20 September 2016
EMA/HMPC/360238/2016
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Salvia officinalis* L., folium (EMA/HMPC/277152/2015)

Final

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Salvia officinalis L.*, folium as released for public consultation on 15 February 2016 until 15 May 2016.

	Organisation and/or individuals
1	Association of the European Self-Medication Industry (AESGP)

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	AESGP welcomes the revision of the above-mentioned European Union herbal monograph which, by providing harmonised assessment criteria for Sage-containing products, should facilitate mutual recognition in Europe. The assessment report mentions a related product containing Salviae flos (page 14). If the monograph on Salviae **folium** is intended to be used also for the assessment of medicinal products containing Salviae **flos**, this should be stated somewhere (as a footnote for example) as this would otherwise create a worrying precedence. In the current draft of the monograph and of the assessment report, the duration of use is limited to 2 weeks for the oral use of medicinal products containing sage. Some sage-containing herbal preparations have very low contents of thujone and the indication requires long-term use. We would therefore suggest that the monograph and the assessment report be amended accordingly.	Endorsed. This information can be deleted as this product is not needed for the assessment of Sage leaf. Partly endorsed. The duration of use is restricted based on the type of indication that is intended and designed for use without the supervision of a medical practitioner. This is now expressed more clearly in the assessment report. The limit for the content of thujone in sage leaf preparations included in the monograph is a daily exposure of 6.0 mg/person. Both in the Public statement (PS) on Salvia officinalis L., aetheroleum and in the PS on thujone the two weeks is only mentioned in the problem statement as a reference to the monograph. Hence, the duration of use was changed in the

Interested party	Comment and Rationale	Outcome
		monograph. Long term use is possible for medicinal products containing Sage leaf for relief of excessive sweating, if the daily exposure is under 6.0 mg/person.

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
Monograph on *Salvia officinalis L., folium* 4.2. Posology and method of administration - Duration of use	AESGP	Duration of use – Assessment of medical and differential diagnostic considerations The maximum duration of use has not been extended in the current draft of the community herbal monograph. The limitation in the former version of the monograph was directly linked to the indications and based on differential diagnostic considerations. This is illustrated, for example, by the fact that the oromucosal use is limited to a shorter duration of use than the oral use, although the intake of thujone is considerably lower in oromucosal use. In the draft of the new monograph, no such link between thujone and the duration of use was established in section 5.3 "preclinical safety data" of the monograph. Accordingly such limitation should be removed.	Partly endorsed. Please see above
Assessment report on *Salvia officinalis L.,*	AESGP	In chapter 2.3 "Overall conclusion on medicinal use" of the revised draft assessment report, the limitation of the duration of use is justified with incomplete safety and toxicity data from long-term studies and harmonisation with duration of use for similar indications in other monographs. Additionally, the duration of use is	Partly endorsed. Please see above

Section number and heading	Interested party	Comment and Rationale	Outcome
folium 2.3. Overall conclusions on medicinal use		also restricted based on the type of indication that is intended and designed for use without the supervision of a medical practitioner. Therefore the duration of oral use is limited to 2 weeks for the indications "relief of mild dyspeptic complaints such as heartburn and bloating" and "relief of excessive sweating". Irrespective of these precise limitations, the same chapter of the assessment report formulates that sage preparations in general should not be taken for more than 2 weeks without providing further justification. *Chapter 3.3.8 "Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof – Conclusions" justifies the limitation of the duration of use to the period of 2 weeks with the toxicological relevance of the constituents of the sage essential oil, mainly thujone.* Certain indications like excessive sweating, the improvement of the general condition in physical and mental stress and the improvement of appetite (not covered by the monograph) often require treatment for a duration much longer than 2 weeks. Some sage-containing traditional herbal medicinal products with such indications have been used for durations longer than 2 weeks prior to the release of the first monograph in 2009. Thus, there is long-standing experience in the use for extended durations of these medicinal products within the EU: they have often been on the market for much longer than 30 years without limitation of the duration of use and without the occurrence of serious adverse events. If such a medicinal product contains only toxicologically harmless amounts of thujone (cf. section 3), this neurotoxic constituent does not pose any relevant risk even at extended	

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		durations of use. The herbal preparation made from sage inflorescences which is referred to in the assessment report (page 14) under 'Information on other products marketed in the EU/EEA (where relevant)' has been marketed for more than 100 years in Germany. Prior to the publication of the monograph on Salviae folium in 2009, the duration of use was not limited for this medicinal product. The indications of the medicinal product (improvement of the general condition in physical and mental stress and the improvement of appetite) require durations of use longer than 2 weeks. So far, less than 10 adverse events have occurred and none of them were serious. An observational study with 300 patients in 1999 demonstrated good tolerability of the herbal preparation at a duration of use of 6-8 weeks. If the symptoms mentioned above do not improve within 6 weeks, it is important to consult a medical practitioner to ensure that the complaints are not caused by any kind of severe illness that requires the supervision of a medical practitioner. In addition sage leaf is generally and regularly consumed as food in Mediterranean countries.	
Monograph on *Salvia officinalis L., folium*	AESGP	Duration of use – Toxicological considerations The current draft of the monograph recommends limiting the intake of thujone from medicinal products made from sage to a maximum of 6 mg per person per day.	Partly endorsed. Please see above

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4.2. Posology and method of administration - Duration of use		The average daily ingestion of thujone from food has been estimated by Lachenmeier and Uebelacker (2010) to 0.25 mg for average consumers, based on published data. Even in high-level consumers, thujone intake from foodstuff has been estimated to not exceed 1 mg per day and person [1]. Based on the data available, the HMPC considers a daily intake of 1 mg thujone per person from foods as uncritical [2, 3]. The Council of Europe, which published a much lower limit (TDI of 10 µg thujone per kg body weight and day) for lifelong exposition, based its values on older studies of shorter duration and did not yet consider the NTP studies on chronic toxicity. For those reasons, a safety factor of 500 instead of the usual 100 was chosen, leading to the low threshold of 10 µg thujone per kg body weight and day [3]. An adequate level of safety for longer-term use of sage-containing traditional medicinal products is provided if the content of thujone per daily dose is lower by a factor of 100 compared to the maximum content considered safe for short-term use, 6 mg. By using salvia containing medicinal product, a maximum of 0.06 mg of thujone will be ingested per day, which is four times less than the average consumer intake by foods per day. For an adult with a body weight of 60 kg, a medicinal product within this limit would provide only an amount of thujone equal to 10 % of the rigorous TDI of the Council of Europe. A limitation of the period of intake due to the content of thujone in a medicinal product made from sage is not justified if the content of thujone per maximum daily dose is 0.06 mg or less.	

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Assessment report on *Salvia officinalis L., folium* 2.3. Overall conclusions on medicinal use	AESGP	Conclusion For a sage-containing traditional herbal medicinal product, a strict limitation of the duration of use to 2 weeks is neither necessary nor appropriate if the medicinal product: - has a low content of thujone (0.06 mg or less per daily dose) - has been traditionally used for durations much longer than 2 weeks (prior to the publication of the first monograph on Salviae folium in 2009) within the EU for at least 30 years - is used on indications for which a duration of use longer than 2 weeks is necessary If the symptoms do not improve within 6 weeks, the presence of severe illness has to be excluded by consulting a medical practitioner. Thus it is recommended in chapter 2.3 "Overall conclusions on medicinal use" of the draft assessment report to complement the verbalisation "Sage preparations should not be taken for more than 2 weeks" with the following wording: "The limitation of the duration of use is not necessary if the medicinal product has been used within the EU for more than 30 years without limitation of the duration of use. It must not contain more than 0.06 mg of thujone per daily dose and the indications must justify long-term periods of use. The patients have to be informed that a medical practitioner needs to be consulted if the symptoms do not improve within 6 weeks."	Partly endorsed. Please see above

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Monograph on *Salvia officinalis L., folium* 4.2. Posology and method of administration - Duration of use	AESGP	For the monograph, a wording as follows is recommended: "For medicinal products with low contents of thujone and indications which justify long-term periods of use: "The duration of use is generally not limited. If symptoms do not improve within 6 weeks, a medical practitioner should be consulted."	Partly endorsed. The duration of use is changed for indication 2 - for relief of excessive sweating : Long term use is possible (see section 4.4 Special warnings and precautions for use). If symptoms do not improve within 6 weeks of use of the medicinal product, a doctor or a qualified
Monograph on *Salvia officinalis L., folium* 4.4. Special warnings and precautions for use	AESGP	The general warning in chapter 4.4 "Special warnings and precautions for use" of the current draft, which states that "If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted", shall not be affected by our proposal.	Endorsed.

1. Lachenmeier, D.W. and M. Uebelacker, *Risk assessment of thujone in foods and medicines containing sage and wormwood - evidence for a need of regulatory changes?* Regul Toxicol Pharmacol, 2010. 58(3): p. 437-43.
2. European Medicines Agency, *Public statement on the use of herbal medicinal products containing thujone. final*, in *EMA/HMPC/732886/2010 Rev.1*. 2012, European Medicines Agency: London. p. 1-9.
3. Pelkonen, O., K. Abass, and J. Wiesner, *Thujone and thujone-containing herbal medicinal and botanical products: toxicological assessment.* Regul Toxicol Pharmacol, 2013. 65(1): p. 100-7.