European Medicines Agency

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Table 1: Organisations and/or individuals that commented on the draft 'Community herbal monographon on *Salvia officinalis* L., folium' as released for public consultation on 14 January 2009 until 15 May 2009.

	Organisations and/or individuals
1	European Scientific Cooperative on Phytotherapy (ESCOP)
2	Association of the European Self-Medication Industry (AESGP)
3	Experts Team "Herbal Medicinal Products" German Pharmaceutical Manufacturers Research Association (FAH e.V.)
4	Kooperation Phytopharmaka GbR, Germany

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	**Comment and Rationale**	**Outcome**
ESCOP	1. ESCOP appreciates the draft for a Community Herbal Monograph on " *Salvia officinalis* L., folium" prepared by the Committee on Herbal Medicinal Products (HMPC). However, we consider the following modification necessary.	Endorsed.
AESGP	AESGP welcomes, in principle, the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for ***Salvia officinalis***-containing products, should facilitate mutual recognition in Europe. We also welcome publication of the draft assessment report in parallel to the draft monograph because it provides useful background information on the preparation of the HMPC draft.	Endorsed.
Kooperation Phytopharmaka	Kooperation Phytopharmaka, a German scientific organisation, in principle welcomes the preparation of the above-mentioned Community herbal monograph. However, we would like to comment on the limit set for thujone as follows:	Endorsed. Comments on thujone limit discussed further down.

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
2.	ESCOP	**Under ii) herbal preparations** we suggest to add the following preparation: Tincture (1:10) in 55% ethanol	Not endorsed. The ethanol percentage in the tincture is not specified in Van Hellemont,1988, or any of the supplied references. Further, the reference, dated 1988, do not provide any information on the period on the market within the European Community. Information on the period on the market within the European Community for 30 years is not provided.
4.2	ESCOP	**Posology and method of administration** **For indication b)** we suggest to add the following dosage recommendation: Tincture (1:10) 75 drops daily.	Not endorsed. The posology recommended in Van Hellemont 1988 is 50 drops 2 hours before sweat outbreak. Documentation for this indication and posology are not found in the available literature. Information on the period on the market within the European Community for 30 years is not accepted.
	ESCOP	**All indications** We suggest to replace the limit for thujone as follows: "should not exceed 5 mg/day" because the Opinion of the Scientific Committee on Food on Thujone (2003) should also be taken into account according to which an intake of 0.08 mg thujone/kg b.w. is acceptable. For a person of 60 kg b.w. this is equal to approximately 5mg/day (or even more for persons with a higher body weight).	Endorsed. An intake of about 0.08 mg thujone/kg bw for a 60 kg adult are assessed as safe when used occasionally in foodstuff and beverages. As serious side effects on the nervous system and the liver, have not been shown in clinical studies and in traditional use, we consider that a precautionary approach is taken with a maximum thujone content of 5 mg/day and a duration of use of maximum 2 weeks. Products exceeding the recommended maximum thujone limit can not be recommended marketed without supplementary safety studies and a detailed benefit/risk assessment.

2.	AESGP	We suggest to add: • Sage oil • Liquid extract (1:3), extraction solvent: water. These preparations are available in the German market in the combination "Salvysat Bürger, Flüssigkeit". The product has been authorised according to section 105 of the German Medicines Law. Furthermore we propose to add a tincture according to Ph. Eur. (formerly EB 6 of the German Pharmacopoeia) and the German Commission E monograph: Tincture (1:10), extraction solvent ethanol 70 % (V/V)	Not endorsed. Sage oil is not covered by this monograph From the information available on the internet this seems to be the composition of "Salvysat Bürger, Flüssigkeit".: Hilfsstoff Macrogol glycerolhydroxystearat + Wirkstoff Salbeiblätter-Extrakt 800 mg Wirkstoff Salbeiöl 1 mg Hilfsstoff Ethanol 22 Vol.-% This product is a combination product and therefore beyond the scope of this monograph. Endorsed. This tinctur and the ethanol percentage is specified as a seperate monograph in Ph.Eur 2008 and the Deutsches Arzneibuch 6. Ausgabe 1926. Spiritus dilutus is Ethanol 68-69% (V/V) = 60-61% (m/m). Information concerning this tincture is documented in earlier German Pharmacopeias (Ergänzungsbuch zum Deutschen Arzneibuch (Erg. B. 6. Stuttgart 1956, 1958 Information on the period on the market within the European Community for 30 years is accepted.
4.1	AESGP	We agree with the second indication: "...for relief of excessive sweating." The above-mentioned product "Salvysat plus Bürger", film-coated tablets (1 tablet contains 300 mg dry extract (4-7:1), extraction solvent: water) was authorised according to Art. 10.1 (a)(ii) of Directive 2001/83/EC as amended (bibliographical application) in 2002. The marketing authorisation holder Johannes Bürger Ysatfabrik GmbH, Bad Harzburg, Germany. The authorised indication of this product is "excessive sweating" (In German: "Vermehrte Schweißbildung. Vor der Einnahme des Präparates ist die vermehrte Schweißbildung ärztlich abzuklären").	Not endorsed. The necessary information and clinical documentation for this extract has not been provided, so well-established use can not be assessed for this extract. The period of time required for establishing a well established medicinal use of herbal substance / herbal preparation must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community. Data will only be assessed if documentation for well-established use if the necessary period of time required is provided.

		As the product has been authorised according to Art. 10.1 (a)(ii) of Directive 2001/83/EC, it might from our point of view be eligible for the "well-established medicinal use". However, if this is not accepted in the HMPC monograph, the indication should be remain within the "lower level", the traditional use. With regard to the proposed preparations "Sage oil" and "Liquid extract (1:3), extraction solvent: water "under Point 2, the indications for the respective product "Salvysat Bürger, Flüssigkeit": "excessive sweating" and "inflammations in the mouth or throat" are already represented in the paragraph "therapeutic indications" of this monograph.	Not endorsed It is unclear if Salvysat is a combination product and therefore beyond the scope of this monograph This product can be covered by the monograph, but it has to be assessed individually in the framework of an application.
4.2	AESGP	**1. Addition of preparations and posology** Under posology for indication b) "... for relief of excessive sweating" the posology of the above-mentioned product "Salvysat plus Bürger" should be added: • Dry extract (4-7:1), extraction solvent: water: Single dose: 300 mg dry extract Daily dose: 900 mg dry extract	Partly endorsed. According to the information received from the German authorities, the film coated tablets has been on the market for oral use in adults and adolescents over 12 years for treatment of exessiv sweating during day and night: The film coated tablets with dry extract (4-7:1), extraction solvent: water has been in traditionally use with the listed posology since 1976. Hence it is included in the monograph: The "well-established use" posology from 2002 can not be included in the monograph as suggested. The necessary information and clinical documentation for this posology have to fulfill the requirements. The period of time required for establishing a well established medicinal use of herbal substance / herbal preparation must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community. Data can be assessed if documentation for well-established use if the necessary period of time

			required is provided.
4.2	AESGP	For the preparations "Sage oil" and "Liquid extract (1:3), extraction solvent: water" proposed for inclusion under point 2, we suggest the following posology according to the products available in the German market: • Sage oil (0.1 – 0.3 g/ 100 g liquid) • Liquid extract (1:3), extraction solvent: water, (80 g/100 g liquid). Indication b): 40-60 drops (= 2-3 ml) three times daily Indication c): undiluted, for direct application several times daily; 5-10 ml (= 1-2 spoons), diluted in a glass of water (ca. 100 ml), for rinsing or gargling several times daily	Not endorsed. This herbal preparation is beyond the scope of the monograph. This new information is not described in the information provided by the member states, Documentation in order to show 30 years on the market with this pososlogy is needed. This product can be covered by the monograph, but it has to be assessed individually in the framework of an application.
		<u>Comment on Sage oil:</u> The recommended dose of sage oil laid down in the German Commission E Monograph (Bundesanzeiger No. 90 of 15 May 1985 and No. 50 of 13 March 1990 (correction) is 2-3 drops equal to 0.040 – 0.060 g in 100ml water for gargling and rinsing mouth and throat (aaccording to DAC 2006, 1 drop essential oil of *Salvia officinalis* L. corresponds to approximately 0,020g). The monograph does not specify the number of administrations per day. For one of the products the maximum administration is 4 times daily corresponding to 4 x 0,0498 g = 0,1992 g sage oil for topical use daily. Taking into account the Commission E recommendation, a daily dose for essential sage oil of 0.1 – 0.3g (single dose for oral use 1-2 drops) is proposed. For the tincture also proposed for inclusion under point 2, we suggest: Indication a) tincture (1:10) 2,5-7,5 g daily, divided in 3 doses.	Not endorsed. This herbal preparation is beyond the scope of the monograph. This monograph refers exclusively to *Salvia officinalis* L., folium. Endorsed. 1 spoon (5 ml) in a glass of water, rinse or gargle, undiluted tincture is applied on the affected regions. For oral use: 40-60 drops (= 2-3 ml) three times daily

4.2	AESGP	• Indication c) 5 g (1 spoon) of tincture, diluted in a glass of water, for rinsing or gargling; tincture (1:10) undiluted, for direct application on the gum.	See above. Since the tincture is described in the information available , these posology can be included. Documentation in order to show 30 years on the market with this pososlogy is found based on Ergänzungsbuch zum Deutschen Arzneibuch (Erg. B. 6). Stuttgart 1953, 1956, 1958 Wichtl 2004 with reference to the German Comission E.
		Continued **2. Restriction to 3.0 mg thujone per day** A limitation of the thujone content of 3.0 mg per day is not justified from our point of view, for the following reasons: Comprehensive comments and explanations from AESGP were submitted and assessed.	Endorsed. During the meetings of the MLWP after the public consultation, the following points led to amendments in the monograph and the assessment report: Based on calculations shown in the assessment rapport and comments and data from this unpublished study, we have limited the posology to 6 g *Salvia officinalis* L., folium daily, a lower daily dose than used traditionally. Since this is not a new chemical, but an herbal preparation, the safety factor is accepted reduced based on the extensive traditional use of a variety of herbal sage leaf covered by the monograph. The safety data available for assessment are from single constituents, and not from sage leaf as a whole. Even when acknowledging that thujone containing essential oils are amongst the essential oils associated with the highest risk, the recommended posology of the preparations covered by the monograph and the restricted duration of use will provide a sufficient safety margin. An intake of about 0.08 mg thujone/kg bw for a 60 kg adult are assessed as safe when used occasionally in foodstuff and beverages. This exposure level is not a recommended daily intake proven safe. However, as serious side effects on the nervous system and the liver, remains to be shown in clinical studies and in traditional use, we consider that a precautionary approach is taken with a maximum thujone content of 5 mg/day and a duration of use of maximum 2 weeks.

4.2	AESGP		Products exceeding the recommended maximum thujone limit can not be recommended marketed without supplementary safety studies and a detailed benefit/risk assessment. The MLWP discussion focused on the lack of adverse drug reactions indicating that thujone could be less neurotoxic than thought in the past. The potential danger of the substance is possibly overrated because of the problems encountered with the consumption/misuse of liquors. Since there are, no side effects reported for sage leaf apart those associated to the misuse of liquors. The limit of 5 mg thujone per day set for food can therefore be justified for traditional use of sage leaf with the recommended restrictions. A restriction of the duration of use appears therefore as a reasonable mean to limit the exposure. Based on an overall picture of the risk benefit assessment of sage leaf, a majority of members voted for the raising of the limit of 3 mg per day to 5 mg per day. Based on calculations presented in the Assessment report and these data from the unpublished study provided by AESGP, we have limited the posology to 6 g *Salvia officinalis* L., folium daily in the monograph, a lower daily dose than used traditionally.
4.2	FAH e.V.	**Comments:** The Ph Eur monograph Salviae folium requires *Salvia officinalis* L. as botanical source. The monograph states under the section "Properties" that the essential oil is rich in thujone with neither minimum nor maximum limits being given. It is bound to occur that the maximum limit proposed in the draft is exceeded by ethanolic preparations, even by hot water preparations (tea), if the herbal drug according to Ph Eur monograph is used. From this background the limit is not understandable, inconsistent	Endorsed. An intake of about 0.08 mg thujone/kg bw for a 60 kg adult are assessed as safe when used occasionally in foodstuff and beverages. As serious side effects on the nervous system and the liver, remains to be shown in clinical studies and in traditional use, we consider that a precautionary approach is taken with a maximum thujone content of 5 mg/day and a duration of use of maximum 2 weeks.

		with the Pharmacopoeial monograph requirements and not acceptable. Please provide a justification for the limit set to exactly 3.0 mg/day. **Proposed change (if any):** The limit has to be reconsidered and increased.	Products exceeding the recommended maximum thujone limit can not be recommended marketed without supplementary safety studies and a detailed benefit/risk assessment. Appropriate chemotypes of Salviae folium can be chosen in order to comply with the monograph for traditional herbal medicinal products. Preparations with less than 5.0 mg thujone/day: Herbal medicinal products complying with the monograph must have a specification showing that the daily amount of thujone do not exceed the set limit with the approved posology. Preparations with more than 5.0 mg thujone/day: These herbal preparations should provide safety studies and a detailed benefit/risk assessment . The thujone content in sage leaf preparations for oral and oromucosal use, are not expected to cause safety concern if dose recommendations are followed and the specified maximum limits of thujone are not exceeded.
4.5	FAH e.V.	**Comments:** "There are no interactions reported." Is the recommendation not to use sage folium concomitantly with certain medicinal products based on in-vitro results only? In this case, as can be supposed from the reference list, the transferability to the in vivo situation is to be doubted. **Proposed change:** The concerned paragraph should be deleted.	Not endorsed. *Drug interactions:* No drug interactions are documented clinically. However, the potential for preparations of sage to interact with other medicines administered concurrently, is the basis for giving this precautionary information about potential interactions. According to the available information, it is given as a precautionary advice that concomitant use of other GABA-acting medicinal products should be avoided in thujone containg herbal medicines. The mechanism of neurotoxicity has been ascribed to the available information regarding α-tjujone and its effect on the γ-aminobutyric acid (GABA) type A

			receptor. When the nerve impulses are inhibited, neurons fire to easily and it is known that this could potentially unbalance the brain's message delivery system causing a sezure or epileptic attack (Hold et al. 2000). This is also harmonized with the monograph on Absinthii herba. This is also in line with the SPC guideline on summary of product characteristics, that describes that this section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and in vivo pharmacokinetic studies of the medicinal product, with a particular emphasis on the interactions, which result in a recommendation regarding the use of this medicinal product. This also includes in vivo interaction results which are important for extrapolating an effect on a marker ('probe') substance such as α-thujone to other medicinal products having the same pharmacokinetic property as the marker.'

4.2	Kooperation Phyto-pharmaka	Under "All indications", we suggest to delete the sentence "The intake of thujone should not exceed 3.0 mg/day." and to insert the following sentence: "The intake of thujone should not exceed 5 mg/day." Comment: Although TDI/ADI values have not yet been established, the Opinion of the Scientific Committee on Food on Thujone (6 February 2003) should also be acceptable for the thujone intake by herbal preparations. According to this Opinion, an intake of 0.08 mg thujone/kg b.w. in alcoholic beverages is regarded as acceptable for a 60 kg adult. For this reason a limit of 5mg/day is justified for herbal preparations. Furthermore the European Pharmacopoeia (Monograph Sage leaf 01/2008-1370) to which the HMPC draft refers as a footnote states that "Sage oil is rich in thujon" without any upper limit. For this reason it does not seem useful to set a limit of 3 mg/day in the HMPC monograph.	Endorsed . See above.