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Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *HUMULUS LUPULUS* L., FLOS' (EMEA/HMPC/513617/2006)

Table 1: Organisation(s) providing comments on the draft 'Community herbal monograph on *Humulus lupulus* L., flos' as released for consultation on 5 July 2007 until 15 October 2007.

	Organisation
1	Dr. Uwe Koetter, Uttwill, Switzerland
2	The Association of the European Self-Medication Industry (AESGP)
3	Schweizerische Medizinische Gesellschaft für Phytotherapie (SMGP)
4	Kooperation Phytopharmaka, Germany
5	The European Scientific Cooperative on Phytotherapy (ESCOP)

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Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT : EMEA/HMPC/513617/2006	
Page 1, third reference duplicate, see also page 5, 6th reference: Humulus lupulus. Alt Med. Rev 2003 Page 5, forth reference after the first line include space, because another reference follows Page 5, sixth reference duplicate, see also page 1, 3rd reference: Anonymous. Humulus lupulus. Alt Med. Rev 2003 page 6, ninth reference first author spells Muller CE, (Mueller CE or Müller CE), not Miller CE: delete, correct reference on page 7 page 7, 11th - 13th reference first author spells to my knowledge Nikolic D (not Nicolic D), correct in No 12 and 13, check and correct 11 page 10, 2nd to last reference Wohlfahrt R, Hänsel R, Schmidt H. Nachweis sedativ-hypnotischer Wirkstoffe im Hopfen. * Planta Med 1982a; 45: 224-228 order of authors is not correct, delete: correct reference is on page 4, 3rd to last: Hänsel R, Wohlfahrt R, Schmidt H. Nachweis sedativ-hypnotischer Wirkstoffe im Hopfen.	Endorsed. Corrections have been taken up in the assessment report.
We welcome, in principle, the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for *Humulus lupulus* containing products, should facilitate mutual recognition in Europe. In general, we would like to mention that there are combination products in the market for which a well-established medicinal use can be justified by clinical studies and bibliographic data.	Endorsed. Another monograph on combination products of valerian and hops extracts will be elaborated.
The draft monograph on *Humulus lupulus*, L., flos provides a narrow view on the use of hops, which does not do justice to the many traditional uses of hops in many European countries. Hence, it is recommend to improve the draft: - by adding dry extracts to the composition - to allow the use of a wide range of alcohol/water mixtures or just water to produce extracts or infusions as known from the past - include solid oral dosage forms to the pharmaceutical forms - and to widen the indications to reflect relevant traditional uses in at least the past 100 years.	- Extracts are added as far as their posology and traditional use for 30 years is known. - No indications are added, which is in accordance with the ESCOP monograph.

GENERAL COMMENTS TO DRAFT DOCUMENT : EMEA/HMPC/513617/2006	
The list of reference is short of a number of noticeable review articles and original publications on hops, which were mostly published by authors related to the brewing industry. However, since medicinal uses are covered, these publications should be taken into account as well. Particularly important is, that these references provide an extensive list on publications on hops important for traditional use. Eisler for example provides in his review a table with traditional uses and lists the sources. For the use as sedative as dry extract in combination with valerian more than references with anecdotal evidence are provided. Further references report on the use of hops or its extract. Other more prominent uses are as a digestive aid to relief dyspepsia and to improve diuresis. For the latter two indications the cited reports are with preparations from hops (Eisler 1940). Piendl, who again provides a list of traditional indications, presents a more recent extensive review on the traditional use of hops. More than 40 reports on the use as sedative and sleep aid are provided for the time between 1922 and 1980. Reports on the use as a tonic, digestive and substance for the relief of dyspepsia cover a time span of 76 years with 27 reports. 19 reports between 1936 and 1979 deal with the use against incontinence and to increase diuresis (Piendl and Schneider 1981). Stocker is mentioned because of his listing of products containing hops as a mono substance and the use of dry extracts. In addition, this publication from a Swiss journal provides references, which have not been included by other authors (Stocker 1967).	References related to the brewing industry have not been taken into account, since they are related to the food area rather than the medicines area.
A number of publications, which report on hops in combination with other sleep aids are not included in the list of references. As recently shown hops contributes distinguishable to the effects of other herbal substances known as sleep aids (Koetter et al. 2007), with a mode of action different to for example valerian (Butterweck et al. 2007). Hence, the list of publications should be extended as supporting evidence for hops. Besides the numerous reports cited in the publications in the previous paragraph these are: (Flesch 1997), (Lataster and Brattström 1996), (Notter et al. 2003), (Petrowicz et al. 2000), (Volk et al. 1999), (Wegener 2003), (Widy-Tyszkiewicz and Schminda 1997).	Endorsed and taken up in the assessment report.
Extending on the previous paragraph, it is pointed out that today with an explanation, how hops works and the numerous clinical reports on successful use of hops in combination with valerian a monograph on well established use for this combination is justified. Different to the traditional use of hops for a number of indications and the well established use is restricted to a fixed combination of valerian with hops, both extracted with methanol 45 %, and employed as dry extracts (Abourashed et al. 2004; Butterweck et al. 2007; Dimpfel et al. 2006; Koetter et al. 2007; Morin et al. 2005; Müller et al. 2002; Schellenberg et al. 2004).The traditional monograph should be extended with the comment, that well established use for dry extracts of Humulus lupulus, L. flos in combination with dry extract of valerian is evident from the scientific literature.	Endorsed since another monograph on combination products containing valerian and hops extracts will be elaborated.

GENERAL COMMENTS TO DRAFT DOCUMENT : EMEA/HMPC/513617/2006	
As a final comment it is recommended to challenge the restriction of use to adolescents over 12 years. It is correct that no formal research has been conducted, however hops is one of the most and widely used herbal substances in massive quantities around the globe. The lack of toxicity and the apparent lack of adverse effects in humans even for extended use beyond the average time spent in childhood should be enough supporting evidence to allow the use from the age of two years on. Secondly, products with hops in combination with other herbal sleep aids are known at least since the 1930s. Even if serious underreporting is taken into account the lack of any report on acute or chronic side effects or misuse should be again enough supporting evidence to allow the use from the age of two years on, especially when one considers than labelling for use in children was common for decades.	Not accepted. The monograph should be in harmony with those of *Valeriana officinalis* L., radix and *Passiflora incarnata* L., herba.
We welcome the preparation of the Community herbal monograph on Lupuli flos which may contribute to the creation of harmonised assessment criteria for herbal medicinal products and thus to facilitation of mutual recognition in Europe. In general, we would like to mention that there are combination products in the market for which a well-established medicinal use can be justified by clinical studies and bibliographic data. For this reason, the following amendments are suggested for the table columns “well-established use” and “traditional use” in the draft community herbal monograph on Lupuli flos.	Endorsed. A separated monograph on combination products of valerian root and hop extracts will be elaborated.
1. On the available evidence we accept that, when used in a mono-preparation, this herbal substance is appropriate for only the traditional use category. 2. However, Lupuli flos (hops) is more commonly used in combination with other herbal sedatives such as Valerianae radix, Passiflorae herba and Melissae folium. In particular, two clinical studies [1,2] have demonstrated the efficacy of valerian-hops combinations in mild sleep disorders; this combination may therefore qualify for the well-established medicinal use category. Separate monographs for certain fixed combinations of hops and other herbal sedatives, particularly valerian, should be considered.	Endorsed. A separated monograph on combination products of valerian root and hops extracts will be elaborated.

SPECIFIC COMMENTS ON TEXT		
Paragraph no.	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	We suggest listing the following herbal preparations **as examples** under ii) in order to cover the existing variability of preparations: Dry extract (4-8:1, ethanol 40 % V/V) Dry extract (4-8:1, methanol 40 % V/V) Dry extract (7-10:1, methanol 45 % m/m) Dry extract (5.5-8:1, water) Tincture (1:5, ethanol 70% V/V) To be consistent with the different preparations listed under section **4.2 Posology and method of administration**, we propose to include separately "powdered herbal substance" and "herbal substance for tea preparation".	We only accept those extracts for which a posology is given in the literature and for which there is evidence of traditional use. Dry extracts are not accepted as traditional use for 30 years is not supported. Powdered herbal substance is a part of comminuted herbal substance.
2. ii) Herbal preparations **2. Qualitative and quantitative composition**	Add: dry extracts prepared with water, or alcohol/water mixtures Rationale for: dry extracts prepared with water, or alcohol/water mixtures Concentrated extracts and dry extracts are traditionally used and mentioned in the scientific literature, review articles or product directories. The solvents in use are either i) water, ii) ethanol/water mixtures of various concentrations, or iii) methanol/water mixtures of various concentrations. No specific concentration should be mentioned, as the preparations are not limited to one specific mixture. Also, in a number of cases companies did not report the particular manufacturing conditions. A reference to alcohol/water appears to be just under these circumstances.	Not endorsed as discussed above. Since the extract of hops is another extract in terms of the European Pharmacopoeia all parameters of preparations should be given as well as the exact posology in order to guarantee the quality of the HMP.

Paragraph no.	Comment and Rationale	Outcome
2. (Conti-nuation)	Examples for various concentrations, where given are provided from the Rote Liste 1990 as a snapshot for the many years dry extracts are marketed: i) Euvegal Dragees N, Spitzner contained dry extract of Humulus lupulus prepared with water ii) Luvaseed, Brenner contained a dry extract of Humulus lupulus prepared with ethanol 35 % (m/m), Nervenruh forte, Divapharm-Knufinke with ethanol 40 % iii) herz plus nerven/Herzpunkt was prepared with methanol 30 %, Hovaletten, Zyma contained two types of Humulus lupulus extract, one made from a methanol/water mixture, the other is another example for i) as the dry extract was prepared with water. Ivel, Knoll was prepared with methanol 45 %. In Switzerland and Lichtenstein products with hop extract manufactured from methanol 45 % are marketed since the eighties. Further evidence for the use of dry extracts are provided in the references listed in the general chapter. Change: - Liquid extract (1:1) prepared with ethanol/water 45 % v/v – to - Liquid extract (1:1) prepared with ethanol/water – Rationale for: Liquid extract (1:1) prepared with ethanol/water The traditional use of liquid extracts is not restricted to one concentration of ethanol as the following examples taken from Rotel Liste 1990 show: Extractum Flores Humuli lupuli in Belladonna-Valobonin, Hänseler was prepared with Ethanol 25 % 1:1, Extractum strobuli lupuli in Euvegal Saft, Spitzner was prepared with ethanol 20 %. Further evidence for the use of numerous ethanol/water combinations are provided in the references listed in the general chapter. Change: - Tincture (1:5) prepared with ethanol/water 60 % v/v - to - Tincture (1:5 – 1:10) prepared with ethanol/water – Rationale for: Tincture (1:5 – 1:10) prepared with ethanol/water –	

Paragraph no.	Comment and Rationale		Outcome
2. (Continu-ation)	The traditional use of tinctures is not restricted to one concentration of ethanol as the following example taken from Rote Liste 1990 show: Tinct. Strobuli lupuli (1:8) was employed in Baldriparan Nerven Tonikum, Scheurich Further evidence is provided in the references listed in the general chapter.		
2. Quali-tative and quantitative composition	Well-established use With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended Herbal preparations Hydroalcoholic liquid or dry extracts in fixed combinations with other herbal preparations Traditional use	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended i) Herbal substance *Humulus lupulus* L., flos (hop strobiles) ii) Herbal preparations - Comminuted herbal substance - Liquid extract (1:1) prepared with ethanol/water 45% v/v - Tincture (1:5) prepared with ethanol/water 60% v/v - solid extract prepared with ethanol/water (hydroalcoholic extracts)	See above outcome on comment related to "dry extracts prepared with water, or alcohol/water mixtures". The preparation of the extracts should be specified and have sufficient traditional use in order to be taken up in the monograph.
	Comment: Preparations made from Lupuli flos in combination with other herbal drugs are used in authorised combination products with other herbal extracts, e.g. with valerian, passionflower or lemon balm in nervous sleep disorders or in cases of nervousness. It should be acknowledged that such products are marketed as well-established herbal medicinal products. Most data are available for solid extracts prepared with ethanol/water or methanol/water as extraction solvent. Therefore, these extracts should be included into the listed extract preparations of both traditional and well-established herbal medicinal products.		

Paragraph no.	Comment and Rationale	Outcome
2. Qualitative and quantitative composition	After ii) Herbal preparations, we propose the insertion of: iii) Corresponding dry extracts This phrase has been accepted in the Community Herbal Monograph on Passiflorae herba. Extracts from hops are used to some extent, e.g. a dry extract from hops (T.T:1,45% methanol)[1] .	Not endorsed see comments above.
3. Pharmaceutical form	According to **2. Qualitative and quantitative composition**, solid preparations are also to be cited. We would therefore suggest mentioning solid dosage forms in the first sentence: *"Herbal substance or herbal preparation in **solid and** liquid dosage forms for oral use."*	Endorsed
3. Pharmaceutical form	Change to: Herbal substance or herbal preparations in liquid or solid dosage forms for oral use. Rationale The use of solid oral dosage forms is according Braungart known for more than 100 years. He recommends on page 779 in his book 'Der Hopfen', published in 1901 the use of powder and pills. He also mentions that Extractum Lupulinae is evaporated and used in such preparations, which accounts for an early reference for the employment of dry extracts. The evaporated extract had to be mixed with carriers to receive either the powder or to be used with other excipients to prepare pills (Braungart 1901). Other examples for the use of solid oral dosage forms can be found in various countries in Europe. The most prominent example is the product Hovaletten, Zyma, which has been marketed since around 1930 as a solid oral dosage form with a combination of hops extracts and valerian extract. Particularly about this product many publications are available, which present in the typical style of the beginning of the last century case reports and successful treatments. Eisler 1940 provides a comprehensive report on these publications with a list of references. Hops has not only be used in combinations but also as mono substance in solid oral dosage forms. Stocker 1967 provides a list of products marketed in the 1930. Add: Herbal substance to be employed in pillows as sleep aids.	Solid dosage form for oral use is endorsed. Herbal substance to be employed in pillows as sleep aid is not accepted, because this use is anecdotal. .

Paragraph no.	Comment and Rationale		Outcome
3. (Continu-ation)	Rationale The use of pillows filled with hops has been successfully employed according the literature for many years. There is anecdotal evidence that goes back to George III (Richter, Ausführliche Arzneimittellehre I, 385, zitiert nach Braungart 1901). According Lewin 1885 the aroma of hops causes somnolence, which led to the use of Humulus lupulus as sleep aid in pillows placed in bed close to the head. Schulz 1929 has employed the pillows successfully and Schilcher reports about it recently (Schulz 1929), (Schilcher and Dorsch).		
3. Pharma-ceutical form	Well-established use Herbal preparations in combination products in liquid and solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	Traditional use Herbal substance or herbal preparations in **solid or** liquid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term	Endorsed
	Comment: Combination products authorised as well-established herbal medicinal products should be addressed. Most data is available for solid extracts obtained from Lupuli flos. Therefore, this pharmaceutical form should be included to the list.		
3. Pharma-ceutical form	Herbal substance or herbal preparation in liquid dosage forms for oral use. Since “comminuted herbal substance” is defined as a herbal preparation under 2. Qualitative and Quantitative Composition, and a single dose of “dried inflorescences (e.g. as powdered herbal substance)” is given as a dosage form under 4.2. Posology and method of administration, it follows that at least one “herbal preparation in a solid dosage form” is included in the monograph. We propose amendment to : Herbal substance or herbal preparations in solid or liquid dosage forms for oral use.		Endorsed
4.1. Thera-peutic indications	We agree with the wording of indications which have been attached to the area of traditional use. In addition we suggest including a statement that the well-established medicinal use has been proven for combination products.		A separate monograph on combinations will be elaborated.

Paragraph no.	Comment and Rationale		Outcome
4.1. Therapeutic indications	Add: Traditional herbal medicinal product for the use as tonic preparation and digestive for the relief of dyspepsia Rationale The draft of this monograph focuses on the use of liquid preparations or the use of tea. Especially these preparations are traditionally known for their tonic and digestive properties to relief dyspepsia. Ives published one of the first reports on rational investigations of hops. He refers to the use as tonic and against dyspepsia in France. As a physician he confirms the positive effects on the stomach (Ives 1820). Braungart cites Sanderer (Allg. Br. u. H. Ztg. 1885, I, 53), who reports about the use of tea prepared from hops as a digestive in Greece. Schulz reports on the traditional use of tea prepared from hops to relief dyspepsia. An extensive compilation of traditional uses is provided by Piendl, which includes these indications and provides the reference for support. Add: Traditional herbal medicinal product for the use as mild diuretic to support treatment of incontinence, cystitis and prostatitis. Rationale As explained in detail in the introduction reviews by Eisler, Stocker and Piendl prepared provide traditional evidence for this indication covering a time span of more than 30 years. Also, Braungart already reports in his book on page 778 on the diuretic effect of Humulus lupulus, which is not associated with the intake of water when drinking beer. Given the numerous reports and the time span covered the addition of this traditional indication is jusitified.		The traditional use as tonic and digestive is not accepted because hops are used in foods for their bitter taste. The same applies for its putative diuretic effect.
4.1. Therapeutic indications	<u>Well-established use</u> In herbal combination products for the treatment and relief of mild nervous tension and sleep disorders.	<u>Traditional use</u> 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 indication exclusively based upon long-standing use.	Traditional use is endorsed but the well established use is not supported

Paragraph no.	Comment and Rationale	Outcome
4.1.(Continuation)	Comment: The available experimental and clinical data of preparations containing preparations from Lupuli flos in combination with other herbal sedatives suggest the addition of a note to justify the application of various products containing Lupuli flos as a combination partner in well-established used herbal medicinal products. Especially this applies for combinations of Lupuli flos with valerian and/or lemon balm and/or passionflower. For such products, pre-clinical and clinical data is available. Appropriate positive monographs suggesting the use of such combinations have been published by the German Commission E and have been accepted in many marketing authorizations.	
4.1. Therapeutic indications	The product is a traditional herbal medicinal product for use in specified indication exclusively based upon long-standing use. Since two indications are given (relief of mild symptoms of mental stress; to aid sleep), we suggest a minor amendment to improve clarity: "…for use in the specified indications based exclusively upon…"	Endorsed
4.2. Posology and method of administration	The single dose is described for different types of preparations (powdered herbal substance, dried inflorescences for preparation of an infusion, liquid extract, tincture). It should not be reintroduced with different figures under the two possible uses (mild symptoms of mental stress and as an aid to sleep). As established for valerian (EMEA/HMPC/340719/2005), only the daily dose (number of single doses) is specified for each use (single dose being defined previously for each type of preparation). In agreement with the published literature (see below), it is proposed to modify singe doses as follows. In addition, for clarity purposes, we suggest not repeating the dosage with the frequency. The text under 'Single dose' should therefore be amended as follows: *"Single dose* - *0.5-1.0 g dried inflorescences (e.g. as powdered herbal substance)* - *0.5-2.0 g dried inflorescences for preparation of an infusion* - *0.5-2.0 ml of liquid extract* - *1.0-2.0 ml of tincture* *For relief of mild symptoms of mental stress, ~~0.5-1.0 g,~~ 2-4 times daily* *To aid sleep, ~~1.0-2.0 g,~~ a single dose half to one hour before bedtime with an earlier dose during the evening, if necessary."*	The proposal on the posology of a single dose has been accepted. Dry extracts have not been included – see comments above. There is no restriction to the duration of use.

Paragraph no.	Comment and Rationale	Outcome
4.2. Posology and method of administra-tion	**References**: British Herbal Pharmacopoeia. Humulus. British Herbal Medicine Association, London 1976, p.111a. Bradley, P.R. (ed). Hops. British Herbal Medicine Association, Dorset 1992, p. 128-130. Wren RC. Hops. Potter's new cyclopedia of botanical drugs and preparations. Essex, UK: Saffron Waldon, C.W. Daniel Co. Ltd.,1989, p. 146. Newal A.C., Anderson, L.A., Phillipson, J.D. Hops. Herbal Medicines. A guide for healthcare professionals. 1st Ed. Pharmaceutical Press, London, Chicago 1996, p.162-3. <u>Extracts</u> We suggest adding: Dry extract (6-8:1, water): 60-80 mg (Commission E) Dry extract (7.7-9.5:1, methanol 45 % m/m): single and daily dose 84 mg <u>Other preparations</u> **In accordance with the ESCOP monograph, we propose inserting: "Other preparations corresponding to the daily dose of 1.5-3 g of the herbal substance" hence mirroring the dosage recommendations of the preparations already on the market**. <u>Combinations</u> In accordance with the Commission E monograph, we suggest mentioning that combinations with other herbal sedatives such as Melissae leaf, Valerian root and/or Passiflora herb exist and are useful.	

Paragraph no.	Comment and Rationale	Outcome
4.2. (Continuation)	**Duration of use** We suggest deleting the restriction of use to two weeks because there is no justification available in scientific literature. The ESCOP monograph states under "Duration of administration: no restriction". The recommended duration of use of not more than 2 weeks is not justified by any precaution of use and not in line with the therapeutic indication (relief of mild mental stress and aid to sleep).	The restriction to the duration of use has been removed.
4.2. Posology and method of administration	Add: Preparations with dry extract prepared accordingly. **References** Abourashed E, Koetter U, Brattstrom A (2004) In vitro binding experiments with a Valerian, Hops and their fixed combination extract (Ze 91019) to selected central nervous system receptors. Phytomedicine 11: 633-638 Braungart R (1901) Der Hopfen als Braumaterial. Verlag von R. Oldenbourg, München Butterweck V, Brattstroem A, Grundmann O, Koetter U (2007) Hypothermic effects of hops are antagonized with the competitive melatonin receptor antagonist luzindole in mice. J Pharm Pharmacol 59: 549-552 Dimpfel W, Brattstrom A, Koetter U (2006) Central Action of a Fixed Valerian-Hops Extract Combination (Ze 91019) in Freely Moving Rats. Eur J Med Res 11: 496 – 500 Eisler O (1940) Das Schriftum über die physiologischen Wirkungen des Hopfens. Gesellschaft für die Geschichte und Bibliographie des Brauwesens E.V., Institut für Gärungsgewerbe, Berlin Flesch P (1997) Hopfen-Baldrian-Kombination als Benzodiazepin-Ersatz? Geriatrie Praxis 1: 21-23 Ives AW (1820) An Experimental Inquiry into the chemical properties and economical and medicinal virtues of the Humulus Lupulus, or the Common Hop. American Journal of Science: 302 – 312	Dry extracts have not been included – see comments above. References on the physiological effects of hops have not been taken on board, the others were included in the assessment report.

Paragraph no.	Comment and Rationale	Outcome
4.2. (Continuation)	Koetter U, Schrader E, Kaufeler R, Brattstrom A (2007) A randomized, double blind, placebo-controlled, prospective clinical study to demonstrate clinical efficacy of a fixed valerian hops extract combination (Ze 91019) in patients suffering from non-organic sleep disorder. Phytother Res 21: 847-851 Lataster MJ, Brattström A (1996) Die Behandlung von Patienten mit Schlafstörungen. Wirksamkeit und Verträglichkeit von Baldrian-Hopfendragées. Notabene medici 4: 182-185 Morin CM, Koetter U, Bastien CH, Ware JC, Wooten V (2005) Valerian-Hops Combination and Diphenhydramine for Treating Insomnia: a Randomized Placebo-Controlled Clinical Trial. Sleep 28: 1307-1313 Müller CE, Schumacher B, Brattström A, Abourashed EA, Koetter U (2002) Interactions of valerian extracts and a fixed valerian-hop extract combination with adenosine receptors. Life Sci 71: 1939-1949 Notter D, Brattstrom A, Morandell D, Polasek W (2003) Wirksamkeit und Sicherkeit eines Baldrian-Hopfen-Kombinationspräparates bei verschiedene Schalfstörungen - Eine Therapiebeobachtung. Phytotherapie 3: 2-7 Petrowicz O, Deitelhoff P, Lange P (2000) P-108: Use of a Fixed Combination of Valerian Root and Hop Strobiles in Sleep Disorders and Psycho-Vegetative Dysfunction. Phytomedicine 7: 106 Piendl A, Schneider G (1981) Über die physiologischen Eigenschaften des Hopfens. Ein Überblick. Brauwelt 121: 600 - 608, 724 - 734 Schellenberg R, Sauer S, Abourashed EA, Koetter U, Brattstrom A (2004) The Fixed Combination of Valerian and Hops (Ze91019) acts via a Central Adenosine Mechanism. Planta Med 70: 594-597 Schilcher H, Dorsch W Phytotherapie in der Kinderheilkunde - Ein Handbuch fur Arzte und Apotheker. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart Schulz H (1929) Vorlesungen über Wirkung und Anwendung der deutscher Arzneipflanzen. Georg Thieme Verlag, Leipzig Stocker HR (1967) Sedative und Hypnogene Wirkung des Hopfens. Schweiz.Brauerei-Rdsch. 78: 80-89	

Paragraph no.	Comment and Rationale		Outcome
4.2. (Continuation)	Volk S, Friede M, Hasenfuß I (1999) Phytosedativum Gegen Nervöse Unruhezustände und Einschlafstörungen: Wirksamkeit und Verträglichkeit eines Pflanzlichen Kombinations-Präparates aus Baldrianwurzeln, Hopfenzapfen und Melissenblättern. Z Phytother 20: 337-344 Wegener T (2003) Phytopharmaka zur Anxiolyse. Dtsch Apoth Ztg 6: 108-115 Widy-Tyszkiewicz E, Schminda R (1997) A randomized double blind study of sedative effects of phytotherapeutic containing Valerian, Hops, Balm and Motherwort versus Placebo. Herba polonica 43: 154-159		
4.2. Posology and method of administration	<u>Well-established use</u> **Posology** For combinations, dosage based on product specific data. **Internal use:** ***Duration of use*** No restriction. If the symptoms persist during the use of the medicinal product, medical advice should be sought. ***Method of administration*** For oral use	<u>Traditional use</u> **Posology** *Adults, elderly, children* Single dose - 0.5 g dried inflorescences (e.g. as powdered herbal substance) - 0.5-2.0 g dried inflorescences for preparation of an infusion For relief of mild symptoms of mental stress, 0.5-1.0 g of the drug or equivalent hydro-alcoholic extract preparations, 2-4 times daily To aid sleep, 1.0-2.0 g of the drug or equivalent hydro-alcoholic extract preparations, a single dose half to one hour before bedtime with an earlier dose during the evening, if necessary 0.5-2.0 ml of liquid extract - 1.0-2.0 ml of tincture	Only the posology of well-characterized preparations has been mentioned. The proposal on the duration of use has been accepted. The proposal to allow the preparations in children below 12 years of age was not accepted in order to be in harmonisation with the monographs on Valerian root and Passiflora herb.

Paragraph no.	Comment and Rationale		Outcome
4.2. (Continuation)		**Duration of use** If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Method of administration** Oral use.	
	Comment: The internal use of Lupuli flos preparations is based on data obtained with well-established combination products. We do not see any risks concerning the use of Lupuli flos in children below 12 years of age. Therefore, the use should not be restricted. There is no need to limit the duration of internal use. Negative long-term effects are not known for Lupuli flos. The general note "If the symptoms persist during the use of the medicinal product, medical advice should be sought" is considered as sufficient. Furthermore, products established as well-established herbal medicinal products should be addressed.		The comment on the limit to the duration of use is accepted.
4.2 Posology and method of administration	**Posology** *Adolescents over 12 years of age, adults, elderly* The single dose of 0.5 g for dried inflorescences is unnecessarily low and rigid. We propose amendment to 0.5-1.0 g, as recommended in several standard texts [3-6]. Compared to the single dose of liquid extract, the single dose of tincture is also too low. In line with a number of long-standing texts [6-8] we suggest that a single dose of 2.0-4.0 ml of tincture would be more appropriate. To improve clarity we propose grouping together all the single dose entries, without interruption by dosages for specific indications:		The posology as presented by ESCOP is endorsed.

Paragraph no.	Comment and Rationale	Outcome
4.2. (Continuation)	Single dose - 0.5-1.0 g dried inflorescences (e.g. as powdered herbal substance) - 0.5-2.0 g dried inflorescences for preparation of an infusion - 0.5-2.0 ml of liquid extract - 2.0-4.0 ml of tincture instead of 1.0-2.0 ml There appears to be no valid reason for stating dosages for specific indications in terms of dried inflorescences only. Furthermore, it would be better to state dosages in terms of multiples of the single dose: For relief of mild symptoms of mental stress, a single dose up to 4 times daily. To aid sleep, 1-2 single doses half to one hour before bedtime with an earlier dose during the evening if necessary. Taking into account item 2 under General Comments (Table 2), it would be helpful to insert a sentence here to the effect that: Combinations with other herbal sedatives, such as valerian root, passion flower and/or melissa herb, are acceptable and may be advantageous.	Endorsed
	Duration of use Not to be taken for more than 2 weeks. The restrictioin to 2 weeks seems unnecessary and we propose that the entire sentence be deleted. We have found no literature support for it, nor any reason on grounds of safety. No such limit has been applied in Community Herbal Monographs relating to other sedatives, i.e. those for *Valeriana officinalis* L., radix or *Passiflora incarnata* L., herba.	The comments on the duration of use are endorsed.
	References 1. Koetter U, Schrader E, Kaufeler R, Brattström A. A randomized, double blind, placebo-controlled, prospective clinical study to demonstrate clinical efficacy of a fixed valerian hops extract combination (Ze 91019) in patients suffering from non-organic sleep disorder. Phytother Res 2007;21:847-51 2. Schmits M, Jackel M. Comparative study for assessing quality of life of patients with exogenous sleep disorders (temporary sleep onset and sleep interruption disorders) treated with a hops-valerian preparation and a benzodiazepine drug. Wien Med Wochenschr 1998;148:291-8 3. Humulus. In: *British Herbal Pharmacopoeia 1983*. Bournemouth: British Herbal Medicine Association, 1983:111-2	Most references have been taken up in the assessment report.

Paragraph no.	Comment and Rationale		Outcome
4.2. (Continuation)	4. Barnes J, Anderson LA, Phillipson JD. Hops. In : *Herbal Medicines – A guide for healthcare professionals*, 2nd ed. London-Chicago: Pharmaceutical Press, 2002:290-2. (Should be corrected!) : 2007; ;354-7, 3nd ed 5. Bradley PR, editor. Hops. In: *British Herbal Compendium, Volume 1. A handbook of scientific information on widely used plant drugs.* Bournemouth: British Herbal Medicine Association, 1992:128-30 6. Wren RC, revised by Williamson EM and Evans FJ. Hops. In: *Potter's New Cyclopaedia of Botanical Drugs and Preparations*. Saffron Walden: C.W. Daniel Company, 1988:145-6 7. Pharmaceutical Society of Great Britain. Lupulus; Tinctura Lupuli. In: *British Pharmaceutical Codex 1934.* London: Pharmaceutical Press, 1934:610-1 and 1484 8. Blacow NW, editor. Lupulus. In: *Martindale – The Extra Pharmacopoeia*, 26th ed. London: Pharmaceutical Press, 1972:327		
4.3. Contra-indications	Well-established use Hypersensitivity to the active substance.	Traditional use Hypersensitivity to the active substance.	Endorsed for combination products.
	Comment: Hypersensitivity should be listed as well for well-established medicinal products.		
4.4. Special warnings and precautions for use	Well-established use None known. For tinctures and extracts, the appropriate labelling for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use", must be included.	Traditional use None known. For tinctures and extracts, the appropriate labelling for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use", must be included.	Endorsed for combination products.
	Comment: As related to published data in the world-wide literature there are no risks, adverse events or adverse drug reactions reported which are related to the internal use of Lupuli flos in children (as well as in adults or elderly). Therefore, such a warning as listed in this section is not justified.		

Paragraph no.	Comment and Rationale		Outcome
4.5. Inter-actions with other medicinal products and other forms of interactions	Well-established use None reported.	Traditional use None reported.	Endorsed.
	Comment: The "precautionary measure" not to be used concomitantly with sedatives is not justified: During the long-term use of preparations containing Lupuli flos there are no data on drug-drug-interactions or any other effect of Lupuli flos concerning the efficacy or safety of other sedatives. The same wording should be listed for well-established combination products.		
4.6. Pre-gnancy and lactation	Well-established use No data available. In accordance with general medical practice, the product should not be used during pregnancy and lactation without medical advice.	Traditional use No data available. In accordance with general medical practice, the product should not be used during pregnancy and lactation without medical advice.	Not accepted. The wording is in harmonisation with that of Passiflora herb.
	Comment: We suggest to use the wording of the ESCOP monograph for both product categories.		
4.7. Effects on ability to drive and use machines	Well-established use None known.	Traditional use None known.	Not endorsed. Harmonisation with Passiflora herb.
	Comment: There is no data available which may give hints that Lupuli flos may negatively affect the ability of driving or using of machines. We therefore suggest using the wording of the ESCOP monograph for both product categories.		
4.8. Undesirable effects	Well-established use None known.	Traditional use None known. If adverse reactions occur, a doctor of a qualified health care practitioner should be consulted.	Not endorsed for well-established use. Some adverse effects have been found in clinical studies with combination products.

	Comment: The same wording – without the additional note for traditional used products - should be listed for well-established combination products.		
4.9. Overdose	Well-established use No case of overdose has been reported**.**	Traditional use No case of overdose has been reported.	Endorsed for combination products.
	Comment: The same wording should be listed for well-established combination products.		
5. Pharma-cological properties			Should be taken on board for combination products.
5.1. Pharma-codynamic properties	Well-established use In some experimental studies preparations of Lupuli flos showed sedative effects. Clinical studies performed with combination products showed improvement of nervous tension and sleep disorders.	Traditional use Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended.	
	Comment: The pharmacodynamic profile is supported by published experimental and clinical studies (see also ESCOP monograph).		
5.2.Pharmac okinetic properties	Well-established use No data available.	Traditional use Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended	Endorsed.

Paragraph no.	Comment and Rationale		Outcome
5.3. Preclinical safety data	Well-established use Tests on genotoxicity were not performed for water extracts. Tests on water/ethanolic extracts were negative. Tests on reproductive toxicity and carcinogenicity have not been performed.	Traditional use Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended~~,~~ unless necessary for the safe use of the product. Tests on genotoxicity were not performed for water extracts. Tests on water/ethanolic extracts were negative. Tests on reproductive toxicity and carcinogenicity have not been performed.	Endorsed for combination products.
	Comment: The same wording should be used for well-established combination products.		
Other comments	**Well-established use of combination products** In the following, controlled and non-controlled clinical studies, which have been performed with a preparation containing 250 mg of valerian extract and 60 mg of hop extract (Ze 91019) as well as with other combinations of valerian and hop, are described. Such information may be useful for the development of a monograph on the combination of hop strobile with other herbal preparations. Controlled Studies In a placebo-controlled, double-blind, randomised parallel group study, the effects of Ze 91019 on sleep architecture were tested in 15 patients with non-organic insomnia. Patients received 2 tablets of Ze 91019 (250 mg of valerian extract and 60 mg of hop extract per tablet; n = 8) or placebo (n = 7). Study duration was 4 weeks. Polysomnographic recordings were obtained in the sleep laboratory at baseline, after 4 weeks of intake of the study mediation, and after a 2-week wash-out period. The application of Ze 91019 significantly decreased slow-wave-sleep percentages and increased sleep stage II as compared to placebo (Rodenbeck and Hajak, 1998). This finding points to GABAergic effects of the herbal combination. Based on their results, Rodenbeck et al. recommend valerian preparation in patients with mild, non-chronified sleep disorders (Rodenbeck et al. 1998).		

Paragraph no.	Comment and Rationale	Outcome
Other comments	A multicentre, randomised, placebo-controlled, parallel-group study conducted in 9 sleep disorders centres throughout the United States was performed to compare the efficacy and safety of a valerian-hops combination Ze 91019 with diphenhydramine in the treatment of mild insomnia. A total of 184 adults (110 women, 74 men; mean age of 44.3 years) with mild insomnia were included. The treatment consisted of (1) two nightly tablets of standardised extracts of a valerian (187 mg native extracts; 5-8:1, methanol 45% m/m) and hops (41.9 mg native extracts; 7-10:1, methanol 45% m/m) combination for 28 days (n = 59), (2) placebo for 28 days (n = 65), or (3) 2 tablets of diphenhydramine (25 mg) for 14 days followed by placebo for 14 days (n = 60). Sleep parameters measured by daily diaries and polysomnography, clinical outcome ratings from patients and physicians, and quality of life measures were analysed (Morin et al. 2005). The first biometrical analysis of the study (Morin et al. 2005) demonstrated modest improvements of subjective sleep parameters for both the valerian-hops combination and diphenhydramine, but few group comparisons with placebo reached statistical significance. Ze 91019 produced slightly greater, though non-significant, reductions of sleep latency relative to placebo and diphenhydramine at the end of 14 days of treatment and greater reductions than placebo at the end of 28 days of treatment. Diphenhydramine produced significantly greater increases in sleep efficiency and a trend for increased total sleep time relative to placebo during the first 14 days of treatment. Patients in the valerian and diphenhydramine groups rated their insomnia severity lower relative to placebo at the end of 14 days of treatment. Quality of life (Physical component) was significantly more improved in the valerian-hops group relative to the placebo group at the end of 28 days. There were no significant residual effects and no serious adverse events with either Ze 91019 or diphenhydramine and no rebound insomnia following their discontinuation (Morin et al. 2005). Another multicentre, randomised, double-blind study investigated the fixed extract combination Ze 91019 (valerian and hops) in comparison with placebo in patients suffering from non-organic insomnia (ICD 10, F51.0-51.2). Objective sleep parameters were registered by means of a transportable home recorder system (QUISI). The primary outcome was the reduction in sleep latency (SL2) which had to be prolonged at baseline ($\geq$ 30 min) as inclusion criteria. The treatment period lasted for 4 weeks with either placebo, single	Most of the controlled and non-controlled studies have been taken up in the assessment report and will be used for the elaboration of the monograph on combination products.

Paragraph no.	Comment and Rationale	Outcome
Other comments (Continued)	valerian extract (Ze 911) or the fixed valerian hops extract combination (Ze 91019). The amoun of the single valerian extract was identical to that amount contained in the fixed extra combination, i.e. 500 mg valerian extractum siccum. In the extract combination 120 mg hop extract siccum was added. Both extracts were prepared with 45% methanol m/m with a drug extract ratio of 5.3:1 (valerian) and 6.6:1 (hops), respectively. The fixed extract combinatio was significantly superior to the placebo in reducing the sleep latency whilst the single valeria extract failed to be superior to the placebo (Koetter et al. 2007).	
Other comments	A placebo-controlled double-blind study was performed in 12 patients (6 men, 6 women) aged 22-27 years, with traffic noise-induced disturbance of sleep. Patients ingested coated tablets with either 60 mg of valerian root extract (Valeriana officinalis, DER 5.5-7.4:1, solvent not given) and 100 mg extract of hop strobile extract (Humulus lupulus, (DER 9-11:1, solvent not given), or placebo. Study duration was 6 nights. During the third, fourth and fifth night traffic noise was simulated during the whole night by playing tape recordings. Six patients received four tablets of verum (corresponding to 240 mg of valerian extract or 1572 mg of valerian root, and 400 mg of hop extract or 4000 mg of hop strobiles) prior to the second, 6 patients prior to the third noisy night. The remaining nights, 4 tablets of placebo were administered. The traffic noise had an influence on sleep architecture (measured by polysomnography), however, an adaptation to the noise could be observed. The results from the two treatment arms (second respectively third noisy night) were not comparable. However, the results clearly showed a beneficial influence of the valerian-hop combination on sleep architecture by countering the stressful effects of noise. Adverse events were not reported (Müller-Limmroth and Ehrenstein 1977). The efficacy of a valerian-hop combination (coated tablets containing 200.2 mg of dry extract of valerian root (DER 5:1) and 45.5 mg of dry extract of hop strobiles (DER 5.5:1); extraction solvents not indicated) was compared to that of 3 mg bromazepam in a two-week reference-controlled, double-blind, randomised clinical parallel group trial with double-dummy technique. 46 patients (37 women, 9 men; mean age 50.3 years) suffering from non-psychiatric sleep disorders were tested for sleep quality, fitness and quality of life by psychometric tests, psychopathologic scales and sleep-questionnaires. All parameters improved in both treatment groups to a similar extent. During treatment with the herbal combination the percentage of patients subjectively feeling “bad” or “moderate” decreased by 62.6% (from 82.6% to 20%), as compared to a reduction of 32.7% (from 56.5% to 23.8%) in patients treated with bromazepam. Seven adverse events were noted, two of which (one case of gastrointestinal complaints in both treatment arms) were considered to have been caused by the medication. (Schmitz and Jäckel 1998).	

Paragraph no.	Comment and Rationale	Outcome
Other comments (Continued)	Non-controlled Studies An open, multicentre post-marketing surveillance study assessed the efficacy and safety of Ze 91019 in 3,447 patients with sleep disorders. With the intake of the drug product the number of patients indicating an uninterrupted sleep increased from 7.6 to 32.9%. Patients said to be more relaxed and have a better performance. Efficacy was judged by the physicians as good-very good in 74.9% of cases, and as acceptable in 16.3%. Only 19 patients reported adverse events, of which 6 were assessed as possibly related to the study medication, all of them gastrointestinal complaints (Brattström 1996; Lataster and Brattström 1996). Benzodiazepine-induced changes in sleep architecture were reported as demonstrated by polysomnography. The report is anecdotal, with no details given. When withdrawn from benzodiazepines and switched to a valerian-hop combination (Ze 91019), the patient's hypnograms distinctly changed towards normal patterns. Tolerability was very good, with the exception of occasional gastrointestinal discomfort (no numbers given) (Flesch 1997). Another open polysomnographic examination was conducted in 30 patients with non-organic sleep disorders. Patients were tested before and after a 14-day intake of two tablets of Ze 91019 two hours before bedtime. Test parameters were EEG measurements, respiration/snoring, sleep quality (verbal rating scale), and a psychometric test for the detection of trouble with focussing and memory. In all patients a shift towards a normalisation of sleep architecture (REM / non-REM phases) was found. Sleep stage 1 was reduced, and slow wave sleep increased. Sleep latency 2 (mean time to reach sleep stage 2) declined significantly within the 2 weeks of treatment, and the total wake time also declined significantly. Correspondingly, sleep efficiency (ratio of true sleep time to time spent in bed) improved significantly. The effects on sleep parameters were paralleled with a subjectively ameliorated feeling of well-being. No adverse effects occurred (Brattström 1996; Füssel et al. 2000). Results of a non-controlled multicentre study with 144 patients (88 women, 56 men; age range 11-91 years) suffering from sleep disorders were reported. Patients received Ze 91019 (1 to 2 coated tablets one hour before bedtime) for 4 weeks. Patients assessed sleep parameters (sleep latency, sleep duration, frequency of awakening) and well-being before and after treatment on a VAS. In 25.9% of patients the sleep disorder had completely resolved after therapy. Severity of the sleep disorders had distinctly shifted towards milder forms	

Paragraph no.	Comment and Rationale	Outcome
Other comments (Continued)	A responder rate of 67% was calculated. Patients with complaints of interrupted sleep reacted best to the treatment (71%), followed by trouble falling asleep (67%) and sleep disorders of psychological origin (67%). The improvement of sleep parameters was paralleled by improvements of well-being (e.g. feeling refreshed) in the same scale. Sleep duration was increased by approximately 1 hour in average. 66.9% of patients indicated an onset of effects within the first 10 days of treatment. Tolerability was judged good-very good by 92% of patients. Adverse events were reported by four patients, and explicitly stated by two: 1x oedema, 1x diarrhoea (Notter et al. 2003). In a non-controlled, multicentre study, 480 patients (305 women, 175 men; mean age 49.5 years) suffering from nervous sleep disorders and restlessness were treated for an average of 22 days with a combination preparation containing 225 mg valerian root extract (DER 6-7:1; 70% ethanol) and 30 mg dry extract of hop strobile extract (DER 11-14:1; 96% ethanol) per coated tablet, corresponding to approximately 1500 mg of valerian root respectively 400 mg of hop strobile per tablet. The mean dose of the combination was 2.6 coated tablets during the day and 1.6 tablets before bedtime in the evening. The mean total daily dose was 3.3 tablets. Main efficacy parameters evaluated were improvement of nervous anxiety and associated psycho-vegetative symptoms (sweating, palpitations, nervous tension) as well as the improvement of sleep disorders. Symptoms were evaluated with a 5-point rating scale (0 = not present to 4 = severe). Therapy with the valerian-hop combination resulted in pronounced improvement of both, anxiety and sleep disorders. The rating of anxiety related symptoms was reduced by 50-57%, symptoms related to sleep parameters were reduced by 58-61%. Global efficacy was assessed as “excellent” or “good” by 24.6% and 57.2% of patients, respectively. No adverse events were reported throughout the study (Wegener 2003). *15 October 2007*	

Paragraph no.	Comment and Rationale	Outcome
	References 1. Brattström A. 1996. Wirksamkeitsnachweis von Phytopharmaka am Beispiel einer Hopfen-Baldrian-Kombination. Forsch. Komplementärmed. 3: 188-195 2. Flesch P. 1997. Hopfen-Baldrian-Kombination als Benzodiazepin-Ersatz? Geriatrie Praxis 1: (Suppl.) 21-23 3. Füssel A, Wolf A, Brattström A. 2000. Effect of a fixed valerian-Hop extract combination (Ze 91019) on sleep polygraphy in patients with non-organic insomnia: a pilot study. Eur. J. Med. Res. 5: (9) 385-390 * 4. Koetter U, Schrader E, Käufeler R, Brattström A. 2007. A randomized, double blind, placebo-controlled, prospective clinical study to demonstrate clinical efficacy of a fixed valerian hops extract combination (Ze 91019) in patients suffering from non-organic sleep disorder. Phytother Res. (submitted) 5. Lataster, M. J., Brattström A. 1996. Die Behandlung von Patienten mit Schlafstörungen. Wirksamkeit und Verträglichkeit von Baldrian-Hopfen-Dragees. notabene medici 4: 182-185 6. Morin C M, Koetter U, Bastien C, Ware J C, Wooten V. 2005. Valerian hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. Sleep. 28: (11) 1465-71 * 7. Müller-Limmroth W, Ehrenstein W. 1977. Untersuchungen über die Wirkung von Seda-Kneipp(R) auf den Schlaf schlafgestörter Menschen. Med. Klin. 72: (25) 1119-1125 * 8. Notter D, Brattström A, Morandell D, Polasek W. 2003. Wirksamkeit und Sicherheit eines Baldrian-Hopfen-Kombinationspräparates bei verschiedenen Schlaf-störungen. Phytotherapie 3: 9-12 9. Rodenbeck A, Hajak G. 1998. Polysomnographische Pilotstudie zur Wirkung von Hopfen/Baldrian auf den Schlaf von Patienten mit primärer Insomnie. Eine doppelblinde, randomisierte, placebokontrollierte Studie im Schlaflabor. Study Report	

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