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Committee on Herbal Medicinal Products (HMPC)

(EMA/HMPC/144006/2009)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Vitex agnus-castus* L., fructus as released for public consultation on 17 September 2009 until 15 February 2010.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	Bio-Health Limited, UK
3	European Scientific Cooperative on Phytotherapy (ESCOP)
4	Kooperation Phytopharmaka, DE
5	Naturex S/A, FR

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	AESGP welcomes the preparation of the above-mentioned Community herbal monograph which may facilitate mutual recognition in Europe by providing harmonised assessment criteria for herbal medicinal products. However we have severe concerns with regard to the assessment as "traditionally used" only.	Well-established use has been introduced into the monograph for a defined herbal preparation with a sufficient set of data.
Bio-Health Ltd	Dosage for herbal substance used in UK, 300mg – 1800mg daily Attached Double - blind clinical trial on Vitex Agnus castus L. by S.Turner and S.Mills	*(Turner S, Mills S. A double-blind clinical trial on a herbal remedy for premenstrual syndrome: a case study. Complementary Therapies in Medicine 1993, 1:73-77)* In the study described 300 mg tablets of powdered Vitex agnus castus in a dosage 1800 mg daily were given. This publication is mentioned in the assessment report in section "II.3.2.2 Clinical studies (case studies and clinical trials)".
	I and my companies have been manufacturing Angus Castus products in the UK since 1979 and we have always used the whole powdered herbal substance in tablet or encapsulated solid dose form for oral use. Since 1979 many tens of millions of tablets/capsules have been manufactured and marketed in the UK at a dose of 300mg or 400mg of the herbal substance. We are not alone, for many other companies also market similar products using the whole herbal substance. It therefore surprised me and my colleagues that no recognition of this use of the herbal substance is given in the draft monograph as published on the 17.09.2009. I would request that consideration be given to the inclusion of the	Taking into account the above mentioned daily drug dosages of 300 mg to 1800 mg daily the dose is about 1.5 to 4.5 fold higher than that of the herbal preparations included in the monograph (including the extract for WEU). The references mentioned by all interested parties demonstrate a traditional use of the powder. However, there is no clearly defined posology and with respect to the safety the data obtained from extracts cannot be transferred to the powder. The MLWP decided to introduce a powder (posology 2 times 400 mg) into the traditional use part of the monograph based on the tradition of products in the United Kingdom.

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	herbal substance as a suitable dosage form for Vitex agnus castus and in support of my request I attach a copy of a clinical trial carried out in 1992 using the very form of Agnus castus as described. I declare a vested interest as my company was the sponsor of the clinical trial but nevertheless it provides solid evidence for the use of Agnus castus as a herbal substance. I trust you will give due consideration to my comments.	
ESCOP	The herbal preparations listed under Qualitative and Quantitative Composition, and the daily dose suggested under Posology and method of administration, are broadly in line with those stated in the German Commission E monograph [1]. However, they do not take into account established traditional use in the United Kingdom of the powdered herbal substance (in tablets or capsules) at far higher daily doses for more than 30 years. At least 7 products currently on sale in the UK (with transitional protection until April 2011 under Directive 2004/24/EC), containing either an extract or the comminuted herbal substance or both, have recommended daily doses corresponding to 500-2000 mg of herbal substance. A product marketed in Spain contains the comminuted herbal substance with a recommended daily dose of 1800 mg (6 × 300 mg tablets) [2]. In low-dose herbal preparations in the form of tinctures and dry extracts the corresponding amounts of herbal substance per daily dose (28-52 mg) may be remarkably different to those used in high-dose products (500-2000 mg), but both dose ranges should be reasonably accommodated in the text.	*(Vanaclocha B, Cañigueral S, editors. Sauzgatillo – Vitex agnus-castus L. In: Fitoterapia – Vademecum de Prescripción, 4th ed. Barcelona-Madrid-Paris: Masson, 2003:456-8)*.

Interested party	Comment and Rationale	Outcome
ESCOP	Agnus castus (Chaste Tree) was added to the UK "General Sale List" [3] in 1994 with no restrictions on the pharmaceutical form or dosage. An application for a UK Traditional Herbal Registration in accordance with Directive 2004/24/EC for a capsule product containing the comminuted herbal drug with a recommended daily dose of 2 × 400 mg is at an advanced stage of preparation and will be submitted in February-March 2010; the MHRA is aware of this forthcoming submission.	*(3: Agnus castus (Chaste Tree). In: UK Statutory Instrument 1994 No. 2410. The Medicines (Products Other Than Veterinary Drugs)(General Sale List) Amendment Order 1994. Schedule 1, Table A;* *4: User Information Leaflet: Periagna (hard capsules containing 400 mg of comminuted dried fruits of Vitex agnus castus-castus L.). Rochester, UK: Bio-Health Limited, 2009:1-4)*
KOOP PHYTO	Kooperation Phytopharmaka, a German scientific organisation, would like to comment on this HMPC draft assessment report on Vitex agnus-castus L., fructus. There are herbal preparations in the European market, which have a well-established use and a traditional use.	See below.

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and Quantitative composition	AESGP	**Monograph text** Traditional use 3) dry extract (7-13: 1), extraction solvent ethanol 60% m/m **Proposed change** Well-established use 3) dry extract (6-13: 1), extraction solvent ethanol 60-70 % m/m About 67 marketing authorisations of Vitex agnus castus (VAC) exist in the EU. Whereas only 9 of them are "traditionally used" the majority (58) were authorised as well-established use (WEU). According to the EMEA points to consider on the evidence of safety and efficacy, "at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy" in the field of a "well established use" (EMEA/HMPC/104613/2005). A recent clinical study published by He et al. (2009) has not been taken into consideration in the draft assessment report. In this prospective, double-blind, placebo- controlled, parallel-group, multicentre clinical trial 217 Chinese women suffering from moderate to severe premenstrual syndrome were randomly assigned into the VAC treatment group (n=108) or the placebo group (n=109). Each tablet of the investigational drug BNO 1095 contains 4.0 mg of dried ethanolic extract (70%) of VAC (8.5 – 12.5:1; corresponding to 40 mg of herbal	*(He Z, Chen R, Zhou Y, Geng L, Zhang Z, Chen S, Yao Y, Lu J, Lin S. Treatment of premenstrual syndrome with Vitex agnus castus: A prospective, randomized, multi-center placebo controlled study in China. Maturitas 2009, 63:99-103)* The publication of He et al. (2009) was originally not taken into consideration because the literature research for the assessment report was conducted in 2008. The study described by He et al. cannot serve as proof of

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		drug). The mean total Premenstrual Syndrome Diary (PMSD) score decreased from 29.23 at baseline to 6.41 at the termination of the 3rd cycle for the treatment group and from 28.14 at baseline to 12.64 at the termination of the 3rd cycle for the placebo group. The total PMSD score of 3rd cycle was significantly lower than the baseline in both groups ($p<0.0001$). The difference in the mean scores from the baseline to the 3rd cycle in the treatment group (22.71±10.33) was significantly lower than the difference in the placebo group (15.50±12.94, $p<0.0001$). According to the results of this study, VAC is a safe, well-tolerated and effective drug for the treatment for women with moderate to severe PMS. In addition the efficacy and safety of VAC has also been proven by Schellenberg et al. (2001) in a placebo-controlled clinical study with a VAC extract DER 6-12:1, 60% ethanol. From our point of view both studies can serve as evidence for the WEU. We therefore propose a range of DER from 6 to 13:1 and the ethanol as extraction solvent in a range from 60 to 70 % for the WEU.	efficacy for the treatment of European women because the study was conducted on Chinese women only. In this context we refer to the 'Reflection paper on the extrapolation of results from clinical studies conducted outside the eu to the eu-population' (EMEA/CHMP/EWP/692702/2008). Furthermore the information on used instruments is insufficient. We agree with this statement. As mentioned in the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract.
	AESGP	***Proposed addition:*** Traditional use Vitex agnus-castus L., dried fruit Herbal preparation: *Tincture (1:10) of dried fruit, extraction solvent ethanol 65% (V/V)* This corresponds to a French product which was authorised in 1965.	This proposal cannot be endorsed because there are no sufficient data to prove the tradition. According to the national competent authority there is no information about this product.

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	ESCOP	Traditional use **ii) Herbal preparations** We recommend addition of the following to the list of herbal preparations: 5) comminuted herbal substance Products containing the comminuted herbal substance are on sale in the United Kingdom [4], Spain [2] and certain other countries. One such product [5] was first marketed in the UK in 1979 and used in a clinical study published in 1993 [6].	*(2: Vanaclocha B, Cañigueral S, editors. Sauzgatillo – Vitex agnus-castus L. In: Fitoterapia – Vademecum de Prescripción, 4th ed. Barcelona-Madrid-Paris: Masson, 2003:456-8;* 4: *User Information Leaflet: Periagna (hard capsules containing 400 mg of comminuted dried fruits of Vitex agnus castus-castus L.). Rochester, UK: Bio-Health Limited, 2009:1-4;* *5: Data Sheet: Agnacast Tablets. Bournemouth, UK: Gerard House Limited, ca. 1992;* *6: Turner S, Mills S. A double-blind clinical trial on a herbal remedy for premenstrual syndrome: a case study. Complement Therap Med 1993, 1:73-77)* The references demonstrate a traditional use of the powder. However, there is no clear posology and with respect to the safety the data obtained from extracts cannot be transferred to the powder. The MLWP decided to introduce a powder (posology 2 times 400 mg) into the traditional use part of the monograph based on the tradition of products in the United Kingdom.

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	KOOP PHYTO	**Comments:** There are further herbal preparations of Agni casti fructus on the market. These preparations should be added for "traditional use" category. Proposed change (if any): a) tincture (1:5), extraction solvent: ethanol 68 % (v/v) b) tincture (1:22,5), extraction solvent: ethanol 60% (?/?) c) dry extract (7-11:1), extraction solvent: ethanol 70% V/V	This proposal cannot be endorsed because no reference is available to prove the tradition.
	Naturex	**Comments:** The ratio proposed for: "(3) dry extract (7-13:1), extraction solvent: ethanol 60% m/m" is too limiting and does not take into account the efficiency of the extraction process and number of extractions. **Proposed change (if any):** "(3) dry extract (6-13:1), extraction solvent: ethanol 68% m/m (75% v/v)" We note that the European Pharmacopoeia monograph (01/2008:2147 corrected 6.2) cited by EMEA is for Agnus castus fruit rather than the extract itself but identifies the key active ingredient of casticin and a minimum content for the dried drug of 0.08%. We present as Annex 1, analysis results for the proposed extract above for 4 production batches showing that they contain casticin at levels of at least 0.25%. As Annex 2 we provide comparison HPLC fingerprints for 68% and 75% ethanol extracts.	There is no traditional use for this extract.

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3. Pharmaceutical form	KOOP PHYTO	**WEU:** **Comments:** Solid dosage forms of the above mentioned extracts were tested in clinical studies. **Proposed change (if any):** Herbal preparation in solid dosage forms for oral use.	The proposal is endorsed for the extract tested in the study of Schellenberg et al. (2001). As mentioned in the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract.
4.1 Therapeutic indications	AESGP	***Monograph text:*** Traditional herbal medicinal product for the relief of *minor* symptoms in the days before menstruation (PMS). ***Proposed change:*** Well-established use: Herbal medicinal product for the treatment of premenstrual syndrome (PMS). As stated above, He et al. (2009) and Schellenberg et al. (2001) provide evidence about the efficacy and safety of VAC in the treatment of PMS. For this reason, the wording "Herbal medicinal product for the treatment of premenstrual syndrome (PMS)" is justified.	The proposal is endorsed for the extract tested in the study of Schellenberg et al. (2001). As mentioned in the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract. The study described by He et al. cannot serve as proof of efficacy as mentioned above.
	ESCOP	Traditional use We recommend replacement of the indication Traditional herbal medicinal product for the relief of minor symptoms in the days before menstruation (PMS). by:	The proposal is rejected. There is no need and no reason for emphasising one of the possible symptoms of PMS. Furthermore in cases of mastodynia/mastalgia a physician has to be contacted for diagnosis and therefore this indication is not appropriate as traditional use – indication.

Section number and heading	Interested party	Comment and Rationale	Outcome
		A) Traditional herbal medicinal product for the relief of symptoms experienced in the days before menstruation (PMS), including symptoms such as mastodynia or mastalgia [7-10]. and B) Menstrual cycle disorders such as polymenorrhoea, oligomenorrhoea or amenorrhoea [10]. <u>Well-established use</u> We consider that the studies performed by He et al. 2009 [7] and Schellenberg et al. 2001 [8] provide sufficient published clinical evidence to support the category of well-established use for herbal preparations 3 and 4 with respect to proposed Indication A (above).	Menstural cycle disorders such a polymennorhoea, oligomenorrhoea and amenorrhoea requires a medical examination and therefore is not appropriate as traditional use – indications. The proposal is endorsed for the extract tested in the study of Schellenberg et al. (2001) for the following indication: "Herbal medicinal product for the treatment of premenstrual syndrome (PMS)". As mentioned in the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract. The study of He et al. cannot serve as proof of efficacy as mentioned above.
	KOOP PHYTO	**Comments:** We propose the well-established use for the following extracts: a) dry extract (6-12:1), extraction solvent: ethanol 60% m/m b) dry extract (7-13:1), extraction solvent: ethanol 60% m/m c) dry extract (10-16:1), extraction solvent: ethanol 60% V/V The above mentioned extracts were tested in randomised controlled clinical studies (evidence level 2) and showed effects with clinical relevance	The proposal is endorsed for the extract tested in the

Section number and heading	Interested party	Comment and Rationale	Outcome
		a) Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. BMJ 2001, 322: 134-137 Type of study: randomized, double-blind, placebo-controlled b) Lauritzen C, Reuter HD, Repges R, Böhnert KJ, Schmidt U. Treatment of premenstrual tension syndrome with Vitex agnus castus. Controlled, double-blind study versus pyridoxine. Phytomedicine 1997, 4(3): 183-189 Type of study: randomized, double-blind, reference-controlled There are no S3-guidelines for the treatment of PMS. Therefore, the comparison of efficacy of VAC (Vitex agnus castus) vs. pyridoxine is acceptable. Some reviews and studies dealt with the use of pyridoxine in the treatment of PMS: • Sharma P, Kulshreshtha S, Singh GM, Bhagoliwal A. Role of bromocriptine and pyridoxine in premenstrual tension syndrome. Indian J Physiol Pharmacol. 2007 Oct-Dec;51(4):368-74. • Bendich A. The potential for dietary supplements to reduce premenstrual syndrome (PMS) symptoms. J Am Coll Nutr. 2000 Feb;19(1):3-12. Review. • Diegoli MS, da Fonseca AM, Diegoli CA, Pinotti JA. A double-blind trial of four medications to treat severe premenstrual syndrome. Int J Gynaecol Obstet. 1998 Jul;62(1):63-7. Diegoli et al. (1998) reported a mean reduction of PMS	study of Schellenberg et al. (2001). As mentioned in the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract. The study described by Sharma et al. cannot serve as proof of efficacy for the treatment with pyridoxine. The authors themselves give the following statement: "However, randomized double blind studies, with larger number of populations are required to substantiate these observations." The authors do not favour the use of pyridoxine for the treatment of PMS: "Women with PMS who choose to take vitamin B6 supplements **despite the lack of clear evidence of efficacy** need to be aware that high doses of this vitamin can cause sensory neuropathy." In the trial described in this publication the average value for the symptom scale after treatment was poorer in the pyridoxine group than in the placebo group! Summing up data of the study described by Lauritzen et

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		symptoms by fluoxetine (10-mg/d) of 65.4%, by propranolol (Dosis) 58.7%, by alprazolam (Dosis) 55.6%, by **pyridoxine (300 mg/d) 45.3% and by placebo 39.4-46.1%. (wieso bei Placebo ein range?)** Welcher score wurde benutzt. In the study of Lauritzen et al. (1997) premenstrual tension syndrome scale scores were reduced by 77% in the VAC group and by 66% in the pyridoxine group (200 mg/d), which shows a superiority of VAC. We do not agree with the comment of the rapporteur: "…it is not explained if PMTS scale according to Steiner is a sufficiently validated tool." The Steiner scale has been used in several clinical trials and can be regarded to be validated: • Steiner M, Streiner DL. Validation of a revised visual analog scale for premenstrual mood symptoms: results from prospective and retrospective trials. Can J Psychiatry. 2005 May;50(6):327-32. • Bergant A, Schneider A, Tran T, Hacket E, Lanczik M, Steiner M. [Diagnosis of premenstrual disorders]. Dtsch Med Wochenschr. 2004 Jan 30;129(5):188-92. German. • Steiner M, Streiner DL, Steinberg S, Stewart D, Carter D, Berger C, Reid R, Grover D. The measurement of premenstrual mood symptoms. J Affect Disord. 1999 Jun;53(3):269-73.	al. cannot be accepted as proof of efficacy because of the lacking placebo control. Treatment with pyridoxine cannot be accepted as standard treatment. Objective of this study was to assess the reliability and validity of VASs that were revised to better reflect the DSM-IV definition of PMDD. As the authors themselves mention, the included population – from an epidemiological point of view – was not representative. Furthermore the included patients were suffering from PMDD, the severe form of PMS. Also in this study included patients were suffering from PMDD. The authors draw the following conclusion: "VASs in combination with PMTS-O are low in burden to the client, reliable, valid and sensitive to change. In light of the current debates regarding instruments most appropriate for the classification and measurement of treatment effects in women diagnosed with premenstrual dysphoria, further refinement of these scales is warranted."

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		c) Milewicz A, Gejdel E, Sworen H, Sienkiewicz K, Jedrzejak J, Teucher T, Schmitz H. Vitex agnus castus-Extrakt zur Behandlung von Regeltempoanomalien infolge latenter Hyperprolaktinämie. Ergebnisse einer randomisierten Plazebo-kontrollierten Doppelblindstudie. Arzneim.-Forsch./Drug Res. 1993, 43(II)(7): 752-756 Type of study: Randomized, placebo-controlled, double-blind Regarding the study of Milewicz et al., we do not agree with the comment of the assessor: "….The (TRH) test is not considered as reliable." We would like stress that the following two tests for stimulation of prolactin are used in the clinical practice: - Metoclopramide stress test - TRH test Thus, TRH test must be assessed to be reliable. **Proposed change (if any):** The above mentioned extracts should be included in the category "well-established use".	(PMTS-O = Premenstrual Tension Syndrome Observer scale) Usually there is no fixed normal range for the prolactin release after injection of TRH. The prolactin value has to be interpreted individually in comparison with the basic value. In this study fixed reference values were given. There are laboratories which do not consider this test as reliable. Besides the results of 37 complete case reports are not sufficient for an only proof of efficacy. Thus the study is not sufficient as proof of efficacy for the below proposed indication: "Herbal medicinal product for the relief of symptoms of latent luteal insufficiency (syn. Corpus luteum insufficiency)". Furthermore hyperprolactinemia is not the only possible reason for a Corpus luteum insufficiency.
	KOOP PHYTO	**WEU:** **Comments:** The above mentioned extracts were tested in clinical studies. For this reason the following therapeutic indications are justified: **Proposed change (if any):** a, b) Herbal medicinal product for the relief of symptoms of the premenstrual syndrome. c) Herbal medicinal product for the relief of symptoms of latent luteal insufficiency (syn. Corpus luteum insufficiency)	The following indication for WEU for the extract tested in the study of Schellenberg et al. (2001) is accepted: "Herbal medicinal product for the treatment of premenstrual syndrome (PMS)". As mentioned in the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract.

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			See above.
4.2 Posology and method of administration	AESGP	***Proposed change:*** Well-established use: Daily dose from 40 to 240 mg herbal substance Taking into account the studies from He et al. (2009) and Schellenberg et al. (2001), it is reasonable to include the dosage of 40 -240 mg herbal substance.	The proposal is accepted for the extract tested in the study of Schellenberg et al. (2001): *"Adolescents, Adults* Daily dose: Once daily 20 mg extract equivalent to 180 mg of the herbal substance" As mentioned in the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract. The study described by He et al. cannot serve as proof of efficacy as mentioned above.
	AESGP	***Monograph text:*** The use in children and adolescents under 18 years of age is not recommended ***Proposed change:*** The use in children and adolescents under 12 years of age is not recommended. We do not agree with the recommendation to use Agnus castus only in women from 18 years of age onwards. PMS is a prevalent disorder and a major problem among	

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		adolescent girls aging 12 to 18 years. Moderate to severe PMS symptoms have been reported by 61% to 88% of the adolescents in this age (Cleckner et al. 1998; Derman et al. 2004; Vichnin et al. 2006). Severity does not differ from adults (Derman et al. 2004). The most severe symptoms were abdominal bloating/cramps/pain (59%), mood swings, anxiety, irritability, abdominal discomfort and sleeping disturbances (Raja et al. 1992; Cleckner et al. 1998; Derman et al. 2004; Vichnin et al. 2006; Dennerstein et al. 2009). Significant association of PMS with dysmenorrhoea and irregular menstrual cycle were found in 53% to 85% of the adolescents (Derman et al. 2004; Vichnin et al. 2006). Depression and PMS were not significantly associated in a study with 384 adolescents aged of 15 years (Raja et al. 1992). PMS has an important impact on school absenteeism and on adolescents' quality of life (Cleckner et al. 1998; Derman et al. 2004; Vichnin et al. 2006). In many cases, adolescents under 18 years of age have been excluded from clinical studies with herbal preparations. However, published post-marketing surveillance studies have tested VAC preparations in adolescent girls (<18 years) for the treatment of PMS. These studies used an ethanolic dry extract or a tincture of VAC as a single herb or in combination with other herbs as homeopathic preparation (Loch et al. 2000; Roeder 1994; Liebl 1992; Propping et al. 1991; Loch et al. 1991). • A dried ethanolic extract of VAC was given to 1634 women	*(Loch EG, Selle H, Boblitz N, Wüstenberg P. Wirksamkeit*

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		(12-58 years old) suffering from PMS at the dose of 20 mg herbal drug/day for 3 months (Loch et al. 2000). A clear improvement in PMS symptoms was reported by 80% of the patients. Fifty-four adolescents under 18 years took part in this study and 94.4% of them reported a good or very good improvement of the PMS symptoms (efficacy). The tolerability was rated as good or very good by 96.2% of the adolescents. The compliance of this subgroup was 100%. • A tincture of VAC was given to 2608 women (12 - 58 years old) suffering from PMS at a dose of 32 mg herbal drug/day for 6 months or longer (Propping et al. 1991; Loch et al. 1991). A good efficacy and tolerability was reported by 86% and 97% of the women, respectively. • The homoeopathic combination of VAC with other herbs was given to 582 women (aged from 14 to 66 years) suffering from hyperprolactaemia, PMS or mastodynia at a dose of 33.4 mg herbal drug/day for 3 months (Roeder 1994; Liebl 1992). • None of these published post-marketing surveillance studies advise against using VAC in adolescent girls under 18 years old. Therefore, the recommendation cited in this draft monograph is not supported by clinical evidence gained during many years of clinical experience. • There are no safety concerns regarding the use of VAC in adolescent girls. • Most of the current pharmacological treatments of PMS such as ovulation inhibitors, hormone therapy, NSAIDs, diuretics or SSRIs are considered inappropriate for	*und Sicherheit eines neuen Vitex agnus castus-Präparates (Femicur® Kapseln) bei der Behandlung des Prämenstruellen Syndroms. Phytopharmakaforschung 2000, Abstracts, 126-127)* The publication does not give any information about the treatment of adolescents and the study described is probably identical with the following publication mentioned in the assessment report: *Loch EG, Selle H, Boblitz N. Treatment of Premenstrual Syndrome with a Phytopharmaceutical Formulation Containing Vitex agnus castus. Journal of Women's Health & Gender-based Medicine 2000, 9(3): 315-320* *(Propping D, Böhnert KJ, Peeters M, Albrecht M, Lamertz M. Vitex agnus castus. Behandlung gynäkologischer Krankheitsbilder. Therapeutikon 1991, 5:581-585; Loch EG, Selle H, Boblitz N. Treatment of premenstrual syndrome with a phytopharmaceutical formulation containing Vitex agnus castus. J Womens Health Gend Based Med. 2000, 9:315-320)* The publication of Propping et al. does not give any information about treating adolescents and the publication of Loch et al. only gives the information that women from 11 to 62 years of age were treated. There is no concrete information about the treatment of adolescents. The safety of using preparations of Vitex agnus castus in adolescents cannot be proven by the use of homeopathic

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		adolescents (Derman et al. 2004; Singleton 2007; Wunder-Galié 2009). Alternative pharmacological treatments for PMS safer than VAC for adolescents younger than 18 years do not exist (Singleton 2007; Wunder-Galié 2009). • In addition, no restriction of age has been made in other monographs on VAC such as WHO (2003) and ESCOP (2003). Therefore we propose to include this treatment option for girls from 12 years of age onwards.	preparations.
	ESCOP	Traditional use *Adults* **Posology** We recommend deletion of the sub-heading "Daily dose" and addition of two further dosages: 5) comminuted herbal substance in hard capsules: 800 mg daily, divided into 2 single doses. 6) comminuted herbal substance in tablets: 1800 mg daily, divided into 3 single doses. Dosage 5 corresponds to a product marketed in the UK [4] and dosage 6 to a product marketed in Spain [2].	*(2: Vanaclocha B, Cañigueral S, editors. Sauzgatillo – Vitex agnus-castus L. In: Fitoterapia – Vademecum de Prescripción, 4th ed. Barcelona-Madrid-Paris: Masson, 2003:456-8;* 4: *User Information Leaflet: Periagna (hard capsules containing 400 mg of comminuted dried fruits of Vitex agnus castus-castus L.). Rochester, UK: Bio-Health Limited, 2009:1-4)* The MLWP accepted the traditional use for powdered herbal substance with reference to products marketed in the United Kingdom. There is a lack of data to accept higher posologies.
	KOOP PHYTO	**WEU:** **Comments:**	The dosage for WEU for the extract tested in the study of Schellenberg et al. (2001) is accepted:

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		Posology 20 mg per day corresponding to approx. 180 mg herbal substance. 4 mg per day corresponding to approx. 28-52 mg herbal substance. 3 mg per day corresponding to approx. 30-48 mg herbal substance. **Proposed change (if any):** The above mentioned posology should be included. Furthermore we suggest to change the sentence: "The use in children and adolescents under 12 years of age is not recommended" to "The use in children under 12 years of age is not recommended" as PMS can occur in adolescent women as well. Evidence for this age group is given by the studies of Loch et al. 2000; Roeder 1994; Liebl 1992; Propping et al. 1991; and Loch et al. 1991. In these studies, either an ethanolic dry extract or a tincture was used as a single herb or in combination. **Duration of use** If the symptoms persist after a continued use over three cycles, a gynaecologist should be consulted.	*"Adolescents, Adults* Daily dose: Once daily 20 mg extract equivalent to 180 mg of the herbal substance" As mentioned in the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract. The study described by He et al. cannot serve as proof of efficacy as mentioned above. There are no data concerning the use in adolescents: *Loch et al., 2000:* The publication does not give any information about the treatment of adolescents. *Roeder 1994 and Liebl: 1992:* The safety of using preparations of Vitex agnus castus in adolescents cannot be proven by the use of homeopathic preparations. *Propping et al., 1991:* The publication does not give any information about the treatment of adolescents. *Loch et al. 1991:* There is no concrete information about the treatment of adolescents.
4.3 et sqq. Well-	KOOP PHYTO	**WEU:** **Comments:**	We agree with this statement for the extract tested in the study of Schellenberg et al. (2001). As mentioned in

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established use		Contraindications, Special Warnings etc. according to "Traditional use".	the assessment report, until now the WEU was not favoured by the HMPC, because the extract has not been on the market in the EU for more than ten years. The ten year – threshold is reached in February 2011 and therefore the rapporteur proposes to accept the WEU for this extract.
4.4 Special warnings and precautions for use	AESGP	***Monograph text:*** Patients who suffer or suffered from an oestrogen-sensitive cancer should consult their doctor before using *Vitex agnus-castus*. ***Proposed change:*** Patient who have had oestrogen sensitive cancer or <u>pituitary disease</u> should consult a doctor before treatment with *Vitex agnus-castus* Based on current pharmacological data, breast cancer and pituitary disease might be the relevant diseases in which the treatment with *Vitex agnus-castus* is contra-indicated. These conditions have already been accepted as contraindications in the past, and the scientific evidence has not significantly changed. For these reasons the proposed changes are regarded as appropriate.	The following advice is given in the monograph: "*Vitex agnus-castus* fruits are thought to act on the pituitary-hypothalamic axis and therefore patients with a history of a pituitary disorder should consult with a doctor before using this product. In cases of prolactin secreting tumours of the pituitary gland the intake of *Vitex agnus-castus* fruits can mask symptoms of the tumour." This advice is sufficient.
	AESGP	***Monograph text:*** The use in children and adolescents under 18 years of age has	See above.

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		not been established due to lack of adequate data. ***Proposed change:*** The use in children and adolescents under 12 years of age has not been established due to lack of adequate data. Same justification as described above.	
	AESGP	***Monograph text:*** If the symptoms worsen during the use of the medicinal product or if they do not abate during the first four days of the menstrual cycle or if they recur before cycle day 13, a doctor or a qualified health care practitioner should be consulted. ***Proposed change:*** If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. We propose to delete the sentence *"or if they do not abate during the first four days of the menstrual cycle or if they recur before cycle day 13"*. This restriction is not justified. Menstruation periods normally vary to a large extent between most of the women. Furthermore this is in agreement with the information stated in Section 4.2 "Duration of use" (*"If the symptoms persist after a continued use over three cycles, a doctor or a qualified health care practitioner should be consulted"*)	The proposal is accepted because in cases of symptoms after day four of the menstrual cycle and before day 13 the indication of a premenstrual syndrome is not given.
4.5 Interaction with other	AESGP	***Monograph text:*** Because of the possible dopaminergic and oestrogenic effects	The proposal is rejected. As mentioned in the assessment report there are opposite results concerning

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medicinal products and other forms of interaction		of Vitex agnus-castus fruits interactions with dopamine agonists, dopamine antagonists, oestrogens and antioestrogens cannot be excluded. ***Proposed change:*** Because of the possible dopaminergic effects of Vitex agnus-castus fruits interactions with dopamine agonists, dopamine antagonists cannot be excluded. Until now no interactions between VAC and oestrogen preparations have been reported in humans. However, caution is recommended on the basis of the mode of action. Whereas a dopaminergic effect of VAC has been described in many in vitro studies, an estrogenic effect of the herbal substance could not be found in animal studies (Monograph 2009). Contrary to initial human studies showing inhibition of FSH and stimulation of LH secretion postulating a downstream of the hormones progesterone and estrogen, recent research indicates a decrease of prolactin secretion by dopamine receptor antagonism (Monograph 2009). We therefore suggest deleting the statement regarding "interactions with oestrogens and antioestrogens".	binding to oestrogen receptor or not.
4.8. Undesirable	AESGP	***Monograph text:*** Severe allergic reactions with face swelling, dyspnoea and	The proposal is rejected. An explanatory statement for the proposal is lacking.

Section number and heading	Interested party	Comment and Rationale	Outcome
effects		swallowing difficulties. Allergic skin reactions, rash and urticaria, headache, dizziness, gastrointestinal disorders (such as nausea, abdominal pain), acne, menstrual disorders have been reported. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted ***Proposed change:*** Isolated severe allergic reactions with face swelling, dyspnoea and swallowing difficulties have been reported. Allergic skin reactions, rash and urticaria, headache, gastrointestinal disorders (such as nausea, abdominal pain), have been reported. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.	
	ESCOP	The initial statement, "Severe allergic reactions with face swelling, dyspnoea and swallowing difficulties", appears unjustified and alarming. No such severe adverse events have been reported in published literature and they must be rare. From a comprehensive 2005 review of adverse events it was concluded that: Data from clinical trials, postmarketing surveillance studies, surveys, spontaneous reporting schemes, manufacturers and herbalist organisations indicate that the adverse events following *Vitex agnus-castus* (VAC) treatment are mild and reversible. The most frequent adverse events are nausea,	The proposal is rejected. In Germany severe allergic reactions are labelled as possible adverse events because there are correspondent reports in the pharmacovigilance database of the BfArM. For adverse events resulting from reports in pharmacovigilance databases the frequency is unknown. Knowledge about adverse events results from the pharmacovigilance database of the BfArM, from controlled trials and from observational trials. The wording of frequencies was decided by MLWP considering the current guidance.

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		headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus and erythematous rash [11]. Another recent clinical review stated that: Adverse events following Vitex agnus-castus treatment are mild and reversible…. It has a safe side effect profile [9]. The statement that "The frequency is not known" is incorrect. Data on the frequency of adverse events can be found in a number of published clinical studies. In larger studies, the drug is typically reported to be well tolerated with a frequency of adverse events between 1% and 5%, and none classified as serious [8,12-14]. In these circumstances we recommend that the text be amended to read: *Vitex agnus-castus* is usually well tolerated. The adverse events most frequently reported are nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus and/or erythematous rash. If adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.	