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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Salvia officinalis* L., folium and *Salvia officinalis* L., aetheroleum

Final

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Salvia officinalis</i> L., folium and <i>Salvia officinalis</i> L., aetheroleum
Herbal preparation(s)	a) Comminuted herbal substance b) Liquid extract (DER 1:1), extraction solvent ethanol 70% V/V c) Dry extract (DER 4-7:1), extraction solvent water d) Liquid extract (DER 1:3.5-5), extraction solvent ethanol 31.5% V/V e) Liquid extract (DER 1:4-5) extraction solvent ethanol 50% V/V f) Liquid extract (DER 1:4-6), extraction solvent liquor wine:ethanol 96% V/V (38.25:61.75 m/m) g) Tincture (ratio of herbal substance to extraction solvent 1:10) extraction solvent ethanol 70% V/V
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use.  Comminuted herbal substance for infusion preparation for oromucosal or cutaneous use.  Herbal preparations in solid or liquid dosage forms for oral use.  Herbal preparations in liquid or semi-solid dosage forms for cutaneous use or for oromucosal use.



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# 1. Introduction

## 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Sage leaf consists of the whole or cut dried leaves of *Salvia officinalis* L. It contains not less than 12 ml/kg of essential oil for the whole drug and minimum 10 ml/kg of essential oil for the cut drug, both calculated with reference to the anhydrous drug. Sage leaf oil is rich in thujone (Ph. Eur. 8.0, ref. 1370).

The essential oil has a very variable composition depending on the source, time of harvesting and other factors (Bradley, 2006). Principal components of the essential oil, in addition to thujone, are 1,8-cineole and camphor. In addition, the leaves contain tannins, diterpene bitter principles, triterpenes, steroids, flavones and flavonoid glycosides (Blumenthal *et al.*, 2000).

- Herbal preparation(s)

Comminuted herbal substance.

Liquid extract (DER 1:1), extraction solvent ethanol 70% V/V

Dry extract (DER 4-7:1), extraction solvent water

Liquid extract (DER 1:3.5-5), extraction solvent ethanol 31.5% V/V

Liquid extract (DER 1:4-5) extraction solvent ethanol 50% V/V

Liquid extract (DER 1:4-6), extraction solvent liquor wine:ethanol 96% V/V (38.25:61.75 m/m)

Tincture (ratio of herbal substance to extraction solvent 1:10) extraction solvent ethanol 70% V/V

Dry extract from fresh leaves (DER 1:17-18), extraction solvent ethanol 68 % V/V

Sage tincture is produced from 1 part of comminuted sage leaf and 10 parts of ethanol (70% V/V), it is a separate monograph in the European Pharmacopoeia. The tincture produced from sage leaf should contain minimum 0.1% m/m essential oil. The European Pharmacopoeia also has a monograph on three-lobed sage leaf from *Salvia fruticosa* Mill. (Ph. Eur. 8.0, ref. 1889 and 1561).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

This assessment report includes data regarding mono-preparations containing *Salvia officinalis* L., folium and herbal preparations from this herbal substance. Literature regarding combination products is not part of the assessment.

- Constituents (Bradley, 2006):

Essential oil (up to 3%)	Monoterpenoids	$\alpha$ -thujone (10-60%), $\beta$ -thujone (4-36%), camphor (5-20%), 1,8-cineole (1-15%)
	Sesquiterpenes	$\alpha$ -humulene, $\beta$ -caryophyllene, viridiflorol
Hydroxycinnamic acid derivates (about 3.5%)	Caffeic acid dimer	rosmarinic acid (up to 3.3%)
	Caffeic acid trimers	melitric acid A, methyl melitrate A, sagecoumarin, salvianolic acid K
	Caffeic acid tetramer	sagerinic acid
	three hydroxycinnamic esters of disaccharides	e.g. 1-caffeoyl-(6'-apiosyl)-glucoside
Phenolic diterpenes	Tricyclic diterpene	↓ carnosic acid which readily auto-oxidises to
	Lactones	↓ carnosol (0.35%) which further degrades to
	Phenolic diterpenes with lactone structures	↓ rosmanol, epirosmanol, 7-methoxy-rosmanol, galdosol
Triterpenes	Pentacyclic triterpene acids	sageone, methyl carnosate, safficinolide, sagequinone methide A
	Triterpene alcohols	ursolic acid (up to 3.5%), oleanolic acid (up to 0.4%)
Flavonoids (about 1.1%)	Flavones and their glycosides	$\alpha$ -amyrin (0.18%), $\beta$ -amyrin (0.10%)
		-luteolin; its 7-glucoside, 7-glucuronide, 3'-glucuronide and 7-methyl ether -6-hydroxyluteolin; its 7-glucoside and 7-glucuronide -6-methoxyluteolin; its 7-methyl ether -apigenin; its 7-glucoside, 7-methyl ether (=genkwanin) -6-methoxy-apigenin (=hispidulin) and its 7-methyl ether (=cirsimaritin) -vicenin-2 (=apigenin 6,8-di-C-glucoside) -5-methoxy-salvigenin
Phenolic glycosides		-picein (4-hydroxy acetophenone glucoside) -4-hydroxy-acetophenone-4-(6'-apiosyl)-glucoside -cis- and trans-p-coumaric acid 4-(2'-apiosyl)-glucoside -isolariciresinol 3-glucoside -1-hydroxy-pinoresinol 1-glucoside -others
Polysaccharides	arabinogalactans	
	high-molecular weight pectin	
	glucuronoxylan-related polysaccharides	
Other constituents	Benzoic acid derivates	<i>p</i> -hydroxybenzoic acid, gentisic acid, syringic acid, other acids
	Phytosterols	$\beta$ -sitosterol, stigmasterol (0.001%)

Some constituents mentioned in other handbooks are borneol, bornyl acetate, isorosmanol (Wichtl, 2004), linalyl acetate, chlorogenic-, ellagic-, ferulic- and gallic phenolic acids (Newall *et al.*, 1996), linalool,  $\alpha$ -pinene, camphene, limonene (Blumenthal *et al.*, 2000), cirsiliol (Harborne *et al.*, 1996), menthol and thymol (Gruzunov *et al.*, 1984).

Numerous articles on *Salvia officinalis* L. and *Salvia fruticosa* Mill. have been published regarding the composition of their essential oil. The considerable variation found may be due to the quality of the plant material (influence of harvest time, different chemical types, use of fertilisers etc.) as well as to the methods used for analysis. Essential oil obtained by steam distillation is influenced to some extent by pH-value of the water used and duration of the steam distillation.

The boiling temperature (corresponding to the ion content of the water) and the degree of grinding have a significant effect on the result (Iconomou *et al.*, 1982 cited in Länger *et al.*, 1996).

An analysis of 50 randomly chosen leaves of a commercial sample of sage leaf showed a considerable inhomogeneity, some leaves showing more 1,8-cineole than thujone and camphor. These inhomogeneities can be explained by intra-individual differences in the production of essential oil.

From the top to the base of an individual plant, the relative contents of  $\alpha$ -thujone and  $\beta$ -thujone decrease, while the amounts of camphor,  $\alpha$ -pinene, camphene and borneol increase. However, the sum of the contents of  $\alpha$ -thujone,  $\beta$ -thujone and camphor remains nearly constant (Länger *et al.*, 1996).

In a study on the relationship of camphor biosynthesis to leaf development in sage, a plot of leaf pair surface area and camphor content as a function of time, clearly indicated that the increase in camphor content closely paralleled leaf expansion. Examination of the second and third leaf pairs as they expanded provided similar results, although the levels of camphor were generally higher from beginning to end, reaching approximately 0.7 mg/leaf pair on full expansion (Croteau *et al.*, 1981).

An excess of the (1R,4R)-enantiomer (d-camphor) characterises the essential oils of sage (50-70% for *Salvia officinalis* L.) (EFSA, 2008a).

## **1.2. Search and assessment methodology**

This report is based on a scientific review of the scientific and traditional literature referring to *Salvia officinalis* L. The following electronic databases were searched 10<sup>th</sup> of February 2015 with these search terms:

Scientific databases: SciFinder

*Salvia officinalis*: 2778 references

*Salvia officinalis* folium: 5 references

Medical databases: The Cochrane Library

Sage leaf: 4

*Salvia officinalis* folium: 0

Toxicological databases: Toxline

*Salvia officinalis*: 182 references

*Salvia officinalis* folium: 3 references

Pharmacovigilance resources:

Pharmacovigilance Insight: 4 references

The World Health Organisation's Uppsala Monitoring Centre (WHO-UMC): 51 case reports

The World Health Organisation's Uppsala Monitoring Centre (WHO-UMC) received 51 reports from national pharmacovigilance centres according to a search performed on 27.02.2015 for sage leaf

The abstracts and references were screened and all articles deemed relevant were accessed.

Data from EU and non-EU regulatory authorities:

Information about products on the market in the EU/EEA Member States (2.2.1)

Other resources: Submission of articles from interested parties.

Books, Book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations (List of references supporting the assessment of *Salvia officinalis* L., folium and *Salvia officinalis* L., aetheroleum)

## 2. Data on medicinal use

### 2.1. Information about products on the market

#### 2.1.1. Information about products on the market in the EU/EEA Member States

##### Information on medicinal products marketed in the EU/EEA

**Table 1:** Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
<b>Austria</b>			
Comminuted herbal substance	Inflammations in the mouth and throat	Herbal tea (infusion): 1 tea bag contains 2.5 g herbal substance. Adolescents, adults: 1 cup several times daily	12.2009 TUR
Comminuted herbal substance	Digestive disorders and bloating; excessive sweating; inflammations in mouth and throat	Herbal tea (infusion): 1 tea bag contains 1.6 g herbal substance. Adolescents, adults: 1 cup 3 times daily	05.2011 TUR
Dry extract of <i>Salviae folium</i> (5-6:1, water); 50 mg Dexpanthenol	Inflammations in the mouth of the gums	Oral solution: 1 g solution contains 10 mg dry extract of <i>Salviae folium</i> (5-6:1, water); 50 mg Dexpanthenol Children 6-12, adolescents, adults: spray several times a day	01.2011 TUR

Active substance	Indication	Pharmaceutical form	Regulatory Status
Comminuted herbal substance	Digestive disorders and bloating; symptomatic treatment of inflammations of mouth and throat, excessive sweating	Herbal tea (infusion): 1 tea bag contains 1.5 g herbal substance  Adolescents, adults: 1 cup, 3 times daily children: not recommended for children < 12 years	02.2013  TUR
1 g contains 150 ml liquid extract of sage leaf, DER 0.9-1.1:1, extraction solvent ethanol 70% V/V	Inflammations of mouth and throat, sore throat	Oromucosal spray, solution  Adolescents, adults: 3 times daily 3 puffs; 1 puff=140 µl=138 mg of finished product	12. 2009 WEU
<b>Croatia</b>			
Dry extract of <i>Salviae folium</i> (5-6:1, water); 50 mg Dexpanthenol	Irritation of the oral mucosa	Oral solution: 1 g solution contains 10 mg dry extract of <i>Salviae folium</i> (5-6:1, water); 50 mg Dexpanthenol  Adolescents, adults: spray a few times daily	06.2013 TUR
<b>Czech Republic</b>			
<i>Salviae officinalis folii</i> tinctura 1:6.6, extraction solvent ethanol 60% (V/V)	Adults and elderly: for symptomatic treatment of stomatitis, gingivitis, pharyngitis; as an adjuvant in antibiotic therapy of tonsillitis, after surgeries in oral cavity, to minimise halitosis	Oral solution: (concentrate for gargle)  For oromucosal use, dosage: ½ tea spoon/150 ml water 3 times daily	TUR 1989
<b>Germany</b>			
Comminuted herbal substance	For relief of excessive sweating	For oral use as a tea preparation 2 g in 150 ml water 2-3 times daily	1976-2012 in Germany, reported as well-established use
<i>Salviae officinalis folium</i>	Symptomatic treatment of mild dyspeptic, complaints  Oral use for relief of excessive sweating.	Herbal tea for internal use (drinking):  >12 years: 1-2 g/150 ml boiling water  several times daily  no limitation in duration of use	TUR  At least since 1976, DE, TUR according to section 105 in combination with section

Active substance	Indication	Pharmaceutical form	Regulatory Status
	Rinsing and gargling for the symptomatic treatment of inflammations in the mouth or the throat.	for external use (rinsing and gargling): >12 years: 1-2 g/100 ml boiling water several times daily no limitation in duration of use	109a of the German Medicinal Products Act
Salviae officinalis folium, cut	Rinsing and gargling for the symptomatic treatment of inflammations in the mouth or the throat	Herbal tea Adults: 1 tea bag containing 2.5 g/100 ml boiling water 3 times daily No longer than 7 days	At least since 1976, DE, current status TUR according to Article 16a of Directive 2001/83/EC
Extract of Salviae officinalis folium (1:4-6), extraction solvent liquor wine: ethanol 96% (38.25:61.75 m/m) <sup>1</sup>	Symptomatic treatment of mild dyspeptic, complaints Oral use for relief of excessive sweating	Liquid for internal use: >12 years: 10 drops (0.43 ml) 3 times daily No longer than 14 days	At least since 1976, DE, TUR according to section 105 in combination with section 109a of the German Medicinal Products Act
	Rinsing and gargling for the symptomatic treatment of inflammations in the mouth or the throat	for external use >4 years: 15 drops (0.65 ml) in 150 ml water 3 times daily No longer than 14 days	
Extract of Salviae officinalis folium (1:4.5), extraction solvent: ethanol 50% (V/V)	Oral use for relief of excessive sweating.	for internal use: >12 years: 50 drops (2 ml) 3 times daily No longer than 14 days	At least since 1976, DE, WEU
	Rinsing and gargling for the symptomatic treatment of inflammations in the mouth or the throat.	for external use (rinsing and gargling): >12 years: 5 ml every 2 hours for 1 minute No longer than 14 days	

<sup>1</sup> Corrected declaration, formerly liquid extract (1:7.2), extraction solvent liquor wine: ethanol 96% (38.25:61.75 m/m)

Active substance	Indication	Pharmaceutical form	Regulatory Status
Expressed juice	Rinsing and gargling for the symptomatic treatment of inflammations in the mouth or the throat.  Oral use for relief of excessive sweating.	Expressed juice for internal use: >12 years: 10 ml  2 times daily before eating  for rinsing and gargling: 10 ml diluted with 100 ml warm water  2-3 times daily	At least since 1976, DE, WEU
Dry extract of <i>Salviae officinalis</i> folium (4-7:1), extraction solvent: water	Oral use for relief of excessive sweating	Coated tablet  80 mg  Adults: 1-2 tablets  3 times daily  No longer than 2 weeks	At least since 1976, DE, TUR since 2011 according to Article 16a of Directive 2001/83/EC
Dry extract of <i>Salviae officinalis</i> folium (4-7:1), extraction solvent: water	Oral use for relief of excessive sweating.	Film-coated tablet  300 mg  >12 years: 1 tablet  3 times daily  No longer than 14 days	2002, DE, WEU
Liquid extract (DER 1:3.5-5) <i>Salviae officinalis</i> folium, extraction solvent: ethanol 31.5% V/V	For symptomatic treatment of inflammations in the mouth or the throat	For oral use 10 drops*  3 times daily in a glass of lukewarm water and rinse or gargle several times	Since 1976 in Germany, reported as well-established use
	For relief of excessive sweating	For oral use 10-20 drops* dissolved in liquid 3 times daily.  For night sweat 30 drops* in liquid 1 hour or directly before bedtime	
Liquid extract (DER 1:1), ethanol 70% V/V	For symptomatic treatment of inflammations in the mouth or the throat	For oromucosal use 250 mg (pea-sized amount) of gel containing 20% liquid extract up to 5 times daily on affected regions, massage gently	1976-2013 in Germany reported as well-established use
Fluid extract of dried sage leaves ( <i>Salvia officinalis</i> L. folium). (1:1, extraction	For the local treatment of inflammations of the oral mucosa.	Oral mucosal gel.  1000 mg gel contains 200 mg sage fluid extract.	1995-2013 registered "healing

Active substance	Indication	Pharmaceutical form	Regulatory Status
solvent: ethanol 70 % (V/V))		A pea-sized amount of the gel (approximately 250 mg) gently massaged onto the affected mucosal area up to 5 times a day. The recommended treatment period is one week.	product" 2013 2013 TUR
<b>Ireland</b>			
Dry extract from fresh Sage ( <i>Salvia officinalis</i> L.) leaves  Extraction solvent: ethanol 68% V/V.	Relief of menopausal hot flushes and excessive perspiration	Tablet  Dry extract from fresh Sage ( <i>Salvia officinalis</i> L.) leaves (equivalent to 795-1370 mg of fresh herb).  Extraction solvent: ethanol 68% V/V. Adults (18 years and over): 1 tablet daily.  This product is not indicated in patients less than 18 years.	05.2013 TUR
<b>The Netherlands</b>			
Dry extract from fresh leaves (1:17-18), extraction solvent ethanol 68% V/V.	Relief of excessive perspiration	Tablet  Dry extract from fresh Sage ( <i>Salvia officinalis</i> L.) leaves (equivalent to 795-1370 mg of fresh herb). Extraction solvent: ethanol 68% V/V. Adults (18 years and over): 1 tablet daily	01.2014 TUR
<b>Poland</b>			
Comminuted herbal substance	In mouth inflammation, throat inflammation, gums purulent inflammations;  for minor epidermis lesions and superficial skin inflammations, even with minor purulent changes	2.5g as an infusion in 2/3 glass (about 150 ml) of boiling water, as a rinse (or washing) in mouth inflammation  As compresses (dressings) for external use in minor epidermis lesions and superficial skin inflammations	Since 1978 in Poland, reported as traditional use
Comminuted herbal substance	Mouth and throat inflammations.	Herbal tea (infusion): 1 tea sachet (=1.3 g) contains: 1.3 g <i>Salviae folium</i> 2 sachets (2.6 g) as an infusion for external use	03.02.2010 TUR

Active substance	Indication	Pharmaceutical form	Regulatory Status
Comminuted herbal substance	Mouth and throat inflammations.	Herbal tea (infusion): 100 g herbal tea contain: 100 g <i>Salviae folium</i> 6 g as an infusion for external use	02.2010 TUR
<i>Salviae folii tinctura</i> (1:5), extraction solvent: ethanol 70% (V/V)	Mouth and throat inflammations.	Oral liquid 100 ml concentrate contain: 100 ml <i>Salviae folii tinctura</i> (1:5), extraction solvent: ethanol 70% (V/V) Diluted tincture (1:10) as a mouth wash	02.2010 TUR
Comminuted herbal substance	Topically: for washing in inflammatory states of oral cavity and throat mucosa. In a form of compresses in mild inflammatory states of skin.  Orally: in mild gastrointestinal symptoms (bloating) and in hyperhidrosis.	Herbal tea (infusion): 100 g herbal tea contain: 100 g <i>Salviae folium</i>  External use: 2.5 g as an infusion for mouth wash  2.5 g as an infusion in 150 ml of boiling water 2-4 times daily for compresses  Oral use: 2 g 3 times daily in digestive disorders 2 g daily in hyperhidrosis	12.2010 TUR
<b>Spain</b>			
Comminuted herbal substance	For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating	For oral use as a tea preparation 1-1.5 g daily dose 2-5 g	Since 1978 in Spain, reported as traditional use
Dry extract from fresh <i>Salvia officinalis</i> L., folium; extraction solvent: ethanol 68%.	Relief of menopausal hot flushes and excessive sweating.	Tablet  Dry extract (1:17-18) from fresh <i>Salvia officinalis</i> L., folium; extraction solvent: ethanol 68% (V/V).  Adults: 1 tablet per day	03.2014 TUR
<b>Sweden</b>			
Dry extract (4-7:1) from <i>Salvia</i>	Temporarily exaggerated sweating	Capsule, hard  Adults and elderly: 1 capsule 3	1997-2009 natural

Active substance	Indication	Pharmaceutical form	Regulatory Status
<i>officinalis</i> L., (Sage) folium. Extraction solvent water		times daily. 1 capsule contains: 120 mg dry extract from <i>Salvia officinalis</i> L., (Sage) folium, corresponding to 500–800 mg of dried leaves of sage.	remedy (Swedish legislation) 2009-2013 TUR
United Kingdom			
Comminuted herbal substance	For the temporary relief of excessive sweating associated with the menopause.	Hard capsules  Each capsule contains 300 mg of dried Sage Leaf.  Women experiencing menopausal symptoms: 1 capsule per day.	09.2009 TUR
Dry extract from fresh leaves (1:17-18), extraction solvent ethanol 68 % V/V.	For the relief of menopausal hot flushes and excessive perspiration	Dried extract from fresh leaves (1:17-18), extraction solvent ethanol 68 % V/V.  Women experiencing menopausal symptoms: 1 tablet daily  1 tablet contains 51 mg of dry extract  There is no relevant use in children and adolescents under 18 years of age.	03.2010 TUR
Norway			
Dry extract (4-7:1) from <i>Salvia officinalis</i> L., (Sage) folium. Extraction solvent water	Temporarily exaggerated sweating	Adults and elderly: 1 capsule 3 times daily. 1 capsule contains: 120 mg dry extract from <i>Salvia officinalis</i> L., (Sage) folium, corresponding to 500–800 mg of dried leaves of sage.	Since 1999 to 2011 natural remedy (Norwegian legislation)

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

\*1 drops equivalent to 0.05 ml

## Information on relevant combination medicinal products marketed in the EU/EEA

**Table 2:** Information on relevant combination medicinal products marketed in the EU/EEA

Latvia
Oromucosal spray: 1 spray contains 40.32 mg of <i>Salviae folium extractum fluidum</i> (1:4-6, extraction solvent: ethanol 70%V/V), 40.32 mg of <i>Thymi herbae extractum fluidum</i> (1:4-6, extraction solvent: ethanol 70% V/V)
Indication: Symptomatic treatment of inflammations in the mouth and throat (e.g., sore throat, hoarseness and difficulties swallowing)
Posology: Not applicable
On the market since January 2013

### Information on other products marketed in the EU/EEA (where relevant)

Not applicable.

### 2.1.2. Information on products on the market outside the EU/EEA

Not applicable

### 2.2. Information on documented medicinal use and historical data from literature

*Salvia officinalis* L. is a perennial plant (subshrub), native to the Mediterranean region, especially in the area of the Adriatic Sea and is cultivated to some extent in different European countries. The material of commerce originates from south eastern European countries (Blumenthal *et al.*, 2000).

Sage leaf was mentioned in the writings of Hippocrates, Paracelsus, Hildegard von Bingen, Lonicerus, Bock and Matthiolus (Madaus, 1938). Its cultivation in northern Europe dates back to medieval times and it was introduced to North America during the 17<sup>th</sup> century. Sage was used in ancient Egyptian, Greek and Roman medicines. Ancient Egyptians used it as a fertility drug. The Greeks used it to stop bleeding of wounds and to clean ulcers and sores, towards hoarseness and cough, enhancing memory functions, for gargles to treat sore mouths and throats. Its uses in traditional Greek medicine spread to India, where the dried leaf (*Salbia-sefakuss* in Hindi) and fluid extract are used in traditional Indian Ayurvedic, Siddha, and Unani medicines (Blumenthal *et al.*, 2000).

Sage is well known for carminative, antispasmodic, antiseptic, astringent and antihidrotic properties. Pharmacognosy handbooks describe that sage has been traditionally used to treat flatulent dyspepsia, pharyngitis, uvulitis, stomatitis, gingivitis, glossitis (internally or as a gargle/mouthwash), hyperhidrosis and galactorrhoea (Barnes *et al.*, 2007). The herbals of Gerard, Culpeper and Hill credit sage with the ability to enhance memory (Culpeper, 1653; Gerard, 1633). The German Commission E approved the internal use of sage for dyspeptic symptoms and excessive perspiration, and the external use for inflammation of mucous membranes of mouth and throat (Blumenthal, 2000).

Medicinal use of *Salvia officinalis* L., folium in herbal teas and herbal preparations has been documented continuously in many pharmacognosy texts, handbooks and compendia.

**Table 3:** Overview of historical data

<b>Documented use / Traditional use</b>	<b>Dosage</b>	<b>Method and Duration of Administration</b>	<b>Handbook Reference</b>
<p>External: Inflammations and infections of the mouth and throat (stomatitis, gingivitis, pharyngitis)</p> <p>Internal: Hyperhidrosis</p>	<p>Topical use: An infusion of 3 g of the drug in 150 ml of water as a mouthwash or gargle (1)</p> <p>Oral use: in hyperhidrosis:</p> <p>Tincture: (1:10) in 55% ethanol, 75 drops daily (2)</p> <p>Infusion 1-1.5 g of dried herb in 150 ml of water, once or several times daily (3)</p> <p>Dry extract: 160 mg of dry aqueous extract corresponding to 880 mg of drug three times daily (4)</p>	<p>Method: For oral administration or topical application</p> <p>Duration: In hyperhidrosis, treatment for 2-4 weeks is recommended, using an aqueous preparation</p>	<p>ESCOP Monographs (2003)</p> <p>(1) Reference source dated 1988, 2002</p> <p>(2) Reference source dated 1988</p> <p>(3) Reference source dated 1988, 2002</p> <p>(4) Reference source dated 1989</p>
<p>Internal: Digestive disorders (dyspepsia, flatulence, poor digestion, bloating) To reduce excessive perspiration, e.g. in the menopause. As a gentle, stimulating tonic.</p> <p>External: Inflammations of the mouth or throat mucosa (pharyngitis,</p>	<p>Internal daily dose: 3-6 g of dried leaf, usually as an infusion (1); liquid extract 1:1 in 45% ethanol, 2-6 ml (2)</p> <p>Topical use: mouthwashes and gargles: 2.5 g of dried leaf to 100 ml of water as an infusion (3)</p>	<p>Method: Oral and topical administration</p> <p>Duration: No information</p>	<p>British Herbal Compendium, (Bradley, 2006)</p> <p>(1) Reference source dated 1983, 1985</p> <p>(2) Reference source dated 1983, 2003</p> <p>(3) Reference source dated 1985</p>

<b>Documented use / Traditional use</b>	<b>Dosage</b>	<b>Method and Duration of Administration</b>	<b>Handbook Reference</b>
tonsillitis, stomatitis, gingivitis, glossitis)			
<p>External: As an antiphlogistic for inflammations of the mouth and throat and for gingivitis and stomatitis</p> <p>Internal: For digestive disturbances, flatulence, inflammations of the intestinal mucosa. Diarrhoea</p>	<p>Tea: Depending on the indication:</p> <p>Gargle: Pour boiling water over 3 g finely cut dried leaf. Steep for 10 minutes, strain (1)</p> <p>To treat night sweats: Prepare the tea like the previous, but let it cool before drinking (2)</p> <p>For gastrointestinal complaints: Pour boiling water over 1.5-2 g finely cut dried leaf. Steep for 5 minutes, strain (3) 1 teaspoon=about 1.5 g</p>	<p>Method: Oral and Topical Administration</p> <p>Duration: No information</p>	<p>Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004) (1) Wichtl, dated 2004 (2) Wichtl, dated 2004 (3) Wichtl, dated 2004</p>
<p>Internal: Digestive complaints with mild spasms in the gastrointestinal tract, feeling of distension, flatulence, excessive perspiration.</p> <p>External: Inflammations of the oral and pharyngeal mucosa</p>	<p>Unless otherwise prescribed, drink one cup of tea infusion 3-4 times daily, prepared as follows:</p> <p>Pour 150 ml boiling water over 1 teaspoonful (about 1.5 g) of sage leaves, or over a corresponding amount in one or more teabags. Steep for about 10-15 minutes, strain (1)</p> <p>For use in the mouth and throat area, rinse or gargle with the tea infusion prepared as follows:</p>	<p>Method: Oral and Topical Administration</p> <p>Duration: In acute cases that last longer than one week or periodically reoccur, it is recommended to seek medical advice</p>	<p>Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004) with reference to The German Standard License, 1996 (1) dated 1996 (2) dated 1996</p>

Documented use / Traditional use	Dosage	Method and Duration of Administration	Handbook Reference
	Pour 100 ml boiling water over an exactly measured 1 1/2 teaspoonful (about 2.5g) of sage leaves. Steep for about 10-15 minutes, strain (2)		
<p>Internal: Digestive complaints excessive perspiration.</p> <p>External: Inflammations of the oral and pharyngeal mucosa</p>	<p>Unless otherwise prescribed: Internal: Daily dose: 4-6 g dried leaf (1), 0.1-0,3 g essential oil (2), 2.5-7.5 g tincture (as per Erg.B.6) (3), 1.5-3 g fluidextract (as per Erg.B.6) (4)</p> <p>Externally: For gargles and rinses: 2.5 g dried leaf or 2-3 drops essential oil in 100 ml of water as an infusion or 5 g alcoholic extract in one glass water (5) As a paint: Undiluted alcoholic extract (6)</p>	<p>Method: Cut dried leaf for infusion, alcoholic extracts and distillates for gargles, rinses and paints, and for internal use and as the pressed juice of fresh plants</p> <p>Duration: No information</p>	<p>Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004) with reference to The German Commission E monograph, 1990)</p> <p>(1) Dated 1990 (2) Dated 1990 (3) Source referred is <i>Ergänzungsbuch zum Deutschen Arzneibuch, 1941</i> (4) Source referred is <i>Ergänzungsbuch zum Deutschen Arzneibuch, 1941</i> (5) Dated 1990 (6) Dated 1990</p>
<p>Internal: Dyspeptic symptoms and excessive perspiration.</p> <p>External: For inflammations of the mucous membranes of nose and throat.</p>	<p>Internal: Dried leaf: 1-3 g, 3 times daily (2) Infusion: 1-3 g in 150 ml water, 3 times daily (3) Dry aqueous extract 5.5:1 (w/w): 0.18-0.36 g, 3 times daily (4) Fluidextract: 1.5-3 g (Erg.B. (6) (5))</p>	<p>Method: Internal or External Administration</p> <p>Duration: No information</p>	<p>Herbal Medicine Expanded Commission E Monographs (Blumenthal, 2000)</p> <p>(1) Blumenthal dated 2000 (2) Blumenthal dated 2000 (3) Blumenthal dated 2000 (4) Blumenthal dated 2000 (5) Source referred is <i>Ergänzungsbuch zum Deutschen</i></p>

Documented use / Traditional use	Dosage	Method and Duration of Administration	Handbook Reference
	<p>Essential oil: 0.1-0.3 ml (7)</p> <p>Succus: Pressed juice of fresh plant in 25% alcoholic Preservation (8)</p> <p>External:</p> <p>Gargle or rinse: Use warm infusion. 2.5 g cut leaf in 100 ml water; or 2 to 3 drops of essential oil in 100 ml water; or use 5 ml of fluidextract diluted in 1 glass water, several times daily (9)</p> <p>Paint:</p> <p>Apply the undiluted alcoholic fluidextract to the affected area with a brush or swab (10)</p>		<p>Arzneibuch, 1941</p> <p>(6) Blumenthal dated 2000</p> <p>(7) Blumenthal dated 2000</p> <p>(8) Blumenthal dated 2000</p> <p>(9) Blumenthal dated 2000</p> <p>(10) Blumenthal dated 2000</p>
<p>Internal:</p> <p>Flatulent dyspepsia, Hyperhidrosis galactorrhoea</p> <p>External:</p> <p>Gargle, mouthwash (pharyngitis, uvulitis, stomatitis, gingivitis, glossitis)</p>	<p>Internal:</p> <p>Leaf:</p> <p>1-4 g as an infusion three times daily (1); 4-6 g daily (2)</p> <p>Liquid extract: 1-4 ml (1:1 in 45% alcohol) 3 times daily (1)</p> <p>External:</p> <p>Gargle/rinses : 2.5 g/100 ml water (2)</p>	<p>Method:</p> <p>Oral administration</p> <p>Duration:</p> <p>No information</p>	<p>Herbal Medicine, (Barnes <i>et al.</i>, 2002; 2007)</p> <p>(1) Reference source dated 1983</p> <p>(2) Reference source dated 1998</p>
<p>Internal:</p> <p>Regulate perspiration (during menopause, nightsweat)</p>	<p>Ordinary dose:</p> <p>Internal:</p> <p>Tincture: 60 drops daily</p>	<p>Method:</p> <p>Internal and external administration</p>	<p>Lehrbuch der Biologischen Heilmittel, Madaus 1938</p> <p>(1) Source referred to is Krahn 1896</p>

<b>Documented use / Traditional use</b>	<b>Dosage</b>	<b>Method and Duration of Administration</b>	<b>Handbook Reference</b>
Lactation inhibition Gastrointestinal complaints External: Respiratory diseases and inflammations in mouth and throat	30-50 drops several times a day  Warm infusion: 2-3 full spoon (=3.4-5.1 g) of the leaves	Duration:  No information	(2) Source referred to is Hager, year not specified
Internal For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating	Tincture (1:10), extraction solvent: ethanol 70% V/V tincture (1:10) 2.5-7.5 g daily, divided in 3 doses.  For oral use 2-3 ml 3 times daily	Duration  No information	This tincture and the ethanol percentage are specified as a separate monograph in Ph. Eur 2008 and the Deutsches Arzneibuch 6. Ausgabe 1926. Spiritus dilutus is Ethanol 68-69% (V/V)=60-61% (m/m).
External For symptomatic treatment of inflammations in the mouth or the throat	(5-10 ml) (1-2 spoon) of tincture, diluted in a glass of water, for rinsing or gargling; tincture (1:10) undiluted, for direct application on the gum.		Information concerning this tincture is documented in earlier German Pharmacopoeias (Ergänzungsbuch zum Deutschen Arzneibuch (Erg. B. 6. Stuttgart 1953)

### 2.3. Overall conclusions on medicinal use

For each of these herbal preparations included in the monograph, the available sources that provide evidence of period of use are shown. 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.

**Table 4:** Overview of evidence on period of medicinal use

<b>Herbal preparation Pharmaceutical form</b>	<b>Indication</b>	<b>Posology, Strength</b>	<b>Period of medicinal use</b>
Comminuted herbal substance as herbal tea for oral use.	Traditional herbal medicinal product for relief of mild dyspeptic complaints such as heartburn and bloating.	Comminuted herbal substance for tea preparation: 1-2 g herbal substance in 150 ml boiling water three times daily.  Daily dose: 3-6 g	Since 1976 in Germany Since 1978 in Spain
	Traditional herbal medicinal product for relief of excessive sweating.	Comminuted herbal substance for tea preparation:  2 g herbal substance in 150 ml boiling water.	Since 1976 in Germany
Comminuted herbal substance (for preparation of an infusion) for oromucosal and cutaneous use.	Traditional herbal medicinal product for relief of inflammations in the mouth or the throat.	Comminuted herbal substance as an infusion: 2.5 g herbal substance in 100 ml boiling water. The infusion is used for gargle 3 times daily.	Since 1976 in Germany Since 1978 in Poland
	Traditional herbal medicinal product for relief of minor skin inflammations.	Comminuted herbal substance as an infusion: 2.5 g herbal substance in 100 ml boiling water 2-4 times daily. For cutaneous use as impregnated dressing.	Since 1978 in Poland
Dry extract (4-7:1), extraction solvent: water	Traditional herbal medicinal product for relief of mild dyspeptic complaints such as heartburn and	320 mg divided in 3-4 doses	Since 1976 in Germany

<b>Herbal preparation Pharmaceutical form</b>	<b>Indication</b>	<b>Posology, Strength</b>	<b>Period of medicinal use</b>
Herbal preparation in solid dosage form for oral use.	bloating.		
	Traditional herbal medicinal product for relief of excessive sweating	80-160 mg 3 times daily No longer than 2 weeks	At least since 1976 in Germany
Liquid extract (1:3.5-5), extraction solvent: ethanol 31.5% V/V  Herbal preparations in solid or liquid dosage forms for oral use.	Traditional herbal medicinal product for relief of mild dyspeptic complaints such as heartburn and bloating.	0.5 ml in water 3 times daily	Since 1976 in Germany
	Traditional herbal medicinal product for relief of excessive sweating.	10-20 drops (0.5-1 ml) dissolved in liquid three times daily. For night sweat: 1 hour directly before bedtime: 30 drops (1.5 ml) in liquid	Since 1976 in Germany
	Traditional herbal medicinal product for relief of inflammations in the mouth or the throat.	0.5 ml three times daily in a glass (150 ml) of warm water for gargle.	Since 1976 in Germany
Liquid extract (1:1), ethanol 70% V/V  Herbal preparations in semi-solid dosage forms for cutaneous use.	Traditional herbal medicinal product for relief of inflammations in the mouth or the throat.	Gel containing 20% liquid extract (1:1), 250 mg of gel up to 5 times daily on affected regions and massage gently.	Since 1976 in Germany
Liquid extract (1:4-5) extraction solvent: ethanol 50% V/V  Herbal preparations in solid or liquid dosage forms for oral use.	Traditional herbal medicinal product for relief of excessive sweating.	50 drops (=2 ml) three times daily.	Since 1976 in Germany
Liquid extract (DER 1:4-6), extraction solvent: liquor wine: ethanol 96% V/V (38.25:61:75)	Traditional herbal medicinal product for relief of mild dyspeptic, complaints such as heartburn and	0.43 ml 3 times daily	Since 1976 in Germany

<b>Herbal preparation Pharmaceutical form</b>	<b>Indication</b>	<b>Posology, Strength</b>	<b>Period of medicinal use</b>
m/m) Herbal preparations in solid or liquid dosage forms for oral use.	bloating.		
Liquid extract (DER 1:4-6), extraction solvent: liquor wine : ethanol 96% V/V (38.25: 61:75 m/m)  Liquid or semi-solid preparations for oromucosal use.	Traditional herbal medicinal product for relief of inflammations in the mouth or the throat.	0.65 ml in 150 ml water for rinse or gargle 3 times daily.	Since 1976 in Germany
Tincture (1:10), extraction solvent: ethanol 70% V/V  Herbal preparations in solid or liquid dosage forms for oral use.	Traditional herbal medicinal product for relief of mild dyspeptic, complaints such as heartburn and bloating.	2-3 ml 3 times daily.	Deutsches Arzneibuch 6. Ausgabe 1926. Spiritus dilutus is Ethanol 68-69% V/V=60-61% (m/m).  German Pharmacopeias (Ergänzungsbuch zum Deutschen Arzneibuch (Erg. B. 6. Stuttgart 1953.)
Tincture (1:10), extraction solvent: ethanol 70% V/V  Liquid or semi-solid preparations for oromucosal use.	Traditional herbal medicinal product for relief of inflammations in the mouth or the throat.	1-2 spoons (5-10 ml) in a glass of water, rinse or gargle, undiluted tincture is applied locally on the affected regions.	Deutsches Arzneibuch 6. Ausgabe 1926. Spiritus dilutus is Ethanol 68-69% V/V=60-61% (m/m).  German Pharmacopeias (Ergänzungsbuch zum Deutschen Arzneibuch (Erg. B. 6. Stuttgart 1953.)

## Indication and duration of use

The duration of use is limited as followed:

Indication 1) Traditional herbal medicinal product for relief of mild dyspeptic complaints such as heartburn and bloating.

If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indication 2) Traditional herbal medicinal product for relief of excessive sweating

Long-term use is possible (see section 4.4 'Special warnings and precautions for use').

If the symptoms do not improve within 6 weeks of use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indication 3) Traditional herbal medicinal product for relief of inflammations in the mouth or the throat

If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indication 4) Traditional herbal medicinal product for relief of minor skin inflammations.

If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

## Method of administration

Indication 1) and 2) oral use

Indication 3) oromucosal use

Indication 4) cutaneous use

### *Assessor's comment:*

The herbal preparations mentioned above (table 4) fulfil all criteria for traditional herbal medicinal products.

These herbal preparations included in the revised European Union monograph have been in medicinal use for 30 years or more according to literature and information about approved products obtained from the Member States.

For herbal preparation c (dry extract with water): Since 1976 in Germany (different indication, but considered comparable with the herbal tea).

For herbal preparation d (liquid extract ethanol 31.5%): Since 1976 in Germany (different indication, but considered comparable with the liquid extract DER 1:4-5, extraction solvent ethanol 50% V/V).

As shown in section 2.1, several herbal medicinal products containing herbal preparations were registered in EU Member states after the publication of the first *Salvia officinalis* L., folium monograph.

## 3. Non-Clinical Data

### 3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

The mechanisms by which clinical effects of sage leaf are achieved are unknown. Sage oil has antimicrobial properties that have been attributed principally to the presence of  $\alpha$ - and  $\beta$ -thujone (Bradley, 2006; Newall *et al.*, 1996). Drinking or gargling sage leaf infusions have been thought to soothe a sore throat or gums, and these effects have been ascribed to volatile compounds such as 1,8-cineole, borneol, camphor and thujones (Ehrnhöfer-Ressler *et al.* 2013).

#### 3.1.1. Primary pharmacodynamics

##### Antibacterial, fungistatic, antiseptic and virustatic activity

The essential oil of sage has shown inhibitory activity against Gram-positive (*Bacillus subtilis*) and Gram-negative (*Escherichia coli*, *Shigella sonnei*, *Salmonella* species, *Klebsiella ozanae*) bacteria as well as against fungi-species (*Candida albicans*, *C. krusei*, *C. pseudotropicalis*, *Torulopsis glabrata*, *Cryptococcus neoformans*). No activity was observed versus *Pseudomonas aeruginosa* (Bradley, 2006). Wichtl, 2004, also mentions antimicrobial activity against *Aspergillus flavus*.

Microencapsulation of the oil into gelatine-acacia capsules introduced a lag-time with respect to the antibacterial activity and inhibited the antifungal activity (Newall *et al.*, 1996; Barnes *et al.*, 2002).

Horiuchi *et al.* (2007) found that a crude extract from *Salvia officinalis* L. leaves showed antimicrobial activity against vancomycin-resistant enterococci (VRE).

The effective compound was identified as oleanolic acid. Also ursolic acid showed antimicrobial activity against VRE. The minimum inhibitory concentrations (MICs) of oleanolic acid and ursolic acid were 8 and 4  $\mu\text{g/ml}$ , respectively. These two compounds also showed antimicrobial activity against *Streptococcus pneumonia* and methicillin-resistant *Staphylococcus aureus* (MRSA), and they showed bactericidal activity against VRE at least for 48 hours when added at concentrations that were two-times higher than their MICs. Neither compound showed antimicrobial activity against Gram-negative bacteria tested (*E. coli*, *P. aeruginosa*, *S. marcescens*) and *Candida albicans*. The antimicrobial activity of oleanolic acid or ursolic acid is not so strong as compared with antimicrobial drugs that are in clinical use, although oleanolic acid and ursolic acid showed fairly high activity.

An aqueous and a 50% ethanolic extract of sage leaf exhibited strong inhibitory effects on the collagenolytic activity of *Porphyromonas gingivalis*. Aerial parts of sage contain diterpenes with antiviral activity against vesicular stomatitis virus (ESCOP, 2003). The effect against vesicular stomatitis virus is also mentioned by Bradley (2006) and the effective diterpenes are identified as saffinolidide and sagone.

The antiviral action has been attributed to the essential oil according to Wichtl (2004).

##### Anti-inflammatory activity

Human gingival fibroblasts (HGF-1) were treated for 6 hours with sage infusion or sage infusion fractions containing either its volatile components and water (aqueous distillate) or its dry matter, and reduced a mean phorbol-12-myristate-13-acetate/ionomycin (PMA/I)-stimulated release of the pro-inflammatory interleukins IL-6 and IL-8 by more than 50% ( $p < 0.05$ ). Cellular uptake experiments and subsequent GC-MS analysis using stable-isotope-labelled internal standards revealed the presence of 1,8-cineole, borneol, camphor, and  $\alpha$ -/ $\beta$ -thujone in sage infusion treated cells; LC-MS analysis

demonstrated the presence of rosmarinic acid. A significant, more than 50% mean inhibition of PMA/I-induced IL-6 and IL-8 release was demonstrated for the volatile compounds 1,8-cineole, borneol, camphor, and thujone, but not for the non-volatile rosmarinic acid when applied in concentrations representative of sage infusion. Hence, the volatile compounds were found to be more effective than rosmarinic acid. According to the authors 1,8-cineole, borneol, camphor, alpha- and beta- thujone seemed to contribute to the anti-inflammatory activity of sage infusion in human gingival fibroblasts (Ehrnhöfer-Ressler *et al.*, 2013).

Chloroform and *n*-hexane dry extracts from sage leaf dose-dependently inhibited *in vivo* croton oil-induced ear oedema in mice, chloroform extracts being the more potent with ID<sub>50</sub> values of 106-140 µg/cm<sup>2</sup>. The main component of the chloroform extract and the major contributor to its anti-inflammatory activity was found to be ursolic acid (ID<sub>50</sub> : 0.14 µM/cm<sup>2</sup>), which had twice the potency of indomethacin (ID<sub>50</sub> : 0.26 µM/cm<sup>2</sup>) in this test (ESCOP, 2003; Wichtl, 2004).

Rosmarinic acid has been shown to have anti-inflammatory activity (Verweij-van Vught *et al.*, 1987).

In this study, rosmarinic acid acted as an inhibitor of the complement activation when the influence of rosmarinic acid on the function of porcine and human polymorphonuclear leucocytes was tested.

In a study to determine the effect of topical application (5% in vehicle) of the anti-inflammatory rosmarinic acid on the progression of plaque induced gingivitis in six Rhesus monkeys, rosmarinic acid significantly lowered both gingival and plaque indices in comparison with placebo (Van Dyke *et al.*, 1986).

Oleanolic acid also showed anti-inflammatory activity but was less effective (ID<sub>50</sub>: 0,36 µM/cm<sup>2</sup>) (ESCOP, 2003).

Cirsiliol occurs on the leaf surface on *Salvia officinalis* L. and is a potent and relatively selective inhibitor of arachidonate 5-lipoxygenase (Harborne *et al.*, 1996 with reference to Matsuura, 1973). It has been shown that cirsiliol is a potent inhibitor of 5-lipoxygenase of rat basophilic leukaemia cells. It also inhibited 12-lipoxygenase from bovine platelets and porcine leucocytes, but the inhibitory activity was less than the one on 5-lipoxygenase (Hirono, 1987).

### **3.1.2. Secondary pharmacodynamics**

#### **Antitussive and immunomodulatory activities**

The antitussive and immunomodulatory activities of pectin and hemicellulose polysaccharides originated from sage was shown in a study performed by Sutovska *et al.* (2007). Sage polysaccharide complex A significantly decreased the number of the cough efforts (NE) and the intensity of inspiratory and expiratory cough attacks (IA- and IA+) of mechanically – induced cough reflex from both, laryngopharyngeal and tracheobronchial areas of airways, without any side effects in non-anaesthetised cats. Antitussive activity tests with some classic drugs, narcotic codeine and non-narcotic dropropizine performed under same experimental conditions demonstrated that antitussive potency of sage polysaccharide complex two fold exceeded cough suppressive effect of peripheral antitussive agent and effectiveness only by 13% lower than opioid receptors agonist.

Furthermore, all fractions of isolated polysaccharides possessed ability to increase rat thymocyte proliferation, which, according to the authors, confirmed their immunological property.

The immunomodulatory activity of water-soluble polysaccharides isolated from aerial parts of sage is also mentioned by Bradley (2006).

### **Carminative, spasmolytic, stimulant and tonic effects on digestion and nervous system**

Sage oil had only a relatively weak spasmolytic effect on isolated guinea pig tracheal and ileal smooth muscle in comparison with oils from other Labiatae such as melissa leaf or thyme (Bradley, 2006).

A water-alcohol extract of *Salvia officinalis* L. demonstrated a marked spasmolytic action on the smooth-muscle contractions caused by four spasmogens (acetylcholine, histamine, serotonin and BaCl<sub>2</sub>) in isolated segments of guinea-pig ileum. The experiments showed that the extract inhibited by 70-85% the smooth-muscle contractions, and its spasmolytic effect was of considerable duration. Newall *et al.* (1996) refer to the same effect of 60-80% inhibition of contraction induced by the four spasmogens. An initial spasmogenic action exhibited by low doses of sage oil, has been attributed to the pinene content. Antispasmodic activity *in vivo* (iv, guinea pig) has been reported for sage oil, which released contraction of Oddi's sphincter induced by intravenous morphine.

The spasmolytic effect of the total flavonoid fraction from *Salvia officinalis* L. was considerably weaker.

It caused inhibition of the contractile smooth-muscle responses to the various spasmogens by 30-60% (Todorov *et al.*, 1984). Pinene, if tested alone in long-strip guinea-pig ileum, showed a weak spasmogenic action and induced an evident increase of the basal tone. An initial stimulating action, especially at the lowest doses, was also seen to be the case of linalyl acetate and limonene in sage essence. The constituents of the essence influenced its action in relation to their concentration and a double spasmogenic-spasmolytic action appeared sometimes in the sage essence (Taddei *et al.*, 1988).

According to Taddei *et al.* (1988) the spasmolytic activity of the components of essential oils probably affects the smooth muscle in direct and indirect ways and modifies the quantity of Ca<sup>2+</sup>.

Cholinesterase (ChE) inhibiting properties of *S. officinalis* on mood, anxiety and performance were studied by Kennedy *et al.* (2006). The sage extract exhibited *in vitro* dose dependent ChE-inhibiting properties, but was a more selective inhibitor of BuChE (butyrylcholinesterase from human serum) than AChE (acetylcholinesterase from human erythrocytes) (IC<sub>50</sub> : 0.054 mg/ml and 0.365 mg/ml, respectively).

Studies on the effect of *Salvia officinalis* L. extracts showed a prolonged latency of the onset of sleep on hexobarbital anaesthesia in mice (Todorov *et al.*, 1984).

Hypotensive activity in anaesthetised cats and CNS-depressant action (prolonged barbiturate sleep) in anaesthetised mice have been reported for sage extract and for the essential oil (Newall *et al.*, 1996).

### **Anti-mutagenic effects**

Some of the terpenoids of sage have demonstrated antimutagenic effects (Wichtl, 2004).

In a study by Patenkovic *et al.* (2009), the antimutagenic effects of *Salvia officinalis* tea have been estimated by the somatic mutation and recombination test (SMART) on *Drosophila melanogaster*. Methyl methanesulphonate (MMS) was used as the mutagen and positive control. Several types of treatment were performed: short acute treatment with sage infusion or MMS, longer (chronic) treatment with sage solution or MMS, and two combined treatments, i.e. short treatment with sage followed by a longer treatment with MMS and vice versa. Sage infusion used in the experiments showed antimutagenic effect by reducing the frequency of mutations induced by MMS. The study did not reveal which components of sage infusion are of particular antimutagenic potential.

Antimutagenic properties of terpenoid fractions of sage (*Salvia officinalis*) were tested by Vujosevic and Blagojevic (2004), in mammalian system *in vivo*. The ability of sage to decrease the frequency of aberrant cells induced by a potent mutagen was examined. First, groups of mice were treated with three concentrations of sage alone and it was established that the frequency of aberrant cells after

treatment with a concentration of 25 µl/kg was not significantly different from the negative control (olive oil), while that after treatment with 50 µl/kg concentration differed significantly.

### **Other effects**

Extracts from *Salvia officinalis* L. contain biologically active substances possessing moderate and prolonged hypotensive action. Applied intravenously and duodenally, aqueous-alcohol extracts caused moderate but prolonged lowering of the blood pressure in cats (Todorov *et al.*, 1984).

Hypoglycaemic activity *in vivo* has been reported for mixed phytotherapy preparations involving various *Salvia* species including *S. officinalis*. Activity in normoglycaemic, hypoglycaemic and in alloxan-diabetic rabbits was observed, although no change in insulin concentrations was noted (Newall *et al.*, 1996). Common sage is said to have mild blood-sugar lowering action but this is unproven (Wichtl, 2004).

Sage used at a concentration of 100 µl/kg was cytotoxic. Mitomycin C (MMC), known as a potent mutagen, was used for induction of chromosome aberrations. Post-treatment with sage suppressed the effects of MMC significantly. Both concentrations (25 µl/kg and 50 µl/kg) produced a significant decrease in the frequency of aberrations relative to MMC alone. The percent of aberrations decreased with increasing concentrations of sage. Results in a study with natural flavonoids on the inhibition of 3H-Diazepine binding to rat cerebral cortical synaptosomal membranes, and the anxiolytic, sedative, myorelaxant, anticonvulsant, amnesic and hypnotic effects of some of them, showed that cirsiolol have sedative and hypnotic effect *in vivo* (Marder & Paladini, 2002).

A methanolic extract from sage leaf showed affinity to human brain benzodiazepine receptors (from post-mortem frontal cortex) by competitive displacement of 3H-flumazenil, a specific benzodiazepine antagonist. Activity-guided analysis revealed five benzodiazepine receptor-active constituents, of which three are flavones and two diterpenes. Compared to diazepam (IC<sub>50</sub>: 0,05 µM) the diterpene galdosol (IC<sub>50</sub>: 0.8 µM ) and the flavone hispidulin (IC<sub>50</sub>:1.3 µM) were the most active; 7-methoxyrosmanol (IC<sub>50</sub>: 7.2 µM) also exhibited strong affinity, while apigenin (IC<sub>50</sub>: 30 µM) and cirsimaritin (IC<sub>50</sub>: 350 µM) were considerably less active (Bradley, 2006).

The anticholinesterase activity of several *Salvia* species and their constituents have been investigated in the search for new drugs for the treatment of Alzheimer`s disease. The inhibition of acetylcholinesterase *in vitro* by an ethanolic extract of *S. officinalis*, L. (2.5 mg/ml) was 68%, and by oils of *S. officinalis* L. and *S. lavandulaefolia* (0.1 µg/ml) was 52% and 63% respectively. The monoterpenes 1,8-cineole and α-pinene from the oil have been identified as the inhibitors of acetylcholinesterase (Barnes *et al.*, 2002).

### **3.1.3. Safety pharmacology**

No data available.

### **3.1.4. Pharmacodynamic interactions**

No data available.

### **3.1.5. Conclusions**

Results from relevant experimental studies on Sage leaf to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

*Salvia officinalis* L. and some of its constituents have been investigated in some preclinical studies.

**Indication 1)** Traditional herbal medicinal product for relief of mild dyspeptic, complaints such as heartburn and bloating:

The indication is supported by the fact that it has been an indication for the traditional use of *Salvia officinalis* L. for a period of at least 30 years in Europe. Further preclinical studies are necessary to clarify this effect.

**Indication 2)** Traditional herbal medicinal product for relief of excessive sweating:

The indication is supported by the fact that it has been an indication for the traditional use of *Salvia officinalis* L. for a period of at least 30 years in Europe. Further preclinical studies are necessary to clarify this effect.

**Indication 3) and 4)** Traditional herbal medicinal product for the symptomatic treatment of inflammations in the mouth or the throat, and minor inflammations of the skin:

Many preclinical studies have been performed investigating the antibacterial and anti-inflammatory effects of *Salvia officinalis* L. and some of its constituents. Many of these studies showed positive results which support this indication. It is further supported by the fact that it has been an indication for the traditional use of *Salvia officinalis* L. for a period of at least 30 years in Europe.

Several other preclinical studies on different plausible effects from sage leaf have also been performed, but further studies are necessary.

### **3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof**

*In vitro* experiments.

No pharmacokinetic (ADME) studies on extracts of *Salvia officinalis* L. were available.

Extract of *Salvia officinalis* L. from a commercial herbal medicinal product (dry extract (DER 4-7:1), extraction solvent: water in capsules that contains 150 mg extract corresponding to 0.6 g leaves) was assessed *in vitro* for its inhibitory potential on isolated human CYP2D6-mediated dextromethorphan metabolism.

IC<sub>50</sub> for this herbal extract of *Salvia officinalis* L. was found to be 0.8 mg/ml and the extent of inhibition was higher than 50%. In this small screening study, *Ginkgo biloba*, common valerian and St. John's wort were suggested as candidates for clinically significant CYP interactions *in vivo* (Hellum & Nilsen, 2007), whereas no conclusions could be drawn about potential interactions of sage leaf.

### **3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof**

#### **3.3.1. Single dose toxicity**

An experimental study of the toxic properties of commercialised essential oil of sage has revealed that the convulsant action was of central nervous system origin in unanaesthetised rats. The dose limit from which the cortical events are subclinical is 0.3 g/kg for sage oil. Above 0.50 g/kg for sage oil, the convulsions appeared, and became lethal above 3.2 g/kg (ESCOP, 2003). The toxicity appeared to be related to the presence of camphor and thujone in *Salvia officinalis* oil (Millet *et al.*, 1981; Newall *et al.*, 2002).

Acute LD<sub>50</sub> values for sage oil are documented as 2.6 g/kg in rats for oral administration (ESCOP, 2003; Bradley, 2006) and 5 g/kg in rabbits for intradermal administration (Barnes *et al.*, 2002).

### 3.3.2. Repeat dose toxicity

In an 8-week toxicity study with groups of 5 white rats, a daily dose of 250 mg/kg bw sage oil was well tolerated when given by oral administration. When the dose was increased to 500 mg/kg bw/day, some convulsing was observed. Upon increase to 1000 mg/kg bw/day, most animals died and all animals died when the level was increased to 1250 mg/kg bw/day. The levels of camphor in 25 different commercial sources of sage leaves varied from 7 to 50% (EFSA, 2008b).

Based on these values, the observed NOAEL of 250 mg sage oil/kg bw/day corresponds to camphor intakes of 18 and 125 mg/kg bw/day, respectively (EFSA, 2008b).

### 3.3.3. Genotoxicity.

Bradley (2006) and ESCOP (2003) refer to tests on genotoxicity performed with sage leaf tincture and sage essential oil. In the study by Zani *et al.* (1991) genotoxic properties of essential oils from different herbs, including *Salvia officinalis* L. and one of its varieties were tested.

ESCOP (2003) with reference to Schimmer *et al.* (1994) describe that a sage leaf tincture (*Salviae tinctura* German Pharmacop. 6<sup>th</sup> ed.) at doses up to 200 µl/plate showed no mutagenic activity in the Ames test using *Salmonella typhimurium* strains TA98 and TA100 with or without S9 metabolic activation system.

*Assessor's comment:*

The study with the essential oil as published by Zani *et al.* (1991) cannot be interpreted because of deficiencies in the performance and analysis of the tests.

Results from tests with the essential oil are not transferable to the herbal substance or other preparations of *Salvia officinalis* L. folium.

The testing of sage leaf tincture by Schimmer *et al.*, 1994 with two strains is not complete (3 strains are missing).

A European Union list entry is not supported for the tincture or other preparations of *Salvia officinalis*, folium due to lack of adequate data on genotoxicity.

### 3.3.4. Carcinogenicity

No studies with *Salvia officinalis* L., either essential oil or extracts, were available.

No oral studies on chronic toxicity or carcinogenicity with camphor are available. In a pulmonary tumour response test D-camphor injected intraperitoneally into strain A/He mice (groups of 15 males and females) 3 times a week for 8 weeks in total doses of 3.6 and 18 g/kg bw induced no increase in primary lung tumours and was not considered by the authors to be carcinogenic for lung (EFSA 2008a, with reference to Stoner *et al.*, 1973).

### 3.3.5. Reproductive and developmental toxicity

No studies with *Salvia officinalis* L., neither essential oil nor extracts, were available.

No experimental data on thujone were available (Scientific Committee on Food, 2003).

No adverse effects on foetal growth, viability, or morphological development were reported on camphor (EFSA 2008a).

### 3.3.6. Local tolerance

Not applicable

### 3.3.7. Other special studies

Not applicable

### 3.3.8. Conclusions

The essential oil of *Salvia officinalis* L. contains constituents like thujone and camphor, which have toxic effects in high doses. Toxicological dose limits have been set based on the available toxicological data and other studies. The toxic effect appears to be of central nervous origin with convulsions as the main symptom. Based on existing data it can be concluded that because of the toxic properties of the essential oil, one should not exceed recommendations concerning the posology of sage leaf.

For further information on these recommendations, see section 5.6 and the Public statement on the use of herbal medicinal products containing thujone (EMA/HMPC/732886/2010 Rev.1).

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

No studies on reproductive toxicity are available for *Salvia officinalis* L. There is no suspicion for a carcinogenic potential.

## 3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on Sage leaf to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

*Salvia officinalis* L. and some of its constituents have been investigated in some preclinical studies.

**Indication 1)** Traditional herbal medicinal product for relief of mild dyspeptic, complaints such as heartburn and bloating:

The indication is supported by the fact that it has been an indication for the traditional use of *Salvia officinalis* L. for a period of at least 30 years in Europe. Further preclinical studies are necessary to clarify this effect.

**Indication 2)** Traditional herbal medicinal product for relief of excessive sweating:

The indication is supported by the fact that it has been an indication for the traditional use of *Salvia officinalis* L. for a period of at least 30 years in Europe. Further preclinical studies are necessary to clarify this effect.

**Indication 3) and 4)** Traditional herbal medicinal product for the symptomatic treatment of inflammations in the mouth or the throat, and minor inflammations of the skin:

Many preclinical studies have been performed investigating the antibacterial and anti-inflammatory effects of *Salvia officinalis* L. and some of its constituents. Many of these studies showed positive results which support this indication. It is further supported by the fact that it has been an indication for the traditional use of *Salvia officinalis* L. for a period of at least 30 years in Europe.

Several other preclinical studies on different plausible effects from sage leaf have also been performed, but further studies are necessary.

Specific data on pharmacokinetics and interactions are not available. Based on the limited data available on pharmacokinetics for the herbal substance, no conclusion can be made. Non-clinical information on the safety of Sage leaf is scarce.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

## **4. Clinical Data**

### **4.1. Clinical pharmacology**

#### **4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

No data available.

#### **4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

No data available regarding the herbal substance.

##### *Camphor*

In humans admitted to hospital in a state of acute intoxication after ingestion of 6-10 g camphor, hydroxylated camphor in the positions 3, 5 and 8 (or 9) were identified as major metabolites in the urine; 5- and 8-(or 9-) hydroxycamphor were subsequently oxidised to the corresponding ketones and carboxylic acids, the latter being conjugated with glucuronic acid (EFSA 2008a).

### **4.2. Clinical efficacy**

#### **4.2.1. Dose response studies**

There are no dose response studies available.

#### **4.2.2. Clinical studies (case studies and clinical trials)**

##### **Perspiration-inhibiting/Antihidrotic effect studies**

Excessive sweat induced by pilocarpine was inhibited by a dialysate of an aqueous extract of fresh sage. In an open study, 40 patients were given dried aqueous extract of sage (440 mg, equivalent to 2.6 g herbs) and 40 were given infusion of sage (4.5 g herb daily). Reduction of sweat (less than 50%) was achieved in both groups of patients with idiopathic hyperhidrosis (the secretion of an abnormally large amount of sweat). It should be noted however, that this study did not include a control group (Barnes *et al.*, 2007, with reference to ESCOP 2003).

Several open studies, carried out mainly in the 1930s on patients or healthy volunteers but also including a larger study from 1989 (unpublished) on 80 patients with idiopathic hyperhidrosis, supported the long-standing assumption that sage leaf aqueous extracts have anti-hyperhidrotic activity (Bradley, 2006).

## **Menopausal symptoms**

Bommer *et al.* (2011) studied treatment of hot flushes and associated menopausal symptoms in an open, multicentre clinical trial conducted in eight practices in Switzerland, 71 patients (intent-to-treat population (ITT), n=69; with a mean age of 56.4±4.7 years, menopausal for at least 12 months, and with at least five flushes daily). The patients were treated with a once-daily tablet of fresh sage leaves for 8 weeks after an introductory baseline week. Parameters for the evaluation of efficacy were the change in intensity and frequency of hot flushes, and total score of the mean number of intensity-rated hot flushes (TSIRHF) as determined by diary protocol over the 2-month treatment period. Other variables included assessment of the Menopause Rating Scale (MRS) by the treating physician at baseline and after 2 months of therapy.

In the ITT population there was a significant decrease in the TSIRHF by 50% within 4 weeks and by 64% within 8 weeks ( $p<0.0001$ ). The mean total number of hot flushes per day decreased significantly each week from week 1 to 8. The mean number of mild, moderate, severe, and very severe flushes decreased by 46%, 62%, 79%, and 100% over 8 weeks, respectively. The MRS and its somato-vegetative, psychological, and urogenital subscales decreased significantly by 43%, 43%, 47%, and 20% respectively. The treatment was very well tolerated. These results support the traditional usage in menopausal hot flushes, as well as to alleviate associated menopausal symptoms (Bommer *et al.*, 2011).

## **Secretion-promoting effects**

In folk medicine, sage is used to promote menstruation (Wichtl, 2004).

Healthy people in a tolerance-test were given a 50 % plant substance preparation (Salvia "Teep" forte), one full teaspoon three times daily; duration of administration not specified. The people who sweat little experienced a more excessive perspiration, and those with already excessive perspiration experienced a reduced perspiration and strong need to urinate with increased amount of urine.

When Salvia was used diluted, as in a 10% plant substance preparation (Salvia "Teep" mite) one tablet 3 times daily, duration of administration not specified, the inhibitory effect was strong (Madaus, 1938).

## **Antilactagogue effects**

In folk medicine, sage is used to facilitate weaning due to a milk-secretion inhibiting action (Wichtl, 2004; Madaus 1938).

## **Memory-enhancing effects and beneficial effects on cognitive performance and mood-studies with sage extract**

In a randomised, double blind, placebo-controlled study, patients aged 65-80 years of age with a diagnosis of mild to moderate dementia and probably Alzheimer's disease were treated for 16 weeks with 60 drops/day of either sage leaf liquid extract (1:1, 45% ethanol; n=15) or placebo liquid (n=15). Compared with the placebo group, patients in the sage leaf group experienced significant benefits in cognitive function by the end of the treatment, as indicated by improved scores in the Clinical Dementia Rating (CDR;  $p<0.003$ ) and the Alzheimer's Disease Assessment Scale (ADAS-Cog;  $p=0.03$ ). Within the limitations of a fairly small number of patients and short period of follow-up, the authors concluded, that the results suggested efficacy of the sage leaf extract in the management of mild to moderate Alzheimer's disease (Bradley, 2006).

In a randomised, placebo-controlled, double blind, balanced, five-period crossover study the acute effects on cognitive performance of a standardised extract of *Salvia officinalis* L. in older adults were investigated. Twenty volunteers (>65 years of age, mean=72.95) received four active doses of extract (167, 333, 666 and 1332 mg) and a placebo with a 7-day wash-out period between visits. Assessment

involved completion of the Cognitive Drug Research computerised assessment battery. On study days, treatments were administered immediately following a baseline assessment with further assessment at 1, 2.5, 4 and 6 hours post treatment.

Compared with the placebo condition (which exhibited the characteristic performance decline over the day), the 333 mg dose was associated with significant enhancement of secondary memory performance at all testing times. Similar effects, although to a lesser extent, were observed with other doses. There also were significant improvements to accuracy of attention following the 333 mg dose. In vitro analysis confirmed cholinesterase inhibiting properties for the extract.

According to the authors, the overall pattern of results is consistent with a dose-related benefit to processes involved in efficient stimulus processing and/or memory consolidation rather than retrieval or working memory efficiency (Scholey *et al.*, 2008).

In a double blind, placebo controlled, crossover study, 30 healthy young volunteers (17 males, 13 females; mean age 24 years) were given, on three separate days at 7-day intervals in accordance with a randomised scheme, different single-dose treatments in identical opaque capsules: 300 mg or 600 mg of dried sage leaf, or placebo. On each test day, at pre-dose time and at 1 hour and 4 hours post-dose each participant underwent mood assessment, requiring completion of Bond-Lader mood scales and the State Trait Anxiety Inventory (STAI) before and after a 20-minute performance on the Defined Intensity Stress Simulator (DISS) computerised multitasking battery. The DISS comprises a set of four cognitive and psychomotor tasks presented concurrently on a split (quartered) screen layout, to which responses had to be made with an external mouse, giving attention simultaneously to all four tasks while monitoring the cumulative score (reflecting accuracy and speed of response) in the centre of the screen. The DISS engenders increases in self-ratings of negative mood, arousal and stress-related physiological responses. Both doses of sage leaf led to post-dose improved ratings of mood before performing on the DISS, with the lower dose reducing anxiety and the higher dose increasing "alertness", "calmness" and "contentedness" on the Bond-Lader scales. However, the lower dose reduced alertness on the DISS and, as a result of performing on the DISS, the previously reduced anxiety effect of this dose was abolished. After the higher dose, task performance on the DISS battery improved at both post-dose sessions, but after the lower dose task performance decreased. The results indicated that single doses of sage leaf can improve cognitive performance and mood in healthy young participants, although the lower dose (300 mg) appeared to fall somewhat below the level required for beneficial effects. It is possible that inhibitor of cholinesterases by sage leaf (demonstrated only in vitro) could be involved in the mechanism causing these effects (Kennedy, 2006).

### **Symptomatic relief of inflammations of the mouth and throat**

Hubbert *et al.* (2006) compared the efficacy and tolerability of a new sage product presented as a pump spray in a glass flacon against placebo in the treatment of patients with acute viral pharyngitis. The therapeutically active principle is a sage leaf fluid extract (1:1, extraction solvent ethanol 70% V/V). The product contains 15% of the extract in an aqueous solution. Placebo was identically composed regarding ethanol and excipient concentration and contained a pharmacologically inactive amount of 0.3% sage leaf extract for appropriate blinding. In this article no similar approved products available on the European market are mentioned. Switzerland is therefore assumed to be the first country to market this spray. The Swiss Agency for Therapeutic Products has the following product information on a spray for similar use available on their website [www.swissmedic.ch](http://www.swissmedic.ch) (retrieved 2008-12-19): *Salviae extractum ethanolicum liquidum* 150 mg, DER 1:1, excipients ad solutionem pro 1 g, corresp. ethanolum 19% V/V.

Methods/Study design: A randomised, double-blind, placebo-controlled, multicentre, parallel group phase II/III study with adaptive two-stage design and interim analysis. The study participants were in

two study parts. A total of 286 patients with subjective and objective evidence of pharyngitis were randomised. In the first study part, 122 patients were recruited from 16 doctor's offices (n=31 on 30% spray, n=31 on the 15% spray, n=30 on the 5% spray, n=30 on placebo) over a period of 3 months. During the interim analysis a sample size re-assessment was done, based on the treatment effect observed in the first study part. Further 80 patients per group were recruited. In the second study part (the main study), 164 patients were included from 21 doctor's offices (n=82 on 15% spray and n=82 on placebo) for a time period of 3 months. The treatment duration per patient was 3 days, including one baseline visit and one final visit at the doctor's office. All applications of the spray were made up of 3 puffs each, containing 140 µl sage extract per dose. Prior to the first application spontaneous throat pain was estimated by the patient on a 100 mm visual analogue scale (VAS) for baseline value. During the first 2 hours pain intensity was assessed every 15 minutes and documented in the doctor's office. Thereafter, all subsequent pain measurements were done accordingly at home in a way explained by the study personnel.

**Inclusion criteria:** were male and female patients aged 18 years and older with symptoms of acute pharyngitis existing for maximum 48 hours. Typical signs (spontaneous pain, local inflammation) of pharyngitis were confirmed by the study physician. All participants had to document their spontaneous pain intensity on a VAS with a minimum value of 40 mm on a VAS 100 mm.

**Exclusion criteria:** were a positive test on group A  $\beta$ -haemolytic streptococci, concomitant illness (rhinosinusitis, laryngitis, tracheitis, bronchitis, fever, wounds or other significant changes in the oral cave), not allowed co-medication, other pain situation (dental or tumour pain, requiring the intake of analgesic medication), operations in the oropharynx area up to 4 weeks prior to the study, seizures, or any known hypersensitivity against the study medication. Pregnant, lactating and women of childbearing potential who were not taking adequate contraceptive precautions were also excluded.

**Measurements/Endpoints:** The primary efficacy variable in both study parts was the change of throat pain intensity documented every 15 minutes within the first 2 hours after the first application as compared to baseline (using VAS, area under curve (AUC), and pain intensity differences (PID)).

The secondary endpoints in both study parts were

- meaningful pain relief (MPR): maximum 50% of the baseline value on VAS
- complete pain reduction after first application
- change of throat pain intensity during study treatment (according to patient's diary)
- number of patients with early treatment discontinuation due to lack of efficacy
- overall efficacy assessment both by the physician and by the patient
- overall safety assessment both by the physician and by the patient
- adverse events (AE)

**Results:** The efficacy analysis demonstrated according to Hubbert *et al.* (2006), that the 15% spray was significantly superior in throat pain reduction, whereas for the 30% and the 5% preparation results made superiority over placebo unlikely in the final analysis. It was not possible to show any dose dependency of the sage spray in the first study part and the authors suggested that a dose-response linearity may not be present for herbal preparations.

Regarding MPR and complete pain reduction within the first 2 hours after the first application, no significant superiority could be shown. A ca. 44% pain reduction within 2 hours following the first application was found in both study parts for the 15% spray, compared to ca 34% pain reduction in

the placebo group. The author's states that this difference can be contributed to the sage fluid extract itself since the placebo contained the same amount of alcohol as the 15% spray.

The magnitude of the mean pain reduction of the 15% spray in the second study part was in the same range as the placebo effect in the first study part on the mm on the VAS. Possible explanations given by the authors are that "pain" is a very subjective parameter which makes interpretation of such studies challenging, and that the two collectives were different to some extent. Also a possible contribution from the placebo-effect itself giving rise to the result of ca 34% is mentioned.

Only minor side effects such as dry pharynx or burning of mild intensity were seen.

*Assessor's comment:*

The product used in this study by Hubert *et al.* (2006), has a concentration of 15%. This does not correspond to the concentration for similar formulations with a marketing authorisation within the European Union for at least 10 years, i.e. the gargle, for external use in the Commission E monograph of 2.5-5%. A gargle and a spray are considered to be different pharmaceutical formulations, and the strength and posology are not equal. 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 European Union.

Therefore, this study cannot be assessed as documentation for well-established use until the necessary period of time required is fulfilled.

### **Glycaemic control and lipid profile**

Randomised placebo-controlled parallel group study is performed to make an evaluation of the efficacy and safety of *Salvia officinalis* L. leaf extract in the treatment of hyperlipidemic type 2 diabetic patients. The efficacy and safety of taking *Salvia officinalis* leaf extract (one 500 mg capsule t.i.d. for 3 months) in treatment of 40 hyperlipidemic (hypercholesterolemic and/or hypertriglyceridemic) type 2 diabetic patients were evaluated and compared with the placebo group (n=40).

The dry *S. officinalis* leaves powder (20 kg) was extracted with ethanol/water (80/20) as the solvent in a percolator for 72 hours, the extract was concentrated by completely evaporating the solvent in a rotary evaporator, toast powder as an excipient was added to and mixed with the concentrated extract and the mixture was ground to a powder. Toast powder was used as an excipient, because with a smaller amount of it compared to other excipients, a fine dry powder of the extract could be produced. The quantity of the dry extract powder produced was 5.1 kg. The excipient constituted 9.8% of the final extract. The extract powder as the drug and toast powder as the placebo were separately filled into oral gelatine capsules with identical appearance by a hand-operated capsule-filling machine (Scientific Instruments and Technology Corporation, USA). The *S. officinalis* capsules contained 500 mg of the extract powder.

Fasting blood levels of glucose, glycosylated haemoglobin (HbA1c), total cholesterol, triglyceride, LDL-C (low density lipoprotein cholesterol), HDL-C (high density lipoprotein cholesterol), SGOT (serum glutamic-oxaloacetic transaminase), SGPT (serum glutamic-pyruvic transaminase) and creatinine.

The extract lowered fasting glucose, HbA1c, total cholesterol, triglyceride and LDL-C but increased HDL-C compared to baseline at endpoint. Percent difference mean (95% confidence interval) between the extract and placebo groups in terms of effects on fasting glucose, HbA1c, total cholesterol, triglyceride, LDL-C and HDL-C at endpoint were 32.2 (26.5, 37.9), 22.7 (16.8, 28.6), 16.9 (9.7, 24.1), 56.4 (36.1, 76.7), 35.6 (29.9, 41.3) and 27.6 (15.8, 39.4) ( $p=0.001$ ,  $p=0.01$ ,  $p=0.01$ ,  $p=0.009$ ,  $p<0.001$  and  $p=0.008$ ), respectively. Moreover, the extract did not have any significant effects on the other parameters compared to the placebo group at endpoint ( $p>0.05$ ). No adverse effects were

reported. Sage leaf extract may be safe and have anti-hyperglycemic and lipid profile improving effects in hyperlipidemic type 2 diabetic patients (Kianbakht & Dabaghian, 2013).

A randomised double-blind placebo-controlled clinical trial with 67 hyperlipidemic (hypercholesterolemic and/or hypertriglyceridemic) patients, the effects of taking sage leaf extract (one 500 mg capsule every 8 hours for 2 months, capsules prepared as in Kianbakht & Dabaghian (2013)) on fasting blood levels of lipids, creatinine and liver enzymes were evaluated in 34 patients and compared with the placebo group (n=33). The extract lowered the blood levels of total cholesterol, triglyceride, LDL and VLDL, but increased the blood HDL compared with the placebo group at the endpoint. No adverse effects were reported. The results suggest that sage may be effective and safe in the treatment of hyperlipidemia (Kianbakht *et al.*, 2011).

### **4.3. Clinical studies in special populations (e.g. elderly and children)**

In a randomised clinical study, 15 elderly patients treated with 60 drops per day of sage leaf liquid extract (1:1.45% ethanol) for 16 weeks experienced slightly more mild gastrointestinal complaints than those receiving placebo, but the differences were not statistically significant (Bradley, 2006).

### **4.4. Overall conclusions on clinical pharmacology and efficacy**

Several clinical studies have been conducted to determine the effectiveness of herbal preparations of *Salvia officinalis* L. Based on these results it is plausible that sage has effects that support the traditional indications; however, the clinical data cannot be considered to fulfil the criteria required for "well-established medicinal use" according to Directive 2001/83/EC.

According to the information available, products used in the studies cannot be considered to be corresponding to any of the products available within the European Union for the required time period of at least 10 years. More studies are needed and this is also mentioned by Barnes *et al.* (2007). Overall the existing data are not sufficient at present to show efficacy of sage in a well-established use. However, the data can be accepted for establishing "plausibility" of the traditional use. Sufficient data are available to support a European Union herbal monograph on the traditional use of sage leaf.

Based on the limited data available on pharmacokinetics for the herbal substance, no conclusion can be made for inclusion in the monograph.

## **5. Clinical Safety/Pharmacovigilance**

### **5.1. Overview of toxicological/safety data from clinical trials in humans**

No data available regarding the herbal substance.

### **5.2. Patient exposure**

Products containing *Salvia officinalis* L., folium is widely available. The products have various regulatory statuses. A considerable patient/consumer exposure must be anticipated as sage is widely used as a natural source of food flavouring (Barnes *et al.*, 2007) and in herbal medicinal products on the market in the European Member States.

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

No special risks have been identified.

### **5.3. Adverse events, serious adverse events and deaths**

#### *Sage essential oil*

After prolonged use of alcoholic extracts or of the pure essential oil, epileptiform convulsions can occur (Wichtl, 2004, with reference to The German Commission E monograph, 1990).

Sage oil is reported to be a moderate skin irritant and is not recommended for use in aromatherapy (Barnes *et al.*, 2007; Newall *et al.*, 2002).

#### *Sage leaf herbal tea*

Case Report: A previously healthy 18 month-old female with 3 days of intermittent vomiting and diarrhoea without fevers, was given a tea made from water and a home-grown herb. Two hours after drinking the tea, the child developed tonic-clonic contractions of the upper extremities, left eye deviation, and unresponsiveness that lasted less than 1 minute. There was no prior history of convulsions. The child was evaluated in the ED, where she was afebrile with a normal physical exam, head CT, CBC, and serum chemistries. She was discharged home, but 18 hours after her initial ingestion, she developed three subsequent seizures requiring treatment with lorazepam. An EEG the following morning showed some parietal lobe slowing, interpreted as a possible seizure focus. A sample of the herb was identified by a botanist as *S. officinalis* L. or sage.

*Conclusion:* Tea made from sage may have kindled convulsions in a child with a previously unmasked seizure focus (Tong *et al.*, 2003).

Allergic contact dermatitis caused by spices is well documented; however, commercial patch tests are unavailable. Between October 1991, and August 1992, a series of fifty-five patients with suspected contact dermatitis were tested at Ochsner Clinic for sensitivity to a group of spices at concentrations of 10% and 25% in petrolatum. Concordant patch test results (positive at concentrations of 10% and 25%) were most common with ginger (7), nutmeg (5), and oregano (4); the remaining spices produced zero or one positive responses. Patients exhibiting positive reactions at only one concentration were more likely to do so at 25%: nutmeg (5), ginger and cayenne (4), curry, cumin, and cinnamon (3), turmeric, coriander, and sage (2), oregano (1), and basil and clove (0). Single responses at this level may represent a threshold for detecting true allergy or, as an alternative, a marginal irritant reaction. Those responding to only 10% concentrations generally did so weakly. Three patients were deemed to have relevant patch test responses to spices (Futrell *et al.*, 1993).

### **5.4. Laboratory findings**

No data available.

### **5.5. Safety in special populations and situations**

Pregnancy and lactation: Sage is contra-indicated during pregnancy and lactation (ESCOP 2003, Barnes *et al.*, 2002, 2007). The volatile oil contains a high proportion of  $\alpha$ - and  $\beta$ - thujones, which are known to be abortifacient and emmenagogic (Barnes *et al.*, 2002, 2007).

The pure essential oil and alcoholic extracts should not be taken during pregnancy (Wichtl 2004, with reference to the German Commission E monograph; Blumenthal *et al.*, 2000).

*Assessor's comment:*

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

### **5.5.1. Use in children and adolescents**

The oral use of sage is not recommended in children due to the lack of adequate data.

The recommended dosage for adults and children over 12 years for oral use is supported by use in member states. There are no studies in adolescents between 12 and 18 years available.

Oromucosal use in children over 4 years is also listed under the reported posologies from the European Member States.

Background for marketing authorisation for oromucosal use in children:

No clinical studies in children are available, but oromucosal use in children was accepted in one member state in 2004 in accordance with the national regulations for the described oromucosal posology. A single dose for oromucosal use was in this safety assessment stated to contain no more than 0.5 mg thujone in 150 ml of water. The absorption is estimated to be negligible and children older than 4 years of age are considered able to rinse or gargle without swallowing.

*Assessor's comment:*

The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

### **5.5.2. Contraindications**

Hypersensitivity to the active substance(s).

### **5.5.3. Special warnings and precautions for use**

No data available.

### **5.5.4. Drug interactions and other forms of interaction**

No data available.

No drug interactions are documented clinically. However, the potential for preparations of sage to interact with other medicines administered concomitantly was the basis for giving this precautionary information about potential interactions. The mechanism of neurotoxicity has been ascribed to the available information regarding  $\alpha$ -thujone and its effect on the  $\gamma$ -aminobutyric acid (GABA) type A receptor. When the nerve impulses are inhibited, neurons fire too easily and this could theoretically unbalance the brain's message delivery system causing a seizure or epileptic attack (Hold *et al.*, 2000).

*Assessor's comment:*

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 resulted in a recommendation regarding the use of this medicinal product in the first version of the monograph has been deleted as no drug interactions are documented clinically.

Other sources have mentioned the hypoglycaemic effects (Newall *et al.*, 1996), but due to limited evidence from non-clinical studies of hypoglycaemic activity (Barnes *et al.*, 2007) this information is not included in the monograph.

### **5.5.5. Fertility, pregnancy and lactation**

Pregnancy and lactation: Sage is contraindicated during pregnancy and lactation (ESCOP 2003, Barnes *et al.*, 2002, 2007). The volatile oil contains a high proportion of  $\alpha$ - and  $\beta$ - thujones, which are known to be abortifacient and emmenagogic (Barnes *et al.*, 2002, 2007).

The pure essential oil and alcoholic extracts should not be taken during pregnancy (Wichtl 2004, with reference to the German Commission E monograph), (Blumenthal *et al.*, 2000).

*Assessor's comment:*

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

No fertility data available.

### **5.5.6. Overdose**

No cases of overdose from sage leaves has been reported. Intake of sage oil has resulted in seizures.

*Sage oil*

A sense of heat, tachycardia, feelings of vertigo and epileptiform convulsions can occur following prolonged intake of ethanolic extracts of the drug or volatile oil, or through overdose (corresponding to more than 15 g of the sage leaves) (Fleming, 2000; Blumenthal *et al.*, 2000; Wichtl, 2004). A case of human poisoning has been documented following ingestion of sage oil for acne (Barnes *et al.*, 2007 with reference to Centini *et al.*, 1987).

Convulsant activity in humans (and animals) has been documented for sage oil. Clinical intoxications were characterised by tonic-clonic or solely clonic convulsions associated with a comatose state, which required admission to an intensive care unit (Millet *et al.*, 1981).

Two cases, those of a newborn and a toddler, who experienced generalised tonic-clonic seizures after exposure to sage oil. A 33-day-old boy presented with generalised tonic-clonic convulsion accompanying nystagmus had been given sage oil instead of an anti-spasmodic agent for the cure of colic. The previously healthy 5-year-old girl, without any risk factors for epilepsy manifested generalised tonic clonic seizures that lasted 10 minutes. The child had taken approximately 5 ml of sage oil for intestinal colic about 20 minutes before admission. Shortly afterwards she experienced the generalised tonic-clonic seizures. No other causes of seizure were detected by clinical inquiries in either of the patients. The seizures occurred as an isolated event in the toddler, but in a repeated manner in the newborn; both patients experienced good outcomes (Halicioglu *et al.*, 2011).

### **5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability**

Ability to drive or operate machinery or impairment of mental ability: No known effects on ability to drive and use machines (ESCOP, 2003).

*Assessor's comment:*

Further clinical studies are needed for assessment of effects on ability to drive or operate machinery or impairment of mental ability and no precautions are included in the monograph.

### **5.5.8. Safety in other special situations**

Not applicable

## **5.6. Overall conclusions on clinical safety**

The presence of thujone in sage leaf preparations in the monograph is restricted to a daily intake of 6.0 mg/person.

Since this is not a new chemical, but a herbal preparation, a reduced safety factor is accepted based on the extensive traditional use of a variety of herbal sage leaf preparations 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, will provide a sufficient safety margin.

It is recommended that the amount of thujone in a preparation needs to be specified and that exposures in the range between 3 and 7 mg/day do not pose special concerns. The amount of dietary intake of 1 mg in average may not cause special concerns. However, for the upper limit of the additional intake from medicinal products, the highest safe amount was reduced by the possible intake by food, to give 6 mg as a limit of daily exposure (for further information please see the Public statement on the use of herbal medicinal products containing thujone EMA/HMPC/732886/2010 Rev.1).

For each of the herbal preparations included in the monograph, the available sources that provide evidence of period of use are shown. 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.

Products exceeding the recommended maximum thujone limit cannot be recommended for marketing without supplementary safety studies and a detailed benefit/risk assessment. The lack of adverse drug reactions indicates that thujone could be less neurotoxic than thought in the past. The potential danger of the substance is possibly overestimated because of the problems encountered with the consumption/misuse of liquors.

#### *Preparations with less than 6.0 mg thujone/day:*

Herbal medicinal products complying with the monograph must have a specification showing that the daily amount of thujone does not exceed the set limit with the approved posology.

#### *Preparations with more than 6.0 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.

Sage leaf can be recognised as safe when used in recommended dosages under specified conditions. If dose recommendations are followed in relation to camphor and the specified maximum limits of thujone content are kept, sage leaf should not be a safety concern in adults.

The maximum daily dose of 6.0 mg thujone/day is supposed to be divided according to listed posologies in the monograph. The content of thujone must be shown for every batch.

## **6. Overall conclusions (benefit-risk assessment)**

There are sufficient data available to develop a European Union monograph on the traditional use of sage leaf. Traditional use has shown that sage leaf can be recognised as safe when used in recommended dosages under the conditions specified in the monograph.

The clinical data cannot be considered to fulfil the criteria required for "well-established medicinal use" according to directive 2001/83/EC.

Traditional medicinal use of sage leaf has been found to fulfil the requirement of medicinal use for at least 30 years (15 years within the European Union) according to Directive 2004/24/EC for following indications:

- Traditional herbal medicinal product for relief of mild dyspeptic complaints such as heartburn and bloating.
- Traditional herbal medicinal product for relief of excessive sweating
- Traditional herbal medicinal product for relief of inflammations in the mouth or the throat
- Traditional herbal medicinal product for relief of minor skin inflammations.

Due to the lack of sufficient safety data the use of sage leaf cannot be recommended during pregnancy and breast-feeding.

As no safety data from the use in children and adolescents are available, the use of sage leaf is not recommended in children under 18 years of age. However, based on the long-standing medicinal use, a set limit for constituents with toxicological concern, as well as the absence of reports of serious adverse events, a sufficient degree of safety as necessary for traditional herbal medicinal products can be assumed.

In conclusion, preparations from sage leaf can be regarded as traditional herbal medicinal products.

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

Sage essential oil is characterised by high levels of thujone. Consumption of sage essential oil in single ingredient products involves a high risk of exceeding the maximum recommended daily intake of thujone (Public statement on the use of herbal medicinal products containing thujone (EMA/HMPC/732886/2010 Rev.1)). Thujone is toxic and may cause seizures at high doses as shown in animal studies and indicated from case reports. The available clinical and toxicological data on sage essential oil cannot be considered adequate to fulfil the criteria required for developing a European Union herbal monograph. For this reason, no monograph will be made on sage essential oil before supplementary information on clinical and toxicological data for sage essential oil are considered adequate to fulfil those criteria.

## **Annex**

### ***List of references***