the final monograph, see above.
	▪ The use of barbiturates is no longer of high relevance so the sentences "An additive effect of … recommended as a general precaution" can be left out. Moreover the last line oft this section seems to be contradict with the traditional and well-established use of different plant combinations used as sedatives. It can be considered to replace this part by: *Co-medication with synthetic sedatives is not recommended.* ▪ Based on the practice of drug regulatory authorities' positive assessment of such rational combinations a statement such as "Combinations of Valerian root preparations with other sedative plant extracts are considered rational" should be added.	Rephrased in the final monograph, see above. Combination products with other extracts are not to be addressed in this monograph.
	▪ We do not agree with the sentences *"An additive effects of barbiturates is possible and could result in excessive sedation. Co-medication with barbiturates is therefore not recommended. Since additive effects with other sedatives cannot be excluded, co-medication is not recommended as a general precaution"*. Since this statement is contradictory to the well-established and traditional use of plausible combinations of different plant extracts used as sedatives, e.g. the combinations with hops, passion flower and/or melissa. Furthermore, barbiturates are no longer of high relevance in therapy. For clarification purposes, the mentioned sentences should be replaced by: "Co-medication with synthetic sedatives is not recommended". A statement on co-medication with synthetic sedatives already covers a potential effect of barbiturates.	Rephrased in the final monograph, see above.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.5 Interaction with other medicinal products Continuation	▪ In addition, a statement such as "Combinations of Valerian root preparations with other sedative plant extracts are considered rational" should be added. This proposal is based on the practice of drug regulatory authorities' positive assessment of such rational combinations.	Combination products with other extracts are not to be addressed in this monograph.
	▪ Combination with other sedative traditional herbal actives should be allowed according to scientific assessment by the competent authority before granting a Traditional Use Registration. The general statement: "Since additive effects with other sedatives cannot be excluded, co-medication is not recommended as a general precaution", should be deleted.	Rephrased in the final monograph, see above. Combination products with other extracts are not to be addressed in this monograph.
	b) Consumption of alcohol ▪ We suggest deleting the statement that the effect of valerian may be increased by alcohol intake. An interaction between alcohol and valerian has never been observed, and an increased sedation following intake of alcohol and valerian is speculative.	We agree to the proposal. It is correct that no specific interaction of valerian and alcohol has been shown. The corresponding warning had been included as a general precaution for sedative treatment. However, in view of the existing data, it is justified to refrain from this advice.
	▪ "The effect of Valerian preparations may be potentiated by alcohol. Excessive concomitant consumption of alcohol should therefore be avoided." Such an interaction between alcohol and valerian never has been observed, an increased sedation after intake of alcohol and valerian intake is speculative. The wording "potentiation" is in any case inadequate, as there exist only a very few examples for proven potentiating effects between drugs in the whole literature. And how to explain an additive effect with a drug lacking sedative effects? "Excessive ~~concomitant~~ consumption of alcohol should therefore be avoided." Though this is true in any case there is no correlation to the use of valerian. In the manner it is cited here it gives the impression that this warning is of special importance when taking valerian.	See above.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.5 Interaction with other medicinal products Continuation	Conclusion: The wording of the precautions should clearly show that these are assumed risks and not proven interactions. This seems essential to give correct informations to the user. In the form presented now there is no clear difference to precautions for the use of benzodiazepines which are used in a comparable indication. For these substances however a pronounced sedation as well as a deleterious interaction with alcohol was proven. In the form presented here there is no distinction to the serious proven risks of benzodiazepine intake and this is regarded as inadequate and dangerous, as the patient must regard the risks to be comparable.	See above.
	▪ "The effect of Valerian preparations may be potentiated by alcohol. Excessive concomitant consumption of alcohol should therefore be avoided." An interaction between alcohol and valerian never has been observed, an increased sedation after intake of alcohol and valerian intake is speculative. The wording "potentiation" is in any case inadequate, as only a very few examples for proven potentiating effects between drugs could be found in the international literature. And how to explain an additive effect with a drug lacking sedating effects? "Excessive ~~concomitant~~ consumption of alcohol should therefore be avoided." Though this is true in any case there is no correlation to the use of valerian. In the manner it is cited here it makes the impression that this warning is of special importance when taking valerian. Conclusion: The wording of the precautions should clearly differentiate between assumed risks and proven interactions. This seems to be essential in order to inform the user correctly. In the form presented now, there is no clear difference to precautions for the use of benzodiazepines which are used in a comparable indication. For benzodiazepines however a pronounced sedation as well as a deleterious interaction with alcohol has been proven. The lack of distinction between the assumed risks of valerian and the serious proven risks of benzodiazepine intake is regarded as inadequate and dangerous, as the patient will regard the risks to be comparable.	See above.
	▪ The interested party proposes to delete "excessive" in "excessive concomitant consumption of alcohol"	See above.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.6 Pregnancy and lactation	▪ We propose to delete the sentence "As there are no sufficient data available, the use is not recommended … ", because this is a contradiction to the statement that there are no reports on any harmful or deleterious effects.	In our view a recommendation of treatment is not justified in general if data on treatment during pregnancy and lactation are missing.
	▪ The following rewording is suggested: Safety during pregnancy and lactation has not been established. Definitely should be deleted. Due to the lack of data, use during pregnancy and lactation is not recommended. The sentence starting "No adverse effects…" should be deleted. It may be considered falsely reassuring. The absence of evidence is not the evidence of absence.	We agree, see rephrased monograph text under 4.6.
4.7 Effects on ability to drive and use machines	▪ We do not agree with the statement that Valerian preparations should not be taken up to 2 hours before driving or using machinery. Although an impairment of vigilance 1-2 hours after administration of Valerian syrup has been deduced from the findings of the study from Gerhard et al published in 1996. In this study, the authors reported a slight but significant decrease in vigilance in the 'valerian syrup group'. According to the results of the study, this statement cannot be confirmed. During the acute phase 1-2 hours after intake of Valerian syrup a comparable, but not decreased vigilance had been observed. The results of the vigilance test showed the same result for placebo and for valerian syrup, thus giving no hint on sedation and impaired vigilance, whereas in the driving simulator, placebo lead to faster reactions than valerian. The overall test for concentration, however, yielded better results for the valerian group. The pre-treatment which showed clear differences renders the evaluation questionable. Furthermore, the valerian syrup group was not blinded so that the volunteers knew that they were treated with a sedative. An impairment of vigilance could not be conformed by a randomised, double-blind, placebo-controlled study in 16 patients suffering from sleeping disorders (Donath et al 2000). The authors observed positive effects on the sleep structure and the subjective well-being, not after acute administration but after 2 weeks. Thus acute sedative effects do not seem probable.	According to the publication, the trial of Gerhard was performed with a placebo control; a double-blind study must therefore be assumed. Because the possibility of these effects cannot be excluded, HMPC decided (July 2006) to include the following text under 4.7 in both parts: "May impair ability to drive and use machines. Affected patients should not drive or operate machinery."

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.7 Effects on ability to drive and use machines Continuation	▪ *Summary of comment:* „should not be taken up to 2 hours before driving or operating machinery." This comment seems to be not justified by the data obtained with different Valeriana preparations. The commentator justifies his statement by describing in detail among other things that in two of five clinical studies a slight acute sedating effect of Valerian could be shown whereas in three other studies no sedation was observed. It seems inadequate to transfer warning notices from two not representative studies yielding a questionable sedation and not to take in account the other investigations which showed no sedation after valerian intake.	See above.
	▪ *Summary of comment:* „should not be taken up to 2 hours before driving or operating machinery." This comment seems to be not justified by the data obtained with different Valeriana preparations. The annotator explains in detail this opinion with several publications. ▪ New reference: Glass JR et al. (2003) J Clin Psychopharmacol 23:260-268	See above. New reference: Glass JR et al. (2003) J Clin Psychopharmacol 23:260-268 A randomized, double blind, cross over, placebo controlled study with 14 healthy volunteers ≥ 65 years without sleeping problems and sedative therapies. They received temazepam (single doses 15/30mg) diphenhydramine (single dose 50/75 mg) valerian root extract (single doses 80/160 mg; DER 5:1, extraction solvent not known) and performed at times (0;0,5;1;2;3;4;6;8 hours postdosing) validated measures of subjective sedation, mood and psychomotor performance. In the group receiving valerian root no drug effects were evident on either objective or subjective measures. Temazepam and diphenhydramine were positive controls. The administered dose covers less than 50% of the monograph conform adult dose. Therefore the study only gives a hint that no severe effects for the higher dose might be expected.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.7 Effects on ability to drive and use machines Continuation	▪ The alcohol interaction should be moved to 4.5. Suggested rewording of the remainder of the text is as follows: May cause drowsiness. Patients should be aware of how they are effected by this product and [Preparation] should not be taken up to 2 hours before driving or operating machinery.	See above.
4.8 Undesirable effects	▪ Gastrointestinal side-effects occur with placebo in many studies (see also monographs of Commission E, ESCOP as well as BfArM standard texts) therefore the cited undesirable effects cannot be attributed to Valeriana specifically. We, therefore, believe that the content of this section should read 'none known' instead.	According to the revised SPC guideline (Oct. 2005) the frequency category should not be based on differences versus placebo but on crude frequency rates. Therefore the chapter 4.8 remains unchanged.
	▪ Clinical studies reported the occurrence of gastrointestinal side-effects for placebo (see for instance the ESCOP monograph). The cited undesirable effect cannot be attributed to Valeriana. Therefore the commentator suggests to replace the wording in this section by "none known".	See above.
	▪ This paragraph should be replaced by "None known." Reasons: To this extent, gastrointestinal side-effects occur with placebo in many studies (see also ESCOP monograph).	See above.
	▪ We suggest changing 'complaints' to 'symptoms' and 'intake' to 'ingestion' ▪ Comment contains report on undesirable effects.	HMPC agreed (July 2006). The listing of undesirable effects of valerian root contains the number of case reports of monopreparations and combinations containing valerian root. They are reflected towards the organ class systems. There is no information available that would enable the rapporteur to evaluate the case reports regarding causality.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
4.9 Overdose	▪ The content of this section should be deleted as it does not fit under this title. The statements in this section do not apply to accidental mistakes or suicide attempts by patients, but to abuse (more than 10- or 20-fold of the recommended dosage). Therefore this information would be misleading in the context of the Guideline on the Summary of Product Characteristics.	The text has been reconsidered with regard to the revised SPC guideline 2005. We do not agree that the text on acute overdose should be deleted; according to the SPC guideline these experiences should be reported in this section. However, we agree to leave out the text on misuse over several years since it does not reflect the usual therapeutic situation.
	▪ The following rewording of the second paragraph is suggested (changes underlined): This should be amended to read: Valerian at a dose of approximately 20 g causes symptoms of (…..) which resolve within 24 hours. Treatment of symptoms should be supportive. ~~After intake of very high doses of valerian root over several years (up to 10g extract daily corresponding to approx. 30g of the drug)~~ ~~w~~Withdrawal symptoms (including delirium) ~~were~~ have been reported.	The proposed text on withdrawal symptoms is misleading because they have not been reported for the recommended dosages but only for misuse of very high doses. We agree to the opinion that this part should be deleted. The first paragraph has been reworded see the final monograph, chapter 4.9.
5.1. Pharmaco-dynamic properties	▪ The commentator has the opinion that inclusion of different kinds of data under 5. Pharmacological properties, should be restricted to data which are clearly based on results of sound pharmacological experiments.	This general remark does not clarify which information should be deleted or changed according to the annotator. A comment is not possible.
	▪ Well-established use: 'Wellbeing' should be written as one word. ▪ The following should be deleted: "which have long been recognised empirically and have been confirmed in preclinical trials and controlled clinical studies." No data supports this statement and it is considered overly promotional. ▪ "possibly" should be placed before improve sleep latency. A sentence should be added to state that the mechanism of action in humans is unknown. The postulated mechanisms of action are unproven and should be deleted.	"Wellbeing" has been deleted. We do not agree to delete the text "which has been (...) clinical studies" because in our view there is clearly enough evidence available from controlled pharmacological and clinical trials to support this statement. For the same reason the inclusion of "possibly" is not adequate. Regarding the mechanism of action, it is the usual way in pharmacology to collect information in preclinical trials. In the sense of the commentator most mechanisms of action of chemical substances should be 'unproven', since they have been investigated preclinically. The text makes sufficiently clear that it is not known which of the identified mechanisms are essential for the clinical effect.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
5.3. Preclinical safety data Continuation	▪ The information given is superfluous, since the "low toxicity" of the preparations is the actual basis of, and is demonstrated by, extensive and long-term human use. The interested party would like to suggest that section 5.3. of the Community herbal monographs focuses on reproductive toxicity (particularly embryo-foetal toxicity), genotoxicity and carcinogenicity as apparent from preclinical safety studies. If no studies/data are available this should be stated.	According to the SPC guideline information should be given on any findings in the preclinical testing which could be of relevance for the prescriber. We do not agree that information on preclinical trials that confirm the low toxicity seen in clinical experience should be left out. The following sentence has been included in the final monograph: "Tests on reproductive toxicity, genotoxicity, carcinogenicity have not been performed."
	▪ The commentator proposes to delete the data regarding the toxicity in rodents, because these data are not automatically applicable to humans.	We do not agree. Information on preclinical testing which could be of relevance has to be given according to the SPC guideline, and relevance of rodent studies for the use in humans cannot be denied.
	▪ Traditional Use The existing statement should be replaced by: "Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended."	The text has been replaced in accordance with the `Template for a Community herbal monograph` (EMEA/HMPC/107436/2005 Revision 2): "Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product."
	▪ With reference to our previous comments concerning extracts for traditional use, under pre-clinical safety data, you have listed extracts with ethanol and one would hope this is an indication you intend to allow extracts under traditional use and therefore would support this statement. Clearly, this would be contradictory if you insist extracts cannot be used in traditional use.	See above.
	▪ Two commentators suggest that in this section (Traditional use) the content should be replaced by the wording "Not applicable as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended" which is in accordance with the final document "Template for a community herbal monograph" (EMEA/HMPC/107436/2005) and draft Community herbal monographs on linseed (EMEA/HMPC/340849/2005) and ispaghula seed (EMEA/HMPC/340861/2005)".	See above.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
5.3 Preclinical safety data Continuation Footnote	▪ We suggest that this footnote is removed completely. The European Pharmacopoeia monograph for Valerianae radix does not include a test for valepotriates. The valepotriates are only relevant for Valeriana mexicana and Valeriana edulis.	We do not agree. Valepotriates are not only relevant for C. mexicana and C. edulis. Dried root of V. officinalis contains 0.5 – 2 % valepotriates.
	▪ Furthermore, your quote under section 6 referring to "the total exposure to valepotriates and baldrinals should not exceed the maximum exposure with herbal tea", is not an issue when Valeriana officinalis is being used and as a quality standard for the use of valerian, must comply with the European Pharmacopoeia which specifies Valeriana officinalis L., we do not see that this note is pertinent or applicable for applicants to demonstrate. It is our understanding that the valepotriates and baldrinals issue may be a problem when related species of valeriana are used, but by definition, these would be excluded with the applicant ensuring that the material used is compliant with the Monograph of the European Pharmacopoeia	The European Pharmacopoeia does not demand testing of valepotriates and baldrinals; as outlined above, this issue is nevertheless relevant for V. officinalis in view of the valepotriate content in the drug because of their toxicological relevance (alkylating and cytotoxic properties).
	▪ We recommend to delete Footnote no. 5 [which is due to changes now footnote 3] completely because the European Pharmacopoeia monograph (see Footnote no. 2 [which is due to changes now footnote 31) does not include a test for valepotriates in Valerianae radix. Valepotriates are only relevant for *Valeriana mexicana* and *V. edulis*. Only traces occur in *Valeriana officinalis* and they are not detected in commercial herbal medicinal products (tinctures, teas and film coated tablets or capsules containing extracts or powdered drug of *V. officinalis* as active ingredients) [Bos et al. 1996, Shohet et al. 2001].	We do not agree. Detection limits of assays vary considerably. The results of the cited publications give a useful hint for the general risk assessment of valerian root preparations, but are not a sufficient justification to waive these tests in general because of the toxicological relevance of the valepotriates and baldrinals (alkylating and cytotoxic properties).

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
5.3 Preclinical safety data Continuation Footnote	As an alternative we propose to re-phrase Footnote no. 5 [which is due to changes now footnote 3] for the following reasons: ▪ 1. The statements on valepotriates are not fully coherent: As in the first sentence reference is made to the herbal tea: "the total exposure to valepotriates and baldrinals should not exceed the maximum exposure with herbal tea" the last sentence should not focus on the absence of valepotriates but also on the herbal tea: "where the applicant cannot demonstrate an acceptable level of valepotriates in the finished product based on exposure with herbal tea...".	1. We agree to re-phrase footnote no. 5 (now footnote no. 4) in the following way: "Where valerian root is used as powder, the total exposure to valepotriates and degradation products such as baldrinals should not exceed the maximum exposure with herbal tea (prepared infusion). Alkylating and cytotoxic properties of valepotriates and baldrinals are normally not relevant for finished products because valepotriates decompose rapidly and only traces of valepotriates or their degradation products such as baldrinals are found. Where the applicant cannot demonstrate that the total exposure to valepotriates with the finished product does not exceed the maximum exposure with herbal tea, he has to provide data on determination of the threshold of toxicological concern compatible with the safe use of the preparation."
	▪ 2. We propose to delete the reference to baldrinals and recommend to restrict comparison to the evaluation of valepotriates in the comments for the following reasons: The valepotriates possess alkylating properties, for which the epoxy group (absent in baldrinals skeleton) is responsible [Braun et al. 1982]. Baldrinal and homobaldrinal inhibit the in vitro colony growth of mouse bone marrow cells and human lymphocytes substantially less than the valepotriates [Braun et al. 1986]. In a more recent study, it was shown that baldrinal and homobaldrinal were 10- to 30-fold less cytotoxic than their parent compounds (valtrate, isovaltrate and acevaltrate) when tested against GLC4, a human small-cell lung cancer cell line and against COLO 320, a human colorectal cancer cell line [Bos et al. 1998]. - As mentioned in the draft proposal, valepotriates decompose rapidly into homobaldrinal and related products. Baldrinals are known also to be very unstable substances which decompose very rapidly. - Moreover determination of valepotriates and baldrinals in herbal medicinal products by HPLC faces the difficulty that no reference substances are available on the market for qualitative and quantitative analyses.	2. We do not agree to delete the reference to baldrinals. Athough they are indeed less cytotoxic than valepotriates, testing is required because of their proven mutagenicity.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
5.3 Preclinical safety data Continuation Footnote e	▪ We recommend deleting this footnote as it is not conform to the European Pharmacopoeia monograph (referred to in the footnote 2 [which is due to changes now footnote 1]). The Eur. Ph. monograph does not include a test for valepotriates in Valerianae radix since the European Pharmacopoeia does not consider them relevant in this species but only in *Valeriana mexicana* and *V. edulis*. These substances are not found in herbal medicinal products containing preparations of *Valeriana officinalis.* (Bos et al. 1996, Sohet et al. 2001) As an alternative we propose to rephrase Footnote 5 [which is due to changes now no. 3] for the following reasons: ▪ 1. The statements on valepotriates are not fully coherent: As the first sentence refers to herbal tea ("the total exposure to valepotriates and baldrinals should not exceed the maximum exposure with herbal tea"), the last sentence should not focus on the absence of valepotriates but also refers to herbal tea. From our point of view it should be clarified that "herbal tea" does not mean the finally prepared infusion but the (comminuted or powdered) herbal drug. The final infusion is not a suitable reference since it does no longer contain these instable compounds. Therefore in the first sentence "herbal tea" should be replaced by "herbal drug" and the last sentence should be modified to read: "where the applicant cannot demonstrate an acceptable level of valepotriates in the finished product based on exposure with herbal drug..."	See above.

Line no or section and paragraph no	Comment and rationale	Rapporteur's response
5.3 Preclinical safety data Continuation **Footnote**	▪ 2.We propose to delete the reference to baldrinals and recommend restricting comparison to the evaluation of valepotriates for the following reasons: - The valepotriates possess alkylating properties, for which the epoxy group (absent in baldrinals skeleton) is responsible [Braun et al 1982]. Baldrinal and homobaldrinal inhibit the in-vitro colony growth of mouse bone marrow cells and human lymphocytes substantially less than the valepotriates [Braun et al 1986]. In a more recent study, it was shown that baldrinal and homobaldrinal were 10- to 30-fold less cytotoxic than their parent compounds (valtrate, isovaltrate and acevaltrate) when tested against GLC_4, a human small-cell lung cancer cell line and against COLO 320, a human colorectal cancer cell line [Bos et al 1998]. As mentioned in the draft proposal, valepotriates decompose rapidly into homobaldrinal and related products. Baldrinals are known also to be very unstable substances which decompose very rapidly. - Moreover determination of valepotriates and baldrinals in herbal medicinal products by HPLC faces the difficulty that no reference substances are available on the market for qualitative and quantitative analyses. These statements are supported by Braun et al. 1982, Braun et al.1986 and Bos et al. 1998.	See above.
	▪ This comment refers to the valepotriates. However, *Valeriana officinalis* in contrast to *Valeriana mexican*a and *Valeriana edulis* contains only small amounts of valepotriates, which mostly break down during processing. Thus, the requirement to prove absence of valepotriates is incomprehensible. For the raw material, the monograph „Radix Valerianae Ph.Eur." does not include testing for valepotriates because of the insignificance of the amount of these constituents. Thus footnote 5 [which is due to changes now no. 3] should be deleted.	See above.
	▪ Supporting literature covering for lacking genotoxicity data: Romero-Jiménez M. et al. (2005) Mutat. Res. 585: 147-155	Somatic Mutation and Recombination Test (SMART) in Drosophila melanogaster showed no genotoxic effects for an infusion of valerian root purchased from a local health food store, raising questions concerning the quality of the drug in relation to pharmaceutical qualities. Therefore the data cannot be accepted to evaluate the absence of genotoxic effects of valerian root.