



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 May 2010
EMA/HMPC/132077/2010
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal

This document was valid from 6 May 2010 until 25 September 2019.

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Valeriana officinalis* L., radix and *Humulus lupulus* L., flos as released for public consultation on 16 June 2010 until 15 September 2010.

	Organisations and/or individuals
1	Czech Plant Commission of Ministry of Health
2	AESGP
3	EHPM



Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	Comment and Rationale	Outcome
CASP http://www.casponline.cz/	<p>It is not clear why this draft of Community herbal monograph on <i>Valeriana officinalis</i> L., radix and <i>Humulus lupulus</i> L., flos is having preference in draft publication prior to first case of "Fixed combination of Primula root and Thyme herb", which was assigned rapporteur on Oct.,31st 2007, its assessment report completed on Nov.,24th 2008 (EMA/HMPC/144474/2006) and overview of comments published also in Nov.2008 (EMA/HMPC/143370/2006).</p> <p>These types of preparations are based on the German Commission E monographs, but the HMPC Monographs list of herbal preparation which are in TU in EU will be most probably incomplete from the point of industry recent practice, negatively afflicting and delaying innovation as the MS authorities will be asking for harmonization with the final Monographs during the on-going and future MA applications.</p>	<p>No preference has been given to this monograph in comparison with other combinations. It is considered to be a further work on the individual monographs of valerian and of hops.</p> <p>All existing combination products in the member states have been taken into account.</p>
CASP http://www.casponline.cz/	Policy of precautionary principle to exclude adolescents and children bellow age of 18 years of age in Posology without any justification or only "lack of adequate data" substantiation is dubious and may be harmful to SME businesses.	<p>Not endorsed.</p> <p>The same precautions as given in the individual monographs on valerian and hops have been included in the monograph on their combinations.</p>

SPECIFIC COMMENTS ON TEXT			
Section number and heading	Interested party	Comment and Rationale	Outcome
4.2.	CASP	Comments:	Endorsed.

SPECIFIC COMMENTS ON TEXT			
Posology of TU	http://www.casponline.cz/	<p>It is not clear to which Herbal Preparation a) to i) are ascribed the single doses given in Posology of TU:</p> <div style="border: 1px solid black; padding: 5px; margin: 10px 0;"> <p><u>Traditional use</u></p> <p>Posology</p> <p><i>Adults, elderly</i></p> <p>Single dose</p> <ul style="list-style-type: none"> - 20 ml of liquid extract (1:6.3) - 40 or 75 drops of liquid extract (1:1) in a half glass of water - Dry extracts </div> <p>Proposed change (if any):</p> <p>To specify dose to each Herbal Preparation a) to i)</p>	The posology is specified for each dry extract including a) - i).
4.1. Indication	<p>CASP</p> <p>http://www.casponline.cz/</p>	<p><u>Traditional use</u></p> <p>Traditional herbal medicinal product for relief of mild symptoms of mental stress (A) and to aid sleep (B).</p> <p>The wording of Traditional use in Community Herbal Monograph by "mild symptom of mental stress" is too soft for traditional medicinal use to distinguish it from herbal non-medicinal products.</p> <p>Proposed change (if any):</p> <p>" Traditional herbal medicinal product for relief of mild nervous</p>	<p>Not endorsed.</p> <p>The wording of the traditional uses of the individual monographs, which have been adopted by the HMPC, has been taken over for the combination products.</p>

SPECIFIC COMMENTS ON TEXT			
		tension and/or difficulty in falling asleep" .	

Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	Comment and Rationale	Outcome
AESGP	<p>AESGP welcomes, in principle, the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for the combination of <i>Valeriana officinalis</i>, radix and <i>Humulus lupulus</i>, flos, should facilitate mutual recognition in Europe of herbal medicinal products containing the combination thereof.</p> <p>In particular, we welcome that both well-established and traditional use have been included in this monograph.</p>	
AESGP	<p>There are numerous products in the market containing this combination (valerian and hops) combined with other plants (e.g. melissa or passiflora). The basic principle i.e. the usefulness of combining sedative herbal drugs in general should be applied also for these combinations. For example, in case of combinations of three sedative herbal drugs with synergistic effect, the German Commission E recommended a much lower dose (30-50%) for each plant in the combination than that of each plant taken individually.</p> <p>In general, it is from our point of view very important that preparations for which a proposed well-established medicinal use is not accepted by the HMPC but which comply with the 'traditional use' criteria remain or be included in the traditional use category.</p>	Agreed.

SPECIFIC COMMENTS ON TEXT			
Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and Quantitative Composition	AESGP	<p>Comments:</p> <p>For both well-established and traditional use preparations, we suggest, for the sake of clarity and simplification, to gather similar products preparation under the same 'heading' and to use only round numbers for characterisation of the DER.</p> <p>It should be considered to mention drug to extract ratios as 'a range'. A fixed value (e.g. 5.5:1) gives the impression that it is a standardised extract, as fixed drug to extract ratios can only be achieved by standardization or quantification. As both extracts from valerian root and hop strobiles are classified as "other extracts" this would be inappropriate. Therefore for all the preparations listed, the drug to extract ratios should be given as a range. This is also a requirement of the EMEA "Guideline on declaration of herbal substances and herbal preparation in herbal medicinal products".</p>	<p>Partially endorsed.</p> <p>It can be agreed to present the DER as a range, but it should be stressed that the DER is not the only parameter to be taken into account. Also the nature and the strength of the solvent used are important. Moreover, the amounts of the different extracts in the combination play a major role for the posology of the herbal medicinal product. Taking into account these three parameters, combinations c) and d) can be accepted for WEU, whereas combinations e), f) and g) are not acceptable for WEU. The combination h) seems only to be commercialized in Switzerland.</p>

¹ Composition of Doppelherz® Energie Tonikum S:
Tincture of Hawthorn fruit (1 : 5)
Extraction solvent: ethanol 70% (V / V) 540 mg
Tinktur aus Baldrianwurzel (1 : 5)
Extraction solvent: ethanol 70% (V / V) 145 mg
Tinktur aus Hopfenzapfen (1 : 5)
Extraction solvent: ethanol 70% (V / V) 145 mg
Riboflavin (Vit. B2) 5.00 mg
Nicotinamide 25.00 mg
Pyridoxin hydrochloride (Vit. B6) 5.00 mg
Cyanocobalamin (Vit. B12) 3.5 µg

Overview of comments received on Community herbal monograph on *Valeriana officinalis* L., radix and *Humulus lupulus* L., flos (EMA/HMPC/132077/2010)

		<p>Proposed change (if any):</p> <ul style="list-style-type: none"> Under <u>well-established medicinal use</u> we propose to add the following combinations: <p>c) Dry extracts of Valerian root (4-5:1, methanol 51.25 % V/V) and hop strobiles (3.4-4.2:1, methanol 51.25 % V/V).</p> <p>d) Dry extracts of Valerian root (4-5:1, methanol 50 % V/V) and hop strobiles (3.4-4.2:1, methanol 50 % V/V).</p> <p>- These preparations are included in the Assessment Report and correspond to the products Klosterfrau Beruhigungs-Kapseln forte and Nervenruh® Einschlaf-Dragees in the German market.</p> <p>e) Dry extracts of Valerian root (4.0-6.7:1, ethanol 70 % V/V) and hop strobiles (4.3-7.7:1, ethanol 40 % V/V)</p> <p>- This preparation (EinschlafDragees Baldrian-Hopfen) has been granted a marketing authorisation according to section 105 of the German Medicines Law on 21 February 2003.</p> <p>f) Dry extracts of Valerian root (4-7:1, ethanol 70 % V/V) and hop strobiles (4-8:1, ethanol 40 % V/V)</p> <p>- This preparation corresponds to the products Ardeysedon® and Ardeysedon® forte (Austria) as well as Ardeysedon®, Ardeysedon® Nacht, Solaguttae® Baldrian/Hopfen Beruhigungs-Dragees and Solaguttae® Baldrian/Hopfen Einschlaf-Dragees (Germany). These preparations are mentioned in the Assessment Report. They have been granted marketing authorisations either according to section 21 or</p>	<p>Combination c (= nr. 34 of Germany): methanol 51.25 % v/v instead of 45% m/m for both val/hops.</p> <p>Posology: 250 mg/65 mg of val/hops instead of 250 mg/60 mg val/hops.</p> <p>Combination d (= nr. 7 of Germany): methanol 50% v/v instead of 45% m/m for both val/hops.</p> <p>Posology: 250 mg/65 mg of val/hops instead of 250 mg/60 mg val/hops.</p> <p>Combination e: ethanol 40% v/v instead of methanol 40% m/m for hops.</p> <p>Posology: 100 mg/32 mg of val/hops instead of 202.2 mg/45.5 mg.</p> <p>Combination f: ethanol 40% v/v instead of methanol 40% m/m for hops.</p> <p>Posology: F1: 100mg/24mg of val/hops; F2:200 mg/68 mg of val/hops instead of 200.2 mg/45.5 mg.</p>
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		<p>according to section 105 of the German Medicines Law.</p> <p>g) Dry extracts of valerian root (5.5-7.4:1, ethanol 85% v/v) and hop strobiles (9-11:1, ethanol 90% V/V)</p> <p>- This preparation (Kneipp® Gute Nacht Einschlafdragees) has been granted a marketing authorisation according to section 105 of the German medicines Law on 9 November 2004.</p> <p>h) Dry extracts of valerian root (5-8:1, methanol 45 % m/m) and hop strobiles (7-10:1, methanol 45 % m/m)</p> <p>- Although clinical data on extracts prepared with methanol 45 % (m/m) (ZE 91019) is available as stated in the assessment report, these extracts are not mentioned in the well-established-use section. As from our point of view the criteria of a well-established use are fulfilled, the combination should be listed in this section. The respective products have been authorised in Switzerland as Zeller Schlaf, coated tablets, and Zeller Schlaf forte, coated tablets, respectively.</p> <ul style="list-style-type: none"> Under traditional use we suggest to add: <p>j) Dry extracts of valerian root (4-7:1) (methanol 45 % V/V) and hop strobiles (4-8:1) (methanol 40 % V/V)</p> <p>- This combination (Avedorm® duo, company: Eberth) is in the German market for many years and should therefore be mentioned as a traditionally used preparation.</p> <p>k) Tinctures of Valerian root (1:5, ethanol 70 % V/V) and hop strobiles (1:5, ethanol 70 % V/V)</p> <p>- This combination is part of the preparation Doppelherz® Energie Tonikum S which is a traditionally used product in the</p>	<p>Combination g: ethanol 85% v/v for val and ethanol 90% v/v for hops instead of ethanol 70% v/v for val and methanol 40% v/v for hops.</p> <p>Posology: 77 mg/18.8 mg of val/hops instead of 200.2 mg/45.5 mg.</p> <p>Combination h: this product corresponds to Ze91019 with whom clinical studies have been carried out but which seems only to be authorized in Switzerland.</p> <p>Not endorsed.</p> <p>Can be considered as well-established use.</p> <p>Tinctures k: not endorsed, since the posology is lacking.</p>
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administration	<p>c) Fixed combinations of respectively 250mg/65 mg dry extracts of Valerian root and hop strobiles</p> <p>d) Fixed combinations of respectively 250mg/65 mg dry extracts of Valerian root and hop strobiles</p> <p>Both preparations are taken 1-2 times per day, corresponding to the products Klosterfrau Beruhigungs-Kapseln forte and Nervenruh® Einschlaf-Dragees in the German market.</p> <p>e) Fixed combinations of respectively 100mg/32 mg dry extracts of valerian root and hop strobiles</p> <p>Treatment of mild nervous tension: up to 3x2 daily</p> <p>Treatment of difficulties to fall asleep: 1x2</p> <p>f1) Fixed combinations of respectively 100mg/24 mg dry extracts of valerian root and hop strobiles</p> <p>Treatment of mild nervous tension: up to 3x2 daily</p> <p>Treatment of difficulties to fall asleep: 1x2</p> <p>f2) Fixed combinations of respectively 200mg/68 mg dry extracts of valerian root and hop strobiles</p> <p>Treatment of mild nervous tension: up to 3x1 daily</p> <p>Treatment of difficulties to fall asleep: 1-2x1</p> <p>These dosage recommendations (with a specific dosage for mild nervous tension) have been accepted in the above mentioned marketing authorisations according to sections 21 and 105 of the German Medicines Law.</p> <p>g) Fixed combinations of 77mg/18.8mg dry extracts of</p>	<p>Posology: OK.</p> <p>Combinations e), f), g) and h) cannot be accepted for WEU (see under point 2).</p>
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		<p>respectively valerian root and hop strobiles</p> <p>Treatment of mild nervous tension: up to 3x2 daily</p> <p>Treatment of difficulties to fall asleep: 1x2</p> <p>These dosage recommendations (with a specific dosage for mild nervous tension) have been accepted in a German marketing authorization of 9 November 2004 according to section 105 of the German Medicines Law.</p> <p>h) Fixed combinations of dry extracts 500mg/120 mg to be taken one hour before bedtime. The dosage can be increased up to 750 mg valerian dry extract and 180 mg hops dry extract.</p> <ul style="list-style-type: none"> Under traditional use, we propose to: <ul style="list-style-type: none"> - Change the posology for preparation h) defined as dry extracts of valerian root (6-7:1, ethanol 70% v/v) and hop strobiles (11-14:1, ethanol 96% v/v). <p>This preparation corresponds to the German product Selon® which, however, has a posology which is different from that of the HMPC draft (fixed combinations of 225 mg/30 mg dry extracts of valerian root and hop strobiles, respectively, daily dosage: 3 x 3 doses for indication 1 and 3 doses 1 h before bedtime for indication 2).</p> <p>The Assessment report, Germany, No 2, states correctly "Indication A 1-3 x daily 1 coated tablet; indication B 1-2 coated tablets 1/2 -1 h before bedtime. Under the last paragraph of II.3.2.1. 'Non controlled clinical studies', reference is made to the product Selon® with an average intake of 2.6 doses during the day (A) and 1.6 doses before</p>	<p>Endorsed for preparation h).</p> <p>Posology: 3x1 doses for indication 1 and 1-2 doses 1 hour before bedtime for indication 2.</p>
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		<p>bedtime (B).</p> <p>The dosage should be adapted to the marketed product as follows: Indication A: 1-3 times daily 1 coated tablet (early morning, morning and/or afternoon); indication B: 1 coated tablet ½ to 1 hour before bedtime. In cases of insufficient efficacy another coated tablet may be taken before dinner.</p> <p>In summary this would mean: Daily dosage: 3 x 1 dose for indication 1 and 1-2 doses 1 h before bedtime for indication 2.</p> <p>- Include in addition preparation j):</p> <p>j) Fixed combinations of dry extracts 600-1200mg/96-144 mg to be taken three times a day according to the dosage recommendation for Avedorm® duo.</p> <p>Restriction of use to persons from 18 years on:</p> <p>We do not agree with this restriction. The wide use of valerian and hops in children has been described in the literature as sedatives [1-2].</p> <p>In an observational study with a combination of valerian, hops and melissa [3], patients from 8 years on were involved.</p> <p>The assessment report for the Valeriana Community monograph includes a clear statement about the use of Valeriana in children from 12 to 18 years old (page 16-17). <i>"There is no need for clinical trials or specific warnings for adolescents between 12 to 18 years of age taking into account the excellent tolerability of valerian root and its preparations".</i></p> <p>Furthermore, according to the already published Community</p>	<p>Endorsed.</p> <p>Taking into account these arguments together with the fact that in both monographs on valerian and hops adolescents over 12 years are allowed to use these products, combination products should be acceptable as well for this category of patients.</p>
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		monographs on valerian and on hops, the use of both herbal drugs and their preparations is not recommended for children below the age of 12 years. This corresponds to the existing marketing authorisations in Germany (below 12 years of age) and in Austria (below 10 years of age). For example, in case of the above-mentioned German marketing authorisations, the dosage recommendations refer to adults and adolescents from 12 years on. For preparation H) (Zeller Schlaf/ Zeller Schlaf forte, proposed above for "well-established use") the posology for children from 6 years on is 250 mg valerian dry extract and 60 mg hops extract as authorised by Swissmedic	
4.4. Special warnings and precautions for use	AESGP	The same applies as stated above with respect to the restriction of use to persons from 18 years on.	Endorsed.
4.5. Interactions	AESGP	The draft states that combination with synthetic sedatives requires medical supervision or is not recommended, respectively. We would like to ask for a justification of this statement, either in the monograph or in the Assessment Report.	Not endorsed. This part has been taken over from the monograph on valerian.
4.7. Effects on ability to drive and use machines	AESGP	From our point of view, the restriction " <i>May impair ability to drive and use machines. Affected patients should not drive or operate machinery</i> " is not justified, in particular for low-dose, traditional preparations. In this respect we refer to a statement of the Society of Medicinal Plant Research [4] as well as to a [5]. In this placebo-controlled cross-over study, the influence of a combination of valerian, hops and melissa on the functional capacity and mental state was investigated in 19 volunteers.	Not endorsed. See under 4.5.

		<p>No significant difference between verum and placebo was found with respect to the psychomotoric functional capacity and mental state. Combination with ethanol did not result in effects exceeding the effects of ethanol alone.</p> <p>For these reasons, the text under 4.7 should be deleted in both columns or replaced by "None known".</p>	
5.1. Pharmacodynamic properties	AESGP	<p>The last sentence "Whether hop strobile extract acts as mild sedative ..." should be deleted since it provides no new information and puts the above-explained usefulness of the combination in question.</p>	<p>Partially endorsed.</p> <p>The wording "or not at all" will be deleted.</p>

References

- [1] Schilcher H, Dorsch W. Phytotherapie in der Kinderheilkunde. 4th edition. Stuttgart: WVG, 2006:69-74.
- [2] Bühring U, Ell-Beiser H, Girsch M. Heilpflanzen in der Kinderheilkunde. Stuttgart: Sonntag, 2008:189-194, 334-335.
- [3] Friede M, Liske E, Woelk H, Wüstenberg P. Pflanzliche Wirkstoffe gegen Schlafstörungen (Herbal substances against insomnia). T&E Neurologie Psychiatrie 1997; 11:697-700.
- [4] Statement of the Society of Medicinal Plant Research (GA) on the EMEA HMPC Draft of the Community Herbal Monograph on Valerian Root. 31 January 2006.
- [5] Friede M, Hasenfuß I, Wüstenberg P. Alltagssicherheit eines Phytosedativums aus Baldrianwurzeln, Hopfenzapfen und Melissenblättern (Everyday safety of a phytosedative from valerian roots, hops and balm leaves). Nervenheilkunde 1999; 18:91-95.

GENERAL COMMENTS		
Interested party	Comment and Rationale	Outcome
EHPM	<p>The interface between medicinal product and food legislation, particularly in relation to therapeutic use/claims and posology/recommended daily amount is complex. The 'borderline' between botanical used in food supplements and traditional herbal medicinal products can be difficult to determine, as is demonstrated by the growing body of European Court of Justice case law dealing with this issue.</p> <p>We are therefore pleased to note from the report of the HMPC meeting of July 15/16 2009 that HMPC has ".....initiated a dialogue with the European Food Safety Agencyon possible coordination at the borderline between herbal medicinal products and food supplements in the clinical data evaluation for efficacy assessment of (Traditional) Herbal Medicinal Products by HMPC and the substantiation of health claims for 'botanicals' by the EFSA-NDA panel." (However, we were surprised to see the reference to 'clinical data' evaluation for efficacy assessment of THMPs, as our understanding is that it is the requisite period of traditional use which provides the evidence for the indication for use).</p> <p>According to medicinal product and food regulation respectively, registered traditional herbal medicinal products (THRs) must carry indications for use. Where substantiated, health claims may be made for botanical food supplements according to the terms of Regulation (EC) No 1924/2006 on Nutrition and Health claims on foods. Thus it is entirely (and legally) possible that the same herb/botanical may be used in both a traditional herbal medicinal product and a food supplement. It is therefore particularly important that therapeutic indications for THRs are for bona-fide, albeit minor and self-limiting, medical/adverse conditions only. Other claims, as in health claims for foods and food supplements, that relate to the maintenance and promotion of the relation</p>	Agreed.

	to health of the particular botanical, can then be made, and can be clearly differentiated from THR claims.	
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SPECIFIC COMMENTS ON TEXT			
Section number and heading	Interested party	Comment and Rationale	Outcome
4.1 Therapeutic indications	EHPM	<p>Well-established use: in the review of comment on the <i>Valeriana officinalis</i> monograph, in relation to well-established use a number of commentators make the point that they do not consider the data to be adequate “...to demonstrate well-established use for the indication ‘.for the relief of sleep disorders’”. This point is not adequately answered by the Rapporteur’s response.</p> <p>This same indication is now proposed for a combination of <i>Valeriana officinalis</i> and <i>Humulus lupulus</i>. However, the data on the properties of <i>Humulus lupulus flos</i> does little to enhance the effect of the two herbs in combination on sleep disorders. We therefore do not consider, from the studies presented, that there is sufficient evidence to support the indication ‘relief of sleep disorders’.</p> <p>Traditional use: In our opinion, ‘mental stress’ (A), is not a clearly defined medical condition. It suggests worry/concern, etc., but ‘mild symptoms’ of it are not medical or adverse conditions susceptible to treatment by a medicine. In our opinion such wording is more appropriate as a ‘health claim’ as defined under the EC Regulation No 1924.2006 on Nutrition and Health claims made on Foods. We therefore propose ‘mild</p>	<p>Not endorsed.</p> <p>Four non-controlled and two randomized placebo-controlled double-blind clinical studies have clearly shown that the fixed combination of extracts of hops and valerian are effective to treat patients suffering from non-organic sleep disorders.</p> <p>Not endorsed.</p> <p>The term “mental stress” has been taken over from both the individual monographs on hops and on valerian.</p>

		<i>nervous tension</i> , which incorporates both physical and mental symptomatology, as being more appropriate for this combination when used in a traditional herbal medicinal product.	
4.4 Special warnings and precautions for use		We question the validity of the apparent overly precautionary restriction of ' <i>these fixed combinations</i> ' for ' <i>sleep disorders</i> ', ' <i>to aid sleep</i> ' to those aged 18 and over. While there may not be specific data on such combinations on those below 18, dosage indications for similar products in other Member States often allow usage certainly from 12 years, sometimes younger. Additionally, it is most unlikely that the tradition of use of these herbs in combination for the indicated conditions will relate only to those over 18.	Endorsed. Adolescents from 12 years till 18 years have been included.