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Committee on Herbal Medicinal Products (HMPC)

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

Draft - Revision

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Salvia officinalis* L., folium and *Salvia officinalis* L., aetheroleum
Herbal preparation(s)	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended *Salvia officinalis* L., folium; *Salvia officinalis* folium (sage leaf) i) Herbal substance Not applicable. ii) Herbal preparations a) Comminuted herbal substance. b) Liquid extract (DER 1:1), 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 (DER 38.25 : 61.75 m/m) g) Tincture (1:10) extraction solvent: ethanol 70% V/V h) Dry extract from fresh leaves (1:17-18), extraction solvent: ethanol 68 % V/V

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Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Salvia officinalis* L., folium and *Salvia officinalis* L., aetheroleum
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Comminuted herbal substance for infusion for oromucosal and 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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Note: This draft assessment report is published to support the public statement on *Salvia officinalis* L., aetheroleum and the public consultation of the draft revised European Union herbal monograph on *Salvia officinalis* L., folium. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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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 15 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., 2008).

Sage tincture produced from 1 part of comminuted sage leaf and 10 parts of ethanol (70% V/V) 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 fructicosa* Mill (Ph. Eur., 2008).

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 cineol 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), 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 (DER 38.25: 61.75 m/m)
Tincture (1:10) extraction solvent: ethanol 70% V/V
Dry extract from fresh leaves (1:17-18), extraction solvent: ethanol 68 % V/V

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

Vitamin(s): Not applicable

Constituents:

(Bradley, 2006)

Essential oil	Up to 3%	Monoterpenoids	-α-thujone -β-thujone -camphor -1,8-cineole	(10-60%) (4-36%) (5-20%) (1-15%)
		Sesquiterpenes	-α-humulene -β-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	
		6-feruloyl-glucose		
		A polyalcohol derivate of 6-feruloyl-glucose		
		Three hydroxycinnamic esters of disaccharides	-1-caffeoyl-(6`-apiosyl)-glucoside -free caffeic acid	
Phenolic diterpenes		Tricyclic diterpene ↓ (which readily auto-oxidises to) ↓ Lactones Phenolic diterpenes with lactone structures	-carnosic acid -carnosol -rosmanol -epirosmanol -7-methoxy-rosmanol -galdosol -safficinolide -sagequinone methide A	(0.35%)
		Sageone		
		Methyl carnosate		
Triterpenes		Pentacyclic triterpene acids	- ursolic acid -oleanolic acid	(up to 3.5%) (up to 0.4%)
		Triterpene alcohols	-α-amyrin -β-amyrin	(0.18%) (0.10%)
Flavonoids	About 1.1%	Flavones and their glycosides	- luteolin, its →7-glucoside →7-glucuronide, →3`-glucuronide →7- methyl ether -6-hydroxyluteolin, its →7-glucoside → 7-glucuronide -6 methoxyluteolin, its →7-methyl ether -apigenin, its →7-glucoside → 7-methyl ether (= genkwanin) -6-methoxy-apigenin (= hispidulin) its →7-methyl ether (=cirsimaritin)	

			-vicenin-2 (= apigenin 6.8-di-C-glucoside) -5-methoxy-salvigenin.	
Phenolic glycosides		A diverse range	-picein (4-hydroxy acetophenone glucoside) -4-hydroxy-acetophenone-4-(6-apiosyl)-glucoside -cis-p-coumaric acid 4-(2-apiosyl)-glucoside -trans-p-coumaric acid 4-(2-apiosyl)-glucoside -- -isolariciresinol 3-glucoside -1-hydroxy-pinoresinol 1-glucoside -caffeoyl-fructosyl glucoside-caffeoyl-apiosyl glucoside -others	
Polysaccharides Polysaccharides		Arabinogalactans High-MW pectin		
		Glucuronoxylan-related polysaccharides		
Other constituents		Benzoic acid derivates	-p-hydroxybenzoic acid -gentisic acid -syringic acid	
		Phytosterols	-β-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, α-pinene, camphene, limonene (Blumenthal *et al*., 2000), cirsiliol (Harborne *et al*., 1996), menthol and thymol (Grzunov *et al*., 1984).

Numerous articles concerning the compositions of *Salvia officinalis* L. and Salvia fructicosa Miller have been published regarding the composition of the 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 (Länger *et al*., 1996, with reference to Iconomou *et al*., 1982).

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 α-thujone and β-thujone decrease, while the amounts of camphor, α-pinene, camphene and borneol increase. However, the

sum of the contents of α-thujone, β-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*., 1980).

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

http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/afc_ej729_camphor_op_en.pdf?ssbinary=true)

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 10th 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
Austria			
Comminuted herbal substance	Inflammations in the mouth and throat	Herbal tea (infusion): 1 tea bag contains 2.5 g herbal substance. Adults, adolescents: 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. Adults, adolescents: 1 cup 3 x daily	05.2011 TUR
Dry extract of Salviae folium (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 Salviae folium (5-6:1, water); 50 mg Dexpanthenol Adults, adolescents, children 6-12: spray several times a day	01.2011 TUR
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 Adults, adolescents: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 Adults, adolescents: 3 x daily 3 puffs; 1 puff = 140 µl = 138 mg of finished product	12.2009 WEU
Crotatia			
Dry extract of Salviae folium (5-6:1,	Irritation of the oral mucosa	Oral solution: 1 g solution contains 10 mg dry extract of	06.2013.

Active substance	Indication	Pharmaceutical form	Regulatory Status
water); 50 mg Dexpanthenol		Salviae folium (5-6:1, water); 50 mg Dexpanthenol Adults, adolescents: spray a few times daily	TUR
Czech Republic			
Salviae officinalis folii tinctura 1 : 6.6, extraction solvent ethanol 60% (V/V)	Adults and elderly: 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
Germany			
1. Salviae officinalis folium	Symptomatic treatment of mild dyspeptic, complaints Rinsing and gargling for the symptomatic treatment of inflammations in the mouth or the throat. 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 for external use (rinsing and gargling): >12 years: 1-2 g/100 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 109a of the German Medicinal Products Act
2. Extract of Salviae officinalis folium (1:4-6), extraction solvent: liquor wine. ethanol 96% (38.25 : 61.75 m/m)	Symptomatic treatment of mild dyspeptic, complaints Oral use for relief of excessive sweating Rinsing and gargling for the symptomatic treatment of inflammations in the mouth or the throat	Liquid for internal use: >12 years: Single dose: 0.43 ml in warm water. Daily dose: 1.29 ml for external use >4 years: Average daily dose: 0.65 ml in 150 ml water for rinse or gargle several 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
3. Salviae officinalis folium, cut	Rinsing and gargling for the symptomatic treatment of inflammations	Herbal tea Adults:	At least since 1976, DE, TUR according to section 105 in

Active substance	Indication	Pharmaceutical form	Regulatory Status
	in the mouth or the throat	1 tea bag containing 2.5 g/100 ml boiling water 3 times daily No longer than 7 days	combination with section 109a of the German Medicinal Products Act
4. Dry extract of Salviae officinalis folium (4-7:1), extraction solvent: water	zur Linderung von vermehrter Schweißabsonderung Oral use for relief of excessive sweating	Coated tablet 80 mg Adults: 1-2 3 times daily No longer than 2 weeks	At least since 1976, DE, TUR according to Article 16a of Directive 2001/83/EC
			WEU
1. Extract of Salviae officinalis folium (1:4.5), extraction solvent: ethanol 50% (V/V)	Rinsing and gargling for the symptomatic treatment of inflammations in the mouth or the throat. Oral use for relief of excessive sweating.	Tincture for internal use: >12 years: 2 ml 3 times daily for external use (rinsing and gargling): >12 years: 5 ml every 2 hours for 1 minute No longer than 14 days	At least since 1976, DE, WEU
2. 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
3. Dry extract of Salviae officinalis folium (4-7:1), extraction solvent: water	Oral use for relief of excessive sweating.	Film-coated tablet 300 mg >12 years: 1 3 times daily No longer than 14 days	2002, DE, WEU

Active substance	Indication	Pharmaceutical form	Regulatory Status
Hungary			
Fluid extract of dried sage leaves (*Salvia officinalis* L. folium). (1:1, extraction solvent: ethanol 70 % (V/V))	For the local treatment of inflammations of the oral mucosa.	Oral mucosal gel. 1000 mg gel contains 200 mg sage fluid extract. 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.	1995-2013 registered "healing product" 2013 2013 TUR
Ireland			
Dry extract from fresh Sage (*Salvia officinalis* L.) leaves Extraction solvent: ethanol 68% v/v.	Relief of menopausal hot flushes and excessive perspiration,	Tablet Dry extract from fresh Sage (*Salvia officinalis* 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
The Netherlands			
Dry extract from fresh leaves (1:17-18), extraction solvent ethanol 68 % V/V.	Relief of excessive perspiration,	Tablet Dry extract from fresh Sage (*Salvia officinalis* 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
Poland			
Comminuted herbal substance	Mouth and throat inflammations.	Herbal tea (infusion): 1 tea sachet (= 1.3 g) contains: 1.3 g Salviae folium 2 sachets (2.6 g) as an infusion for external use	03.02.2010 TUR
Comminuted herbal substance	Mouth and throat inflammations.	Herbal tea (infusion): 100 g herbal tea contain: 100 g Salviae folium 6 g as an infusion for external use	02.2010 TUR
Salviae folii tinctura (1:5), extraction solvent: ethanol 70% (V/V)	Mouth and throat inflammations.	Oral liquid 100 ml concentrate contain: 100 ml Salviae folii tinctura (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	Herbal tea (infusion): 100 g herbal tea contain: 100 g Salviae folium External use:	12.2010 TUR

Active substance	Indication	Pharmaceutical form	Regulatory Status
	inflammatory states of skin. Orally: in mild gastrointestinal symptoms (bloating) and in hyperhidrosis.	2.5 g as an infusion for mouth wash 2.5 g as an infusion 2-4 times daily for compresses Oral use: 2 g 3 times daily in digestive disorders 2 g daily in hyperhidrosis	
Spain			
Dry extract from fresh *Salvia officinalis* L., folium; extraction solvent: ethanol 68 % .	Relief of menopausal hot flushes and excessive sweating.	Tablet Dry extract (1:17-18) from fresh *Salvia officinalis* L., folium; extraction solvent: ethanol 68 % (V/V) corresponding to 3400 mg of tincture. Adults: 1 tablet per day	03. 2014 TUR
Sweden			
Dry extract from *Salvia officinalis* L., (Sage) folium. Extraction solvent water	Temporarily exaggerated sweating	Capsule, hard Adults and elderly: 1 capsule 3 times daily. 1 capsule contains: 120 mg dry extract from *Salvia officinalis* L., (Sage) folium, corresponding to 500 – 800 mg of dried leaves of sage.	Since 1997 natural 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: Take 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 There is no relevant use in children and adolescents under 18 years of age.	03. 2010 TUR
Norway			
Dry extract from *Salvia officinalis* 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 *Salvia officinalis* 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.

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

Active substance	Indication	Pharmaceutical form	Regulatory Status
Czech Republic			
Salviae officinalis herba	a) For symptomatic treatment of mild dyspeptic, complaints such as heartburn and bloating b) For relief of excessive sweating c) For the symptomatic treatment of inflammations in the mouth or the throat	Herbal tea (infusion): 1 tea bag contains 1.5 g herbal substance indication a) 1 tea bag/250 ml of boiling water 3 times daily indication b) 2 tea bags/250 ml of boiling water 3 times daily indication c) 2 tea bags/250 ml of boiling water several times daily Duration of use: 2 weeks There is no relevant use in children and adolescents under 18 years of age.	On the market since 1997 04.2011 TUR
Latvia			
Oromucosal spray: 1 spray contains 40.32 mg of Salviae folium extractum fluidum (1:4-6, extraction solvent - ethanol 70%V/V), 40.32 mg of Thymi herbae extractum fluidum (1:4-6, extraction solvent: ethanol 70% V/V) Indication: Indications: 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)

Information on related herbal substances marketed medicinal products marketed in the EU/EEA

Germany			
Soft extract from fresh Salviae flos (2.2-2.7:1), extraction solvent: ethanol 68%	To improve general condition in physical and mental stress, to improve appetite	Oral liquid: 100 ml liquid contain: 102.04 g soft extract from fresh Salviae flos (2.2-2.7:1), extraction solvent: ethanol 68% Between 15 drops up to 5 ml 3 times daily	24.02.2011

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

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, and 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 17th 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. 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.

Medicinal use of *Salvia officinalis* L., folium in herbal teas and herbal preparations has been documented continuously in many pharmacognosy texts, handbooks and compendia. The following traditional uses and posologies have been recorded for Sage leaf:

Traditional use	Dosage	Method and Duration of Administration	Handbook Reference
External: Inflammations and infections of the mouth and throat (stomatitis, gingivitis, pharyngitis) Internal: Hyperhidrosis	Topical use: An infusion of 3 g of the drug in 150 ml of water as a mouthwash or gargle (1) Oral use: in hyperhidrosis: Tincture: (1:10) in 55% ethanol, 75 drops daily (2) Infusion 1-1.5 g of dried herb in 150 ml of water, once or several times daily (3) Dry extract : 160 mg of dry aqueous extract corresponding to 880 mg of drug three times daily (4)	Method: For oral administration or topical application Duration: In hyperhidrosis, treatment for 2-4 weeks is recommended, using a aqueous preparation	ESCOP Monographs (2003) (1) Reference source dated 1988, 2002 (2) Reference source dated 1988 (3) Reference source dated 1988, 2002 (4) Reference source dated 1989
Internal: Digestive disorders (dyspepsia, flatulence, poor digestion, bloating) To reduce excessive perspiration, e.g. in the menopause. As a gentle, stimulating tonic. External: Inflammations of the mouth or throat mucosa (pharyngitis, tonsillitis, stomatitis, gingivitis, glossitis)	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) Topical use: mouthwashes and gargles: 2.5 g of dried leaf to 100 ml of water as an infusion (3)	Method: Oral and topical administration Duration: No information	British Herbal Compendium, (Bradley, 2006) (1) Reference source dated 1983, 1985 (2) Reference source dated 1983, 2003 (3) Reference source dated 1985
External: As an antiphlogistic for inflammations of the mouth and throat and for gingivitis and stomatitis Internal: For digestive disturbances, flatulence, inflammations of the intestinal mucosa. Diarrhoea	Tea: Depending on the indication: Gargle: Pour boiling water over 3 g finely cut dried leaf. Steep for 10 minutes, strain (1) To treat night sweats: Prepare the tea like the previous, but let it cool before drinking (2) For gastrointestinal complaints: Pour boiling water over 1.5-2 g finely cut dried leaf. Steep for 5 min, strain (3) 1 teaspoon=about 1.5 g	Method: Oral and Topical Administration Duration: No information	Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004) (1) Wichtl, dated 2004 (2) Wichtl, dated 2004 (3) Wichtl, dated 2004

Traditional use	Dosage	Method and Duration of Administration	Handbook Reference
Internal: Digestive complaints with mild spasms in the gastrointestinal tract, feeling of distension, flatulence. excessive perspiration. External: Inflammations of the oral and pharyngeal mucosa	Unless otherwise prescribed, drink one cup of tea infusion 3-4 times daily, prepared as follows: Pour 150 ml boiling water over 1 teaspoonful (about 1.5g) of sage leafs, or over a corresponding amount in one or more teabags. Steep for about 10-15 minutes, strain (1) For use in the mouth and throat area, rinse or gargle with the tea infusion prepared as follows: Pour 100 ml boiling water over an exactly measured 11/2 teaspoonful (about 2.5g) of sage leaves. Steep for about 10-15 minutes, strain (2)	Method: Oral and Topical Administration Duration: In acute cases that last longer than one week or periodically reoccur, it is recommended to seek medical advice	Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004) with reference to The German Standard License, 1996 (1) dated 1996 (2) dated 1996
Internal: Digestive complaints excessive perspiration. External: Inflammations of the oral and pharyngeal mucosa	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) 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)	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 Duration: No information	Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004) with reference to The German Commission E monograph, 1990) (1) Dated 1990 (2) Dated 1990 (3) Source referred is Ergänzungsbuch zum Deutschen Arzneibuch, 1941 (4) Source referred is Ergänzungsbuch zum Deutschen Arzneibuch, 1941 (5) Dated 1990 (6) Dated 1990
Internal: Dyspeptic symptoms and excessive perspiration. External: For inflammations of the mucous membranes of nose and throat.	Internal: Dried leaf: 1-3 g, three times daily (2) Infusion: 1-3 g in 150 ml water, three times daily (3) Dry aqueous extract 5.5:1 (w/w): 0.18-0.36 g, three times daily (4) Fluidextract: 1.5-3 g (Erg.B. (6) (5) Essential oil: 0.1-0.3 ml. (7) Succus: Pressed juice of fresh plant in 25% alcoholic Preservation (8) External: Gargle or rinse: Use warm infusion. 2.5 g cut leaf in 100 ml water;	Method: Internal or External Administration Duration: No information	Herbal Medicine Expanded Comission E Monographs (Blumenthal, 2000) (1) Blumenthal dated 2000 (2) Blumenthal dated 2000 (3) Blumenthal dated 2000 (4) Blumenthal dated 2000 (5) Source referred is Ergänzungsbuch zum Deutschen Arzneibuch, 1941 (6) Blumenthal dated 2000 (7) Blumenthal dated 2000 (8) Blumenthal dated 2000

Traditional use	Dosage	Method and Duration of Administration	Handbook Reference
	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) Paint: Apply the undiluted alcoholic fluidextract to the affected area with a brush or swab (10)		(9)Blumenthal dated 2000 (10) Blumenthal dated 2000
Internal: Flatulent dyspepsia, Hyperhidrosis galactorrhoea External: Gargle, mouthwash (pharyngitis, uvulitis, stomatitis, gingivitis, glossitis)	Internal: Leaf: 1-4 g as an infusion three times daily; 4-6 g daily1 Liquid extract: 1-4 ml (1:1 in 45% alcohol) three times daily External: Gargle/ rinses : 2.5 g/100 ml water (3)	Method: Oral administration Duration: No information	Herbal Medicine, (Barnes et.al., 2002; 2007) (1)Reference source dated 1983,1998 (2) Reference source dated 1983 (3) Reference source dated 1998
Internal: Regulate perspiration (during menopause, nightsweat) Lactation inhibitation Gastrointestinal complaints External: Respiratory diseases and inflammations in mouth and throat	Ordinary dose: Internal: Tincture: 60 drops daily 30-50 drops several times a day Warm infusion: 2-3 spoonfuls (=3.4-5.1g) of the leaves	Method: Internal and external administration Duration: No information	Lehrbuch der Biologischen Heilmittel, Madaus 1938 (1) Source referred to is Krahn 1896 (2) Source referred to is Hager, year not specified
Internal For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating External For symptomatic treatment of inflammations in the mouth or the throat	Tincture (1:10), extraction solvent: ethanol 70% V/V tincture (1:10) 2.5-7.5 g daily, divided in 3 doses. 5-10 g (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.	Duration No information	This tincture and the ethanol percentage is specified as a seperate monograph in Ph. Eur 2008 and the Deutsches Arzneibuch 6. Ausgabe 1926. Spiritus dilutus is Ethanol 68-69% (V/V) = 60-61% (m/m). Information concerning this tincture is documented in earlier German Pharmacopeias (Ergänzungsbuch zum Deutschen Arzneibuch (Erg. B. 6. Stuttgart 1956, 1958

Traditional use	Dosage	Method and Duration of Administration	Handbook Reference
Internal For the relief of excessive perspiration	Dry extract from fresh leaves (1:17-18), extraction solvent ethanol 68 % V/V	Method: Oral administration Duration: No information	Sales lists 1974 Sweden 1976 Switzerland 1986 Denmark In tablets from 2005

The following herbal substances and herbal preparations have been on the European market for a period of 30 years and are proposed for the monograph on traditional use:

a) Comminuted herbal substance.

b) Liquid extract (1:1), ethanol 70% V/V

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

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

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

f) Liquid extract (1:7.2), extraction solvent: liquor wine: ethanol 96% V/V (38.25 : 61:75 m/m)

g) Tincture (1:10), extraction solvent: ethanol 70% V/V

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

Table 2: Overview of historical data

Herbal preparation	Documented use / traditional use	Pharmaceutical form	Reference
a) Comminuted herbal substance	For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating	For oral use as a tea preparation. 1-3 g 3 times daily	Since 1976 in Germany, reported as well-established use
		For oral use as a tea preparation 1-1.5 g 2-3 times daily	Since 1978 in Spain, reported as traditional use
	For treatment of minor skin inflammations	For topical use as an infusion or decoction in compresses: 2 spoons of herbal substance in one glass of water	Since 1978 in Poland, reported as traditional use
	For relief of excessive sweating	For oral use as a tea preparation 2 g in 160 ml water	Since 1976 in Germany, reported as well-established use
	For symptomatic treatment of inflammations in the mouth or the throat	For oromucosal use as a tea preparation 2.5 g in 100 ml water for gargle	Since 1976 in Germany reported as well-established use
b) Liquid extract (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 up to 5 times daily on affected regions, massage gently	Since 1976 in Germany reported as well-established use
c) Dry extract (4-7:1), extraction solvent: water	For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating	For oral use 320 mg divided in 3-4 doses	Since 1976 in Germany, reported as well-established use
d) Liquid extract (1:3.5-5), extraction solvent: ethanol 31.5% V/V	For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating	For oral use 10 drops* 3 times daily in some liquid	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	Since 1976 in Germany, reported as well-established use
e) Liquid extract (1:4-5) extraction solvent: ethanol 50% V/V	For relief of excessive sweating	For oral use 50 drops* (= 2 ml) 3 times daily	Since 1976 in Germany, reported as well-established use

Herbal preparation	Documented use / traditional use	Pharmaceutical form	Reference
f) Liquid extract (1:4-6), extraction solvent: liquor wine : ethanol 96% V/V (38.25 : 61.75 m/m)	For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating	For oral use Single dose: 0.43 ml in warm water. Daily dose: 1.29 ml	Since 1976 in Germany, reported as both traditional and well-established use
f) Liquid extract (1:4-6), extraction solvent: liquor wine : ethanol 96% V/V (38.25 : 61.75 m/m)	For symptomatic treatment of inflammations in the mouth or the throat	For oromucosal use average daily dose: 0.65 ml in 150 ml water for rinse or gargle several times daily.	Since 1976 in Germany, reported as well-established use
g) Tincture (1:10): ethanol 70% V/V	For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating	For oral use 2-3 ml three times daily	Ph. Eur monograph 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 1956, 1958.)
	For symptomatic treatment of inflammations in the mouth or the throat	For oromucosal use 3 spoons (15 ml) in a glass of water, rinse or gargle	
h) Dry extract from fresh leaves (1:17-18), extraction solvent ethanol 68 % V/V.	Relief of excessive perspiration	For oral use 1 tablet daily	Since 1974 in Sweden, 1976 Switzerland, 1986 Denmark In tablets from 2005

*1 drops equivalent to 0.05-0.1 ml

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. Incomplete safety and toxicity data from long-term studies makes limitations in the duration necessary is often the case for traditional herbal medicinal products, and the limits are chosen based on the harmonisation with duration of use for similar indications in other monographs. The duration of use is also restricted based on the type of indication that is intended and designed for use without the supervision of a medical practitioner.

The duration of use is limited as followed:

Duration of use

Indications 1) and 2)

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

Traditional herbal medicinal product for relief of excessive sweating.

Oral use

Sage preparations should not be taken for more than 2 weeks.

Indication 3)

Traditional herbal medicinal product for relief of inflammations in the mouth or the throat.

Oromucosal use.

Sage preparations should not be taken for more than 1 week.

Indication 4)

Traditional herbal medicinal product for relief of minor skin inflammations.

Cutaneous use.

The average duration of use is 2 weeks.

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

Sage leaf cannot be recommended for oral use in children and adolescents under 18 years of age due to lack of adequate data.

Table 3: Overview of evidence on period of medicinal use for herbal preparations included in the monograph

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted herbal substance as herbal tea for oral use.	Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic, complaints such as heartburn and bloating.	Comminuted herbal substance for tea preparation: 1-2 g herbal substance in boiling water three times daily.	Since 1976 in Germany, reported as well-established use Since 1978 in Spain, reported as traditional use
Comminuted herbal substance as herbal tea for oral use.	Traditional herbal medicinal product for relief of excessive sweating.	Comminuted herbal substance for tea preparation: 2 g herbal substance in 160 ml boiling water.	Since 1976 in Germany, reported as well-established use
Comminuted herbal substance (for preparation of an infusion) for oromucosal and cutaneous use.	Traditional herbal medicinal product for the symptomatic treatment 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.	Since 1976 in Germany reported as well-established use
Comminuted herbal substance (for preparation of an infusion) for oromucosal and cutaneous use.	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.	Since 1978 in Poland, reported as traditional use
Herbal preparations in solid or liquid dosage forms for oral use. Dry extract (4-7:1), extraction solvent: water	Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic, complaints such as heartburn and bloating.	Dry extract: 320 mg divided in 3-4 doses.	Since 1976 in Germany, reported as well-established use
Herbal preparations in solid or liquid dosage forms for oral use. Liquid extract (1:3.5-5), extraction solvent: ethanol 31.5% V/V	Traditional herbal medicinal product for relief of excessive sweating.	Liquid extract (1:3.5-5): 10-20 drops dissolved in liquid three times daily, for night sweat 1 hour directly before bedtime: 30 drops in liquid	Since 1976 in Germany, reported as well-established use
Herbal preparations in semi-solid dosage forms for cutaneous use. Liquid extract (1:1), ethanol 70% V/V	Traditional herbal medicinal product for the symptomatic treatment of inflammations in the mouth or the throat.	Gel 20% liquid extract (1:1), 250 mg of gel up to 5 times daily on affected regions and massage gently.	Ph. Eur monograph 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 1956, 1958.)

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Herbal preparations in solid or liquid dosage forms for oral use. Liquid extract (1:7.2), extraction solvent: liquor wine: ethanol 96% V/V (38.25 : 61:75 m/m)	Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic, complaints such as heartburn and bloating.	Liquid extract (1:7.2): 20 drops three times daily.	Since 1976 in Germany, reported as both traditional and well-established use
Herbal preparations in solid or liquid dosage forms for oral use. Liquid extract (1:4-5) extraction solvent: ethanol 50% V/V	Traditional herbal medicinal product for relief of excessive sweating.	Liquid extract (1:4-5): 50 drops (=2 ml) three times daily.	Since 1976 in Germany, reported as well-established use
Herbal preparations in solid or liquid dosage forms for oral use. Liquid extract (1:3.5-5), extraction solvent: ethanol 31.5% V/V	Traditional herbal medicinal product for the symptomatic treatment of inflammations in the mouth or the throat.	Liquid extract (1:3.5-5): 15 drops three times daily in warm water for gargle.	Since 1976 in Germany, reported as well-established use
Herbal preparations in solid or liquid dosage forms for oral use. Liquid extract (1:3.5-5), extraction solvent: ethanol 31.5% V/V	Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic, complaints such as heartburn and bloating.	Liquid extract (1:3.5-5): 10 drops three times daily in some liquid.	Since 1976 in Germany, reported as well-established use
Liquid or semi-solid preparations for oromucosal use. Liquid extract (1:7.2), extraction solvent: liquor wine : ethanol 96% V/V (38.25 : 61:75 m/m)	Traditional herbal medicinal product for the symptomatic treatment of inflammations in the mouth or the throat.	Liquid extract (1:7.2): 3 spoons (15 ml) in a glass of water rinse or gargle.	Since 1976 in Germany, reported as both traditional and well-established use
Herbal preparations in solid or liquid dosage forms for oral use. Tincture (1:10), extraction solvent: ethanol 70% V/V	Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic, complaints such as heartburn and bloating.	Tincture: 2-3 ml three times daily.	Ph. Eur monograph 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 1956, 1958.)

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Liquid or semi-solid preparations for oromucosal use. Tincture (1:10), extraction solvent: ethanol 70% V/V	Traditional herbal medicinal product for the symptomatic treatment of inflammations in the mouth or the throat.	Tincture: 1-2 spoons (5-10 ml) in a glass of water, rinse or gargle, undiluted tincture is applied locally on the affected regions.	Ph. Eur monograph 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 1956, 1958.)
Herbal preparations in solid or liquid dosage forms for oral use. Dry extract from fresh leaves (1:17-18), extraction solvent ethanol 68 % V/V	Traditional herbal medicinal product for relief of excessive perspiration	Dry extract: 3.4 g once daily.	Dry extract 1974 Sweden 1976 Switzerland 1986 Denmark Dry extract in tablets from 2005 51 mg

Assessors comment:

The herbal preparations mentioned above (table 3) fulfil all criteria for traditional herbal medicinal products.

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

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. A new herbal preparation is included in the revised monograph as a 'corresponding products' has shown 30 years on the market with relief of excessive sweating as the documented traditional usage according to new information.

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 has been attributed principally to the presence of thujones (Bradley, 2006; Newall et al., 1996), and drinking or gargling Sage leaf infusions thought to soothe a sore throat or gums, has also been ascribed to volatile compounds such as 1.8-Cineole, borneol, camphor, and thujones (Badie et al. 2012).

Data on antimicrobial effects are presented under 3.1.1 Primary pharmacodynamics.

3.1.1. Primary pharmacodynamics

Data on antibacterial, fungistatic , antiseptic and virustatic activity

Inhibitory activity of the oil against Gram-positive and Gram-negative bacteria and against a range of fungi has been demonstrated, such as Escherichia coli, Shigella sonnei, Salmonella species, Klebsiella ozanae (Gram-negative), Bacillus subtilis (Gram-positive), and fungi-species like 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 gelatin-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 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 µg/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 safficinolide and sagone.

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

Anti-inflammatory activity

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).

Human gingival fibroblasts (HGF-1) were treated with sage infusion or sage infusion fractions containing either its volatile components and water (aqueous distillate) or its dry matter for six hours 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-labeled internal standards revealed the presence of 1,8-cineole, borneol, camphor, and alpha-/beta-thujone in sage infusen 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 nonvolatile rosmarinic acid when applied in concentrations representative of sage infusion. Hence, the volatile compounds were found to be more effective than rosmarinic acid. 1,8-Cineole, borneol, camphor, alpha- and beta- thujone seems 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_{50} values of 106-140 µg/cm2. The main component of the chloroform extract and the major contributor to its anti-inflammatory activity was found to be ursolic acid (ID_{50} : 0.14 µM/cm2), which had twice the potency of indomethacin

(ID_{50} : 0.26 µM /cm2) in this test (ESCOP, 2003; Wichtl, 2004).

Oleanolic acid also showed anti-inflammatory activity but was less effective (ID_{50} : 0,36 µM/cm2) (ESCOP, 2003).

3.1.2. Secondary pharmacodynamics

The antitussive and immunomodulatory activities of pectin and hemicellulose polysaccharides orginated 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 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 BaCl2) 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, shows a weak spasmogenic action and induces an evident increase of the basal tone. An initial stimulating action, especially at the lowest doses, is also seen to be the case of linalyl acetate and limonene in sage essence. The constituents of the essence influence its action in relation to their concentration and a double spasmogenic-spasmolytic action appears sometimes in the sage essence (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 Ca2+(Taddei *et al*., 1988).

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_{50} : 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).

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 normoglyaemic, hypoglyaemic 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).

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 does not reveals which components of sage infusion are of particular antimutagenic potential.

Antimutagenic properties of terpenoid fractions of sage (*Salvia officinalis*) were tested by Vujosevic *et al*., 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 found after treatment with the 50 µL/kg concentration differed significantly.

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.

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).

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 cirsiliol have sedative and hypnotic effect *in vivo* (Marder *et al*., 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_{50} : 0,05 µM) the diterpene galdosol (IC_{50} : 0.8 µM) and the flavone hispidulin (IC_{50} :1.3 µM) were the most active; 7-methoxyrosmanol (IC_{50} : 7.2 µM) also exhibited strong affinity, while apigenin (IC_{50} : 30 µM) and cirsimaritin (IC_{50} : 350 µM) were considerably less active (Bradley, 2006).

3.1.3. Safety pharmacology

3.1.4. Pharmacodynamic interactions

3.1.5. Conclusions

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 (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_{50} for this herbal extract of *Salvia officinalis* L were found to be 0.8 mg/ml and the extent of inhibition was higher than 50%. In this small screening study, G. biloba, common valerian and St. John's wort were suggested as candidates for clinically significant CYP interactions *in vivo* (Hellum *et al*., 2007), whereas no conclusions can 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

Sage oil:

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_{50} 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 (Newall *et al*., 2002).

3.3.2. Repeat dose toxicity

Sage oil:

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 (EFSA 2008, with reference to Skramlik, 1959).

The levels of camphor in 25 different commercial sources of sage leaves varied from 7 to 50% (EFSA 2008, with reference to Lawrence (1998).

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 2008, accessible at:

http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/afc_ej729_camphor_op_en.pdf?ssbinary=true)

3.3.3. Genotoxicity

Herbal preparations of Salviae folium

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. 6th ed.) at doses up to 200 µl/plate showed no mutagenic activity in the Ames test using Salmonella typhimurium strains TA98 and TA 100 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).

Based on the available data for the tincture, the requirements for a list entry are not fulfilled.

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) three 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 2008, with reference to Stoner *et al*., 1973).

3.3.5. Reproductive and developmental toxicity

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 2008, with reference to NTP, 1992b).

3.3.6. Local tolerance

Not applicable

3.3.7. Other special studies

Not applicable

3.3.8. Conclusions

Pharmacodynamics

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

Indication 1) Traditional herbal medicinal product for relief of 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 show 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.

These indications are 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.

Pharmacokinetics

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

Toxicology

There is a lack of safety and toxicity data for the long-term effects, hence limitations in duration of use are recommended. 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 time of use and posology of sage leaf. The duration of human treatment is recommended limited for maximum 2 weeks.

No studies on reproductive toxicity or carcinogenity are available for *Salvia officinalis* L. There is no suspicion for a carcinogenic potential. Inclusion to the Community list of traditional herbal substances,

preparations and combinations thereof for use in traditional herbal medicinal products can not be recommended for any preparations.

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.

Specific data on pharmacokinetics and interactions are not available.

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.

Oral, cutaneous and oromucosal administration of Sage leaf can be regarded as safe at traditionally used doses with the exception of patients with severe renal or cardiac disease e.g. renal and heart failure.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

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

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 hyperhidriosis (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 ESCO 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 idiopatic 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, multicenter 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 (Bommer *et al*. 2011). These results support the traditional usage in menopausal hot flushes, as well as to alleviate associated menopausal symptoms.

Secretion-promoting effects

In folk medicine, sage is used to promote menstruation (unproven) (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 three 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 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 h 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.

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).

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).

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. According to this article there are no similar approved products available on the European market. No information about any marketing authorisation has been submitted from the member states. Switzerland is therefore assumed to be the first country to market this spray. The Swiss Agency for Therapeutic Products have the following product information on a spray for similar use available on their website www.swissmedic.ch (retrieved 2008-12-19):

Salviae extractum ethanolicum liquidum 150 mg, DER: 1:1, excipiens 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 max. 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 β-haemolytic streptococci, concomitant illness (rhinosinusitis, laryngitis, tracheitis, bronchitis, fever, wounds or other significant changes in the oral cave), unallowed comedication, 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): max. 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.

Assessors 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, 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. According to the information available there have not been any equivalent products available within the Community for at least 10 years. The period of time required for establishing a well-established medicinal use of herbal substance/herbal preparation must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

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. (S. officinalis) leaf extract in the treatment of hyperlipidemic type 2 diabetic patients. The efficacy and safety of taking S. 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 for72 h, 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 9.8percent of the final extract. The extract powder as the drug and toast powder as the placebo were separately filled into oral gelatin 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 S, Dabaghian FH 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 h for 2 months, capsules prepared as in Kianbakht S, Dabaghian FH 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).

4.1.2. 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, camphor hydroxylated 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 2008, with reference to Köppel *et al*., 1982) (Accessible at: http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/afc_ej729_camphor_op_en.pdf?ssbinary=true)

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)

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

In a randomised clinical study, 15 elderly patients treated with 60 drops/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 Community 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 Community 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

5.2. No data available regarding the herbal substance.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 min. 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 percent and 25 percent in petrolatum. Concordant patch test results (positive at concentrations of 10 percent and 25 percent) were most common with ginger (seven), nutmeg (five), and oregano (four); 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 percent: nutmeg (five), ginger and cayenne (four), curry, cumin, and cinnamon (three), turmeric, coriander, and sage (two), oregano (one), and basil and clove (zero). 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 percent 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 α- and β- 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).

Assessors 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

No data available. Use in children and adolescents under 18 years of age is not recommended because data are not sufficient and medical advice should be sought.

The oral use of sage is not recommended in children due to the lack of adequate data, and the presence of compounds (such as thujone and camphor) with neurotoxic effects.

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.

5.5.2. Contraindications

No data available.

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.

Drug interactions: No drug interactions are documented clinically. However, the potential for preparations of sage to interact with other medicines administered concurrently is the basis for giving this precautionary information about potential interactions. According to the available information, it is given as a precautionary advice that concomitant use of other GABA-acting medicinal products should

be avoided in thujone containing herbal medicines. The mechanism of neurotoxicity has been ascribed to the available information regarding α-thujone and its effect on the γ-aminobutyric acid (GABA) type A receptor. When the nerve impulses are inhibited, neurons fire to easily and it is known that this could potentially unbalance the brain's message delivery system causing a seizure or epileptic attack (Hold *et al*. 2000).

Assessors 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 result in a recommendation regarding the use of this medicinal product, can be useful. This also includes *in vivo* interaction results which are important for extrapolating an effect on a marker ('probe') substance such as α-thujone to other medicinal products having the same pharmacokinetic property as the marker.'

Other sources has also mentioned the hypoglycemic effects (Newall *et al*., 1996), but due to limited evidence from preclinical studies of hypoglycemic 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 contra-indicated during pregnancy and lactation (ESCOP 2003, Barnes *et al*., 2002, 2007). The volatile oil contains a high proportion of α- and β- 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).

Assessors 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.

5.5.6. 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, 1999; 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-spamatic 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-clinic 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).

Assessors 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 for a maximum duration of 2 weeks as no data were retrieved for more serious conditions that could alter the benefit/risk assessment. There is limited safety and toxicity data for the long-term effects, hence limitations in duration of use are recommended.

Since this is not a new chemical, but an 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 and the restricted duration of use will provide a sufficient safety margin. The amount of dietary intake of 1 mg in average may not cause special concerns. This exposure level is not a recommended daily intake proven safe. However, as serious side effects on the nervous system and the liver, remains to be shown in clinical studies and in traditional use, we consider that a precautionary approach is taken with a maximum thujone content of 6.0 mg/day and a duration of use of maximum 2 weeks. For each of these herbal preparations included in the monograph, the available sources that provide evidence of period of use are shown. Incomplete safety and toxicity data from long-term studies makes limitations in the duration necessary is often the case for traditional herbal medicinal products, and the limits are chosen based on the harmonisation with duration of use for similar indications in other monographs. The duration of use is also 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 overrated because of the problems encountered with the consumption/misuse of liquors. There are no side effects reported for the Salviae folium.

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 Community 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 Community) according to Directive 2004/24/EC for following indications:

1) Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating.
2) Traditional herbal medicinal product for relief of excessive sweating
3) Traditional herbal medicinal product for symptomatic treatment of inflammations in the mouth or the throat
4) 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 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. 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 Community 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