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ASSESSMENT REPORT ON
SALVIA OFFICINALIS L., FOLIUM AND
SALVIA OFFICINALIS L., AETHEROLEUM

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I. REGULATORY STATUS OVERVIEW¹

MA: Marketing Authorisation;

TRAD: Traditional Use Registration;

Other TRAD: Other national Traditional systems of registration;

Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments
Austria	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Belgium	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combinations
Bulgaria	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combinations
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No reply
Czech Republic	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Denmark	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Estonia	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No MA
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No reply
Germany	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No reply
Hungary	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No MA
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No reply
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combination
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combinations
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No reply
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No reply
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No MA
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No MA
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No MA
Norway	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Poland	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No MA
Romania	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No MA
Slovenia	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combinations
Sweden	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combination
United Kingdom	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combinations

¹ This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

II. ASSESSMENT REPORT

SALVIA OFFICINALIS L., FOLIUM and *SALVIA OFFICINALIS* L., AETHEROLEUM

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Salvia officinalis</i> L., folium ; [<i>Salvia officinalis</i> L., aetheroleum]
Herbal preparation(s)	Comminuted herbal substance. Liquid extract (1:1), ethanol 70% V/V Dry extract (4-7:1), extraction solvent: water Liquid extract (1:3.5-5), extraction solvent: ethanol 31.5% V/V Liquid extract (1:4-5) extraction solvent: ethanol 50% V/V Liquid extract (1:7.2), extraction solvent: liquor wine : ethanol 96% V/V (38.25 : 61.75 m/m) Tincture (1:10) extraction solvent: ethanol 70% V/V
Pharmaceutical forms	Herbal substance as herbal tea for oral and topical use. Herbal preparations in liquid or solid dosage forms for oral use. Liquid or semi-solid preparations for oromucosal use.
Rapporteur	Gro Anita Fossum
Assessors	Karl Egil Malterud Anne-Cecilie Østensvig

II.1 INTRODUCTION

II.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 fruticosa* 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 (1:1), ethanol 70% V/V

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

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

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

Liquid extract (1:7.2), extraction solvent: liquor wine : ethanol 96% V/V (38.25 : 61.75 m/m)

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

Combinations of herbal substance(s) and/or herbal preparation(s) *Salvia officinalis* L. is used in combinations with many other herbal substances/herbal preparations. Combination products in member states consists of *Salvia officinalis* L. in combination with:

<i>Bellidis flos</i>	<i>Foeniculi fructus</i>	<i>Cardui mariae herba</i>	<i>Melissae folium</i>
<i>Herba Viola arvensis</i>	<i>Thymi herba</i>	<i>Carvi fructus</i>	<i>Coriandri fructus</i>
<i>Fructus juniperi</i>	<i>Menthae piperitae folium</i>	<i>Berberidis radix</i>	<i>Alchemillae acutifoliae herba</i>
<i>Folium juglandis</i>	<i>Chelidonii herba</i>	<i>Millefolii herba</i>	<i>Hyperici herba</i>
<i>Betulae folium</i>	<i>Curcumae xanthorizae rhizoma</i>	<i>Chamomillae anthodium</i>	<i>Foeniculi fructus</i>
<i>Tiliae flos</i>	<i>Melissae herba</i>	<i>Graminis rhizoma</i>	<i>Salicis cortex</i>
<i>Sambuci flos</i>	<i>Urticae folium</i>	<i>Equseti herba</i>	<i>Urticae radix</i>
<i>Chamomillae flos</i>	<i>Agrimoniae herba</i>	<i>Rosmarini folium</i>	<i>Uvae ursi folium</i>
<i>Anisi fructus</i>	<i>Frangulae cortex</i>	<i>Millefolli herba</i>	
<i>Taraxaci radix cum herba</i>	<i>Cichorii radix</i>	<i>Cucurbitae semen</i>	

This monograph refers exclusively to products containing only *Salvia officinalis* L..

Vitamin(s): Not applicable

Mineral(s):

The contents of sodium, potassium, magnesium, calcium, iron, manganese, zinc and copper have been determined in dry sage leaves, and the kinetics of extraction of these metals have been studied with cold water, hot water, 0.05 M and 0.01 M citric acid solutions, 0.1 M ascorbic acid and 70% ethanol by Zimna et al., (1984). The leaves have been found to be very rich in iron and magnesium especially. The total contents of the eight elements were determined in a commercial specimen of sage leaves and in sage leaves collected in the Garden of Medicinal Plants at the Medical Academy in Gdansk in Poland. The results were :

Sodium (Na)	91 ppm
Potassium (K)	14.9 g/kg
Magnesium (Mg)	4.1 g/kg
Calcium (Ca)	10.1 g/kg
Iron (Fe)	885 ppm
Manganese (Mn)	52.7 ppm
Zink (Zn)	145 ppm
Copper (Cu)	6.9 ppm

(ppm = parts per million. 1 ppm = 0.0001%)

Zimna et al. (1984) also specified the quantities of the metals present in a decoction prepared under usual conditions: a glass (= 250 ml) of hot water poured onto 10 g of dried leaves and set aside for 30 minutes. According to Zimna et al. (1984) the decoction contains about:

Sodium (Na)	1 mg
Potassium (K)	190 mg
Magnesium (Mg)	32 mg
Calcium (Ca)	57 mg
Iron (Fe)	0.05 mg
Manganese (Mn)	0.6 mg
Zink (Zn)	0.16 mg
Copper (Cu)	0.02 mg

II.1.2 Specified products on the market in the European Member States

European Member State	Specified products on the market
Austria	<ol style="list-style-type: none"> 1. Dry extract (4-7:1), extraction solvent: water, capsules 1 capsule contains 150 mg extract corresponding to 0.6 g Leaves, min. 2.5% rosmarinic acid 2. Liquid extract 1:1, extraction solvent ethanol 70% 3. Herbal substance as herbal tea (oral use, oromucosal use) 4. Liquid extract, extraction solvent water, min 0.2% rosmarinic acid
Estonia	Herbal substance, as herbal tea (oral use)
Germany	<ol style="list-style-type: none"> 1. Dry extract (4-7:1), extraction solvent: water (oral use, oromucosal use) 2. Liquid extract (1:7.2), extraction solvent: liquor wine : ethanol 96% V/V (38.25 : 61:75 m/m) (oral use, oromucosal use) 3. Dry extract (4-7:1), extraction solvent: water (oral use) 4. Liquid extract (1:3.5-5), extraction solvent: ethanol 31.5% V/V 5. Liquid extract (1:1), extraction solvent: ethanol 70% V/V (oromucosal gel) 6. Liquid extract (1:4-5) extraction solvent: ethanol 50% V/V 7. Herbal substance, cut 8. Liquid extract (1:7.2), extraction solvent: liquor wine : ethanol 96% V/V (38.25 : 61:75 m/m)
Hungary	<ol style="list-style-type: none"> 1. Liquid extract (1:1), extraction solvent: ethanol 20% (V/V) (cutaneous use) 2. 2) Liquid extract (1:1), ethanol 70% V/V , (oromucosal gel)
Latvia	1) Herbal substance (oromucosal use)
Norway	1) Dry extract (4-7:1), extraction solvent: water (capsules) 1 capsule contains 150 mg extract corresponding to 0.6 g leaves
Poland	<ol style="list-style-type: none"> 1. Herbal substance (oral use, oromucosal use, cutaneous use) 2. Liquid extract (1:1), extraction solvent: ethanol 70% V/V , (oromucosal use) 3. Tinctura Salviae - (1:5), extraction solvent – ethanol 70% (v/v) (oromucosal use) 4. Salviae unguentum - Salviae folii extractum (cutaneous use)
Romania	1. Herbal substance (oral use, oromucosal use)
Slovenia	1. Dry extract (4.5-6.5:1), extraction solvent: water, lozenge
Spain	<ol style="list-style-type: none"> 1. Herbal substance (for tea preparation) 2. Herbal substance (capsules) 3. Tincture (1:10) extraction solvent: ethanol 55 % V/V
Sweden	1. Dry extract (4-7:1), extraction solvent: water, capsules 1 capsule contains 150 mg extract corresponding to 0.6 g leaves

Brand names have been deleted. This table is based on information provided by the National Competent Authorities.

II.1.3 Search and assessment methodology

- Databases assessed (date, search terms) and other sources used

The following electronic databases were searched on 16th of June 2008 with the search term “*Salvia officinalis*, *Salvia officinalis folium* OR Garden Sage OR Dalmatian Sage OR True Sage”.

Results:

PubMed:

Salvia officinalis: 239 references

Salvia officinalis folium: 4 references (No case report of safety concern)

Garden Sage: 10 references (No case report of safety concern)

Dalmatian Sage: 3 references (One case report of safety concern)

True Sage: 25 references (No case report of safety concern)

Toxline:

Salvia officinalis: 101 references

Salvia officinalis folium: 3 references (No case report of safety concern)

Garden Sage: 7 references (No case report of safety concern)

Dalmatian Sage: 10 references (One case report of safety concern)

True Sage: 4 references (No case report of safety concern)

Scifinder:

Salvia officinalis: 3430 references

Salvia officinalis folium: 37 references (No case report of safety concern when phrase “toxicity” and “safety” were combined)

Garden Sage: 2045 references (Several case reports of safety concern -animal studies)

Dalmatian Sage: 78 references (No case report of safety concern when phrase “toxicity” and “safety” were combined)

True Sage: 388 references (No case report of safety concern when phrase “toxicity” and “safety” were combined)

Assessors comment: Since this database covers both chemical abstracts and Medline, some references may be cited twice

The Cochrane Library:

Salvia officinalis: 4 references

Salvia officinalis folium: 1 reference

Garden Sage: 0 references

Dalmatian Sage: 0 references

True Sage: 5 references

This report is based on a scientific review of the scientific and traditional literature referring to *Salvia officinalis* L.

Available handbooks have been searched for relevant references and information. Bibliographic searches have been done after the same procedure as described for the bibliographic review of safety data.

II.2 HISTORICAL DATA ON MEDICINAL USE

II.2.1 Information on period of medicinal use in the Community

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. Pharmacognostical handbooks describe that traditionally, sage has been 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.

II.2.2 Information on traditional/current indications and specified substances/preparations

II.2.3 Specified strength/posology/route of administration/duration of use for relevant preparations and indications

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

Posology and indications for traditional herbal substance and preparations of *Salvia officinalis* L. folium

Herbal substance/ Herbal preparations	Indication	Posology	Single dose	Daily dose	On the market
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	1-3 g	3-9 g	Since 1976 in Germany, reported as well-established use
		For oral use as a tea preparation 1-1.5 g 2-3 times daily	1 - 1.5 g	2-5 g	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	2 spoons	2 spoons	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	2 g	2 g	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	2.5 g	2.5 g	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	250 mg	1250 mg	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	For oral use 320 mg divided in 3-4 doses	80-106 mg	320 mg	Since 1976 in Germany, reported as well-established use

	such as heartburn and bloating				
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	10 drops	30 drops	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	10-20 drops 30 drops	30-60 drops 30 drops	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	50 drops	150 drops	Since 1976 in Germany, reported as well-established use
f) Liquid extract (1:7.2), 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 20 drops 3 times daily	20 drops	60 drops	Since 1976 in Germany, reported as both traditional and well-established use
	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			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	2-3 ml	6-9 ml	Ph. Eur monograph Deutsches Arzneibuch 6. Ausgabe 1926. Spiritus dilutus is Ethanol 68-69% (V/V) = 60-

	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			61% (m/m). German Pharmacopeias (Ergänzungsbuch zum Deutschen Arzneibuch (Erg. B. 6. Stuttgart 1956, 1958.)
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Assessors comment:

There is a lack of safety and toxicity data for the long-term effects, hence limitations in the duration of use are recommended.

Furthermore, in order to harmonize with similar indications in other monographs, the duration of use is limited as followed:

Oromucosal use: Not more than 1 week

Oral use: Not more than 2 weeks

II.3 OVERVIEW OF AVAILABLE PHARMACOLOGICAL DATA REGARDING THE HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) AND RELEVANT CONSTITUENTS THEREOF

II.3.1 Composition

Constituents:

(Bradley, 2006)

Essential oil	Up to 3%	Monoterpenoids	- <i>α</i> -thujone - <i>β</i> -thujone -camphor -1,8-cineole	(10-60%) (4-36%) (5-20%) (1-15%)
		Sesquiterpenes	- <i>α</i> -humulene - <i>β</i> -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	- <i>carnosic acid</i>	(0.35%)
		Phenolic diterpenes with lactone structures	- <i>rosmanol</i> - <i>epirosmanol</i> - <i>7-methoxy-rosmanol</i> - <i>galdosol</i> - <i>safficinolide</i> - <i>sagequinone methide A</i>	
		Sageone		
		Methyl carnosate		
Triterpenes		Pentacyclic triterpene acids	- <i>ursolic acid</i> - <i>oleanolic acid</i>	(up to 3.5%) (up to 0.4%)
		Triterpene alcohols	- <i>α-amyrin</i> - <i>β-amyrin</i>	(0.18%) (0.10%)
Flavonoids	About 1.1%	Flavones and their glycosides	- <i>luteolin</i> , its →7-glucoside →7-glucuronide, →3'-glucuronide →7-methyl ether - <i>6-hydroxyluteolin</i> , its →7-glucoside →7-glucuronide - <i>6-methoxyluteolin</i> , its →7-methyl ether - <i>apigenin</i> , its →7-glucoside →7-methyl ether (= genkwanin) - <i>6-methoxyapigenin</i> (= hispidulin) its →7-methyl ether (=cirsimaritin) - <i>vicenin-2</i> (= apigenin 6,8-di-C-glucoside) - <i>5-methoxysalvigenin</i> .	
Phenolic glycosides		A diverse range	- <i>picein</i> (4-hydroxy acetophenone glucoside) - <i>4-hydroxy-</i>	

			<i>acetophenone-4-(6-apiosyl)-glucoside</i> <i>-cis-p-coumaric acid 4-(2-apiosyl)-glucoside</i> <i>-trans-p-coumaric acid 4-(2-apiosyl)-glucoside --</i> <i>-isolariciresinol 3-glucoside</i> <i>-1-hydroxy-pinoresinol 1-glucoside</i> <i>-caffeoyl-fructosyl glucoside-caffeoyl-apiosyl glucoside</i> <i>-others</i>	
Polysaccharides		Arabinogalactans		
		High-MW pectin		
		Glucuronoxylan-related polysaccharides		
Other constituents		Benzoic acid derivates	<i>-p-hydroxybenzoic acid</i> <i>-gentisic acid</i> <i>-syringic acid</i>	
		Phytosterols	<i>-β-sitosterol</i> <i>-stigmasterol</i>	(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 fruticosa* 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 fertilizers 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 an 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 (1*R*, 4*R*)-enantiomer (*d*-camphor) characterizes 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.

According to information from handbooks, *Salvia officinalis* L., folium is often used as an infusion in dosages ranging from 1 to 9 g daily. As pointed out by Bradley, 2006, sage contains up to 3% essential oil. The essential oil consists of 10-60% α -thujone, 4-36% β -thujone and 5-20% camphor. Using the results from the study of Langer et al; 1996 (with reference to Diploma thesis by Harrer, 1993), for the daily dosage of sage leaf (1-9 g), the amount of thujone and camphor can be calculated as follows:

Amount of <i>Salvia officinalis</i> folium daily (between 1-9 g)	Amount of essential oil (up to 3%)	Amount of β -thujone (between 4-36%)	Amount of α -thujone (between 10-60%)	Total amount of thujone (α - and β) extracted from 150 ml hot water (17.6%)	Amount of camphor (between 5-20%)	Total amount of camphor extracted from 150 ml hot water (35.4%)
1g	3% = <u>30 mg</u>	4% = <u>1.2 mg</u>	10% = <u>3 mg</u>	17.6% = <u>0.7 mg</u>	5% = <u>1.5 mg</u>	35.4% = <u>0.53 mg</u>
		36% = <u>10.8 mg</u>	60% = <u>18 mg</u>	17.6% = <u>5.0 mg</u>	20% = <u>6 mg</u>	35.4% = <u>2.1 mg</u>
9g	3% = <u>270 mg</u>	4% = <u>10.8 mg</u>	10% = <u>27.0 mg</u>	17.6% = <u>6.7 mg</u>	5% = <u>13.5mg</u>	35.4% = <u>4.77 mg</u>
		36% = <u>97.2 mg</u>	60% = <u>162 mg</u>	17.6% = <u>45.6 mg</u>	20% = <u>54 mg</u>	35.4% = <u>19.1 mg</u>

These results show that the amount extracted varies according to the wide range of thujone-and camphor content in the essential oil. In 1 g and 9 g sage leaf containing 3% essential oil, the extraction amount of thujone will theoretically vary between 0.7-5.0 mg, and 6.7-45.6 mg with an extraction efficiency of 17.6%.

Assessor's comment:

Based on these calculations and data from one unpublished study, we have limited the posology to 6 g *Salvia officinalis* L., folium daily, a lower daily dose than used traditionally.

II.3.2 Non-clinical pharmacology

Antibacterial, fungistatic, antiseptic and virustatic effects

Sage oil has antimicrobial properties, attributed principally to the presence of thujones (Bradley, 2006; Newall et al., 1996).

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.

From a study by Viuda-Martos et al. (2008) on the effectiveness of the essential oils from oregano (*Origanum vulgare*), thyme (*Thymus vulgaris*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), cumin (*Cuminum cyminum*) and clove (*Syzygium aromaticum*) on the growth of some bacteria commonly used in the food industry, it could be concluded that these essential oils possess *in vitro*, antibacterial activity against *Lactobacillus curvatus*, *Lactobacillus sakei*, *Staphylococcus carnosus*, *Staphylococcus xylosus*, *Enterobacter. gergoviae* and *Enterobacter amnigenus*. The effects of thyme, rosemary and sage essential oils are dose-dependent.

The antibacterial efficiency of essential oils is diminished when they are added to more complex materials (such as food products). This must be taken into account when essential oils are applied as antibacterials in foods.

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 (ESCOV, 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).

Antioxidant effects

In a study performed by Chang et al. 1977, a decrease in the rate of formation of peroxides was used as a measurement of the antioxidant activity of rosemary and sage extracts. The antioxidant activity of the purified antioxidant prepared from sage was shown to be comparable to that of rosemary. It appeared that the rosemary extract is as effective as the commercial antioxidant Tenox VI (Tenox VI is a mixture of BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), propyl galate, and citric acid) when used in animal fat and is superior to Tenox VI in vegetable oils. The antioxidants also appeared to be able to improve the flavour stability of soybean oil, as well as the flavour stability of potato chips.

The antioxidant activity of six isolated compounds (1-*O*-(2,3,4-trihydroxy-3-methyl) butyl-6-*O*-feruloyl- β -D-glucopyranoside, ethyl β -D-glucopyranosyl tuberonate, *p*-hydroxybenzoic acid, (-)-hydroxyjasmonic acid, caffeic acid, and 4-hydroxyacetophenone 4-*O*-[5-*O*-(3,5-dimethoxy-4-hydroxybenzoyl)- β -D-apiofrunosyl]- β -D-glucopyranoside; all isolated from the *n*-butanol-soluble fraction of sage leaf extracts was tested in a study by Wang et al. (2000). At the concentration of 30 µM, all of the compounds showed DPPH (radical 2,2-diphenylpicrylhydrazyl) radical scavenging activity. Caffeic acid was the most active compound. According to Bradley (2006) the antioxidant activity is attributable to hydroxycinnamic acid derivatives, notably rosmarinic acid. The antioxidant activity of the carnosol and carnosic acid is also mentioned by EFSA (2008).

The antioxidant activity of eight aromatic herbs was assessed by the b-carotene bleaching test (diffusion and spectrophotometric methods) by Dapkevicius et al. (1998). Thyme and sage acetone oleoresins

showed high antioxidant activity in the tests performed and were regarded as promising sources of natural antioxidants.

Lipid peroxidation in both enzyme-dependent and enzyme-independent test systems was inhibited more effectively by a dry 50%-methanolic extract from aerial parts of sage leaf than by α -tocopheryl acid succinate (as a positive control). The antioxidant activity was attributed mainly to phenolic compounds, rosmarinic acid being the main contributor due to its high concentration in the main extract (Bradley, 2006).

Two phenolic glycosides isolated from sage leaf, 6-O-caffeoyl- β -D-fructofuranosyl-(2 \rightarrow 1)- α -D-glucopyranoside and 1-O-caffeoyl- β -D-apiofuranosyl-(1 \rightarrow 6)- β -D-Glucopyranoside, were found to have moderate antioxidant activity in the DPPH and metmyoglobin test (ES COP 2003)

Aqueous methanolic extracts of 9 spices were investigated for their phenolic compounds composition and antioxidant properties, amongst them *Salvia officinalis* L. The extract of sage (not specified to only concern folium) showed in the applied *in vitro* test system better antioxidant properties than ascorbic acid which was used as a control (Muchuweti et al., 2007).

To study the phytosterol components of *Salvia officinalis* L. infusion (sage tea) and its antioxidant and hypocholesterolemic function, rats were divided into 4 groups; normal control group I, Group II, in which animals were fed on normal diet and received sage tea in a dose of 35 mg/kg bw/day. Group III, where rats were maintained on high cholesterol diet for 4 wk. Group IV, in which rats were maintained on high cholesterol diet while receiving sage tea in a dose of 35 mg/kg bw/day for 4 wk. Blood plasma transaminases, cholesterol, triglycerides, LDL, and lipid peroxides, liver GSH, and its related enzymes, glutathione-S-transferase (GST) and glutathione reductase (GR) activities were measured to study biosafety of sage and its protective effect against hypercholesterolemia. Treatment with sage tea resulted in a significant decrease in total cholesterol, triglycerides, LDL, and lipid peroxides of rats maintained on high cholesterol diet, (Group IV) compared to group III. The present study showed no toxicity to the liver and no adverse effects on growth parameters in rats. It also showed positive effects on the antioxidant status of the liver, mainly the GSH, GST, and GR activities of the rat livers. It was concluded that, phytosterols (β -sitosterol and stigmasterol) in sage tea act as an antioxidant and exert protective effect against hypercholesterolemia (El-Desouki et al., 2007).

Anti-inflammatory/ Antiphlogistic activity effects

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 ID₅₀ values of 106-140 μ g/cm². The main component of the chloroform extract and the major contributor to its anti-inflammatory activity was found to be ursolic acid (ID₅₀ : 0.14 μ M/cm²), which had twice the potency of indomethacin (ID₅₀ : 0.26 μ M/cm²) in this test (ES COP, 2003; Wichtl, 2004).

Oleanolic acid also showed anti-inflammatory activity but was less effective (ID₅₀ : 0,36 μ M/cm²) (ES COP, 2003).

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).

The antitussive and immunomodulatory activities of pectin and hemicellulose polysaccharides originated from sage was shown in a study performed by Sutovska et al. (2007). Sage polysaccharide complex A significantly decreased the number of the cough efforts (NE) and the intensity of inspiratory and expiratory cough attacks (IA⁻ and IA⁺) of mechanically – induced cough reflex from both,

laryngopharyngeal and tracheobronchial areas of airways, without any side effects in non-anaesthetized 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) (IC₅₀: 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 anaesthetized cats and CNS-depressant action (prolonged barbiturate sleep) in anaesthetized 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 normoglycaemic, hypoglycaemic and in alloxan-diabetic rabbits was observed, although no change in insulin concentrations was noted (Newall et al., 1996). Common sage is said to have mild blood-sugar lowering action but this is unproven (Wichtl, 2004).

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 do not reveal which components of sage infusion are of particular antimutagenic potential.

Antimutagenic properties of terpenoid fractions of sage (*Salvia officinalis*) were tested by Vujosevic 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 (IC₅₀ : 0,05 µM) the diterpene galdosol (IC₅₀ : 0.8 µM) and the flavone hispidulin (IC₅₀ :1.3 µM) were the most active; 7- methoxyrosmanol (IC₅₀ : 7.2 µM) also exhibited strong affinity, while apigenin (IC₅₀ : 30 µM) and cirsimaritin (IC₅₀ : 350 µM) were considerably less active (Bradley, 2006).

II.3.3 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 the commercial herbal medicinal product, Nosweat®, was assessed *in vitro* for its inhibitory potential on isolated human CYP2D6-mediated dextromethorphan metabolism. IC₅₀ for *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.

In vivo experiments

Thujone:

In mice treated intraperitoneally with α -thujone, the brain levels of α -thujone and 7-hydroxy- α -thujone were dose- and time dependent, but α -thujone appeared at much lower levels and was less persistent than 7-hydroxy- α -thujone. The latter compound is less toxic to mice; at 50 mg/kg administered intraperitoneally, α -thujone was less lethal but 7-hydroxyl- α -thujone and other metabolites were not lethal (ESCOP, 2003).

α -Thujone is metabolized by cytochrome P450 to form at least three monohydroxylated derivatives, which are detected by GC-CI-MS in the brain of thujone-treated mice (Hold et al., 2000).

After oral administration to male rabbits of a mixture of α - and β -thujone (ratio 9:2) at a dose level of about 650-800 mg/kg bw, two neutral urinary metabolites were identified as 3- β -hydroxy- α -thujane and 3- β -hydroxy- β -thujane indicating that the reduction was stereo-specific in spite of the different configurations of the methyl group (Scientific Committee on Food, 2003 with reference to Ishida et al., 1989).

Camphor:

Camphor is easily absorbed in the gastrointestinal tract. In rabbits, orally administered *d*- and *l*-camphor were shown to be oxidized to 5-*endo*-hydroxycamphor and 3-*endo*hydroxycamphor, the former predominating in each case. A reduction to borneol was also observed to some extent (EFSA, 2008 with reference to Robertson and Hussain, 1969).

In dogs, the major hydroxylation products of *d*- and *l*-camphor detected in urine after extraction and hydrolysis were 5-*endo* and 5-*exo*hydroxycamphor, and probably the *endo*-stereoisomer of 3-hydroxycamphor. *In vitro* studies with liver preparations from rats and rabbits demonstrated these reactions to occur in liver microsomes. A small amount of 2,5-bornanedione was also formed in liver microsomes. The 5-keto group of 2,5-bornanedione was reduced in liver cytosol, and there was interconversion between the *endo*- and the *exo*isomers of 5-hydroxycamphor in the presence of both microsomes and cytosol, but this interconversion could not account for the production of both 5-hydroxy isomers from camphor in liver microsomes. The 2-keto group of *d*-camphor underwent no detectable reduction in rat liver preparations; *l*-camphor was reduced to a small extent. However, rabbit liver cytosol mediated a vigorous stereo specific *endo*-reduction of *d*-camphor to borneol; a small amount (1%) of isoborneol was also formed (EFSA, 2008 with reference to Leibman and Ortiz, 1973).

II.3.4 Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Acute and repeated dose toxicity

Sage oil:

An experimental study of the toxic properties of commercialized essential oil of sage has revealed that the convulsant action was of central nervous system origin in unanaesthetized 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 LD₅₀ 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).

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).

Thujone:

α -Thujone, which is more toxic than β -thujone and is present as a higher proportion of the essential oil, is a convulsant. Its intraperitoneal LD₅₀ in mice is about 45 mg/kg, while 60 mg/kg causes a tonic convulsion leading to death within 1 minute (ESCOP, 2003; Bradley, 2006), whereas at 30-45 mg/kg mice either die or recover (ESCOP, 2003). The mechanism of α -thujone neurotoxicity has been shown to be a modulation of the γ -aminobutyric acid (GABA) type A receptor (Scientific Committee on Food 2003, with reference to Meschler & Howlett, 1999, Höld et al., 2000). Observations suggest that α -thujone acts as a GABA-gated chloride channel blocker; the poisoning signs are similar to those of picrotoxin (Scientific Committee on Food 2003, with reference to Hold et al., 2000).

However, α -thujone is rapidly detoxified in mice by conversion to less toxic metabolites (ESCOP, 2003; Bradley, 2006).

Suggestions that thujone activates the CB1 cannabinoid receptor, based on structural similarities of thujone enol to tetrahydrocannabinol, have not been supported experimentally (Scientific Committee on Food 2003, with reference to Meschler & Howlett, 1999).

Subcutaneous LD₅₀ values in mice were determined as 87.5 mg/kg body weight (bw) for α -thujone and 442.4 mg/kg for β -thujone, thus α -thujone present in a higher proportion of the essential oil, is more toxic than β -thujone.

The oral LD₅₀ of α - and β thujone (+) in rats was found to be 192 mg/kg and 500 mg/kg bw, respectively (Scientific Committee on Food 2003, with reference to Margaria, 1963). In subchronic toxicity tests in rats, thujone ($\alpha + \beta$) given orally to rats at 10 mg/kg daily produced convulsions in only 1 out of 20 animals by the 38th day (ESCOP, 2003).

Thujone is much more acutely toxic after parenteral administration and the intravenous LD₅₀ in the rabbit is stated to be 0.031 mg/kg bw (Scientific Committee on Food 2003, with reference to NLM, 1997)

In rats, i.p. injections of thujone induced electro-cortical seizures associated with myoclonic activity and the convulsant and lethal effects occurred at similar doses of 0.2 ml/kg bw. Thujone was administered to rats by gavage at doses of 12.5, 25 or 50 mg/kg bw/day on five days per week for 13 weeks. There was an increased lethality of 60% in females and 37% in males at the top dose level. The NOEL (No-Observed Adverse-Effect Level) for convulsions in the males was 12.5 mg/kg bw but no NOEL could be established in females in this study (Scientific Committee on Food 2003, with reference to Surber, 1962).

In a further study, thujone was administered to rats by gavage at doses of 0, 5, 10 or 20 mg/kg bw/day 6 times per week for 14 weeks. There were 3 deaths in females and 1 in males associated with convulsions at the top dose level. The NOEL for convulsions was reported to be 10 mg/kg bw in males and 5 mg/kg bw in females; no changes were reported in haematologic or histopathologic examinations (Scientific Committee on Food 2003, with reference to Margaria, 1963).

In a 14-day study, α -thujone was administered by gavage to B6C3F1 mice and to Fischer 344 rats at doses of 0, 1, 3, 10, 30 or 100 mg/kg bw. In mice, mortality was 4/5 males and 5/5 females in the top dose

group; mortality was not increased in the lower dose groups. The increased mortality was associated with indications of neurotoxicity (hyperactivity, tremors, tonic seizures).

Histological changes observed only at the top dose level included only mild renal tubular dilatation/focal degeneration, increased haematopoiesis in spleen, and bone marrow myeloid cell hyperplasia. No increased mortality occurred in male rats but there was increased mortality (3/5 animals) in females of the top dose group. As in mice, the increased death rate was associated with convulsions/seizures.

In the 14-day study on the mixture of α - and β -thujone (detailed composition not available), similar doses were administered by gavage to mice and rats of the same strains. In mice, at the top dose level there was increased mortality in males (5/5) and females (2/5) but not associated with any notable gross or histopathological causation. In rats, there was death of 1/5 males in the highest dose group but gross and histological effects were minimal (Scientific Committee on Food, 2003).

Consumption of as much as 1 liter of an alcoholic beverage containing 5 mg/l, the maximum permitted level of thujone in alcoholic beverages with up to 25% alcohol, would result in an intake of about 0.08 mg thujone/kg bw for a 60 kg adult.

This intake is about 100 times lower than the NOEL derived from a 14 week study in rats (Scientific Committee on Food, 2003).

Although the toxic effects of thujone are evident, the concentrations found in sage leaves are low according to calculations made by Länger et al., 1996.

Investigations showed that only 17% of the genuine thujone content could be extracted with hot water corresponding to 2.5 mg thujone per cup of tea (the most common preparation of sage leaves). A cup of tea prepared from 3.0 g sage leaves and 150 ml boiling water contained 3.8 mg thujone, which is approximately only 17% of the thujone present in the herbal substance. Twenty-three per cent of the cineol and 35% of the camphor present in the herbal substance were extracted (according to e-mail from Länger with reference to Diploma thesis by Harrer, 1993). The use of chemotypes low in thujone should be preferred in order to minimize the exposure to thujone.

Genotoxicity

Single constituents

Negative results have been reported from in-vitro mutagenicity tests in *Salmonella typhimurium* with α -thujone. The test was performed with the strains TA1535, TA100, TA97 and TA98 with and without metabolic activation. First toxicity signs were seen in dose units of 100. Negative results have also been reported from in-vitro mutagenicity tests in *Salmonella typhimurium* with a mixture of α - and β -thujone. The test was done with the strains TA1535, TA100, TA97 and TA98 with and without metabolic activation. First toxicity signs were seen in dose units of 333.

In-vivo mouse micronucleus test was negative in males and positive in females with a mixture of α - and β -thujone. Tested concentrations were 0-25 mg/kg (males) and 0-50 mg/kg (females), respectively [NTP 2003].

Thujone was tested at 1.5 and 3% in DMSO (dimethyl sulfoxide) for its effect on the mutagenicity of aflatoxin B1 in *Salmonella typhimurium* strain TA100. The plates treated with thujone showed evidence of colony damage which indicates some mutagenic activity on the part of thujone (Kim et al. 1992).

Gomes-Carneiro (1998) investigated the mutagenic potential of six monoterpenoid compounds: two aldehydes citral and citronellal, a ketone (+-camphor.), an oxide (*l,8*-cineole, also known as eucalyptol), and two alcohols terpineol and (-)-menthol.

No mutagenic effect was found with (+) camphor, citral, citronellal, *l,8*-cineole, and (-)-menthol.

The results from this study therefore suggest that, with the exception of terpineol, the monoterpenoid compounds tested are not mutagenic in the Ames test.

A rosemary extract, and its main active components, carnosic acid and carnosol, were checked for their potential mutagenicity in the bacterial Ames test. Purified carnosol and carnosic acid were not mutagenic in the test (EFSA, 2008).

Other studies with rosemary extract and carnosic acid has demonstrated antimutagenic activity in bacteria (EFSA, 2008 with reference to Minnuni et al., 1972; Santamaria et al., 1987) and in *in vitro* human liver and bronchial cell models (EFSA 2008, with reference to Offord et al., 1997).

Camphor did not show mutagenic activity in *Salmonella typhimurium* strains TA 1535, TA 1538, TA 98 and TA 100 with and without S9 activation (Anderson and Styles, 1978). No mutagenic effect was found with *d,l*-camphor in strains TA 97a, TA 98, TA 100 and TA 102 with and without metabolic activation (Gomes-Carneiro et al., 1998).

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.

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).

Carcinogenity

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).

II.3.5 Overall conclusions on non-clinical data

Pharmacodynamics

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

Indication a) Traditional herbal medicinal product for symptomatic treatment 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 b) 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 c) 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.

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 is 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 carcinogenicity 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.

II.4 CLINICAL DATA

II.4.1 Clinical Pharmacology

II.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 hyperhidrosis (the secretion of an abnormally large amount of sweat). It should be noted however, that this study did not include a control group (Barnes et al. 2007, with reference to 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 idiopathic hyperhidrosis, supported the long-standing assumption that sage leaf aqueous extracts have anti-hyperhidrotic activity (Bradley, 2006).

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 randomized, 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 randomized, placebo-controlled, double blind, balanced, five-period crossover study the acute effects on cognitive performance of a standardized 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 computerized 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 randomized 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) computerized 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 authorization 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, excipients ad solutionem pro 1 g, corresp. ethanolum 19% V/V.

Methods/Study design: A randomised, double-blind, placebo-controlled, multicentre, parallel group phase II/III study with adaptive two-stage design and interim analysis. The study participants were in two study parts. A total of 286 patients with subjective and objective evidence of pharyngitis were randomized. 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 analog 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 -hemolytic 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 analgetic 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 has 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 can not be assessed as documentation for well-established use until the necessary period of time required is fulfilled.

II.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)

II.4.2 Clinical Efficacy

The following traditional uses, dosages, method and duration of administrations have been recorded for *Salvia officinalis* L., folium in the handbooks:

Traditional use	Dosage	Method and Duration of Administration	Handbook Reference
<p><u>External:</u> Inflammations and infections of the mouth and throat (stomatitis, gingivitis, pharyngitis)</p> <p><u>Internal:</u> Hyperhidrosis</p>	<p><u>Topical use:</u> An infusion of 3 g of the drug in 150 ml of water as a mouthwash or gargle¹</p> <p><u>Oral use:</u> in hyperhidrosis: <u>Tincture:</u> (1:10) in 55% ethanol, 75 drops daily² <u>Infusion :</u> 1-1.5 g of dried herb in 150 ml of water, once or several times daily³</p> <p><u>Dry extract :</u> 160 mg of dry aqueous extract corresponding to 880 mg of drug three times daily⁴</p>	<p><u>Method:</u> For oral administration or topical application</p> <p><u>Duration:</u> In hyperhidrosis, treatment for 2-4 weeks is recommended, using a aqueous preparation</p>	<p>ESCOP Monographs (2003)</p> <p>¹ Reference source dated 1988, 2002</p> <p>² Reference source dated 1988</p> <p>³ Reference source dated 1988, 2002</p> <p>⁴ Reference source dated 1989</p>
<p><u>Internal:</u> Digestive disorders (dyspepsia, flatulence, poor digestion, bloating) To reduce excessive perspiration, e.g. in the menopause. As a gentle, stimulating tonic.</p> <p><u>External:</u> Inflammations of the mouth or throat mucosa (pharyngitis, tonsillitis, stomatitis, gingivitis glossitis)</p>	<p><u>Internal daily dose:</u> 3-6 g of dried leaf, usually as an infusion¹; liquid extract 1:1 in 45% ethanol, 2-6 ml²</p> <p><u>Topical use:</u> mouthwashes and gargles : 2.5 g of dried leaf to 100 ml of water as an infusion³</p>	<p><u>Method:</u> Oral and topical administration</p> <p><u>Duration:</u> No information</p>	<p>British Herbal Compendium, (Bradley, 2006)</p> <p>¹ Reference source dated 1983, 1985</p> <p>² Reference source dated 1983, 2003</p> <p>³ Reference source dated 1985</p>

<p><u>External:</u> As an antiphlogistic for inflammations of the mouth and throat and for gingivitis and stomatitis</p> <p><u>Internal:</u> For digestive disturbances, flatulence, inflammations of the intestinal mucosa. Diarrhoea</p>	<p><u>Tea:</u> Depending on the indication:</p> <p><i>Gargle:</i> Pour boiling water over 3 g finely cut dried leaf. Steep for 10 minutes, strain¹</p> <p><i>To treat night sweats:</i> Prepare the tea like the previous, but let it cool before drinking²</p> <p><i>For gastrointestinal complaints:</i> Pour boiling water over 1.5-2 g finely cut dried leaf. Steep for 5 min, strain³ 1 teaspoon=about 1.5 g</p>	<p><u>Method:</u> Oral and Topical Administration</p> <p><u>Duration:</u> No information</p>	<p><u>Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004)</u> ¹ Wichtl, dated 2004 ² Wichtl, dated 2004 ³ Wichtl, dated 2004</p>
<p><u>Internal:</u> Digestive complaints with mild spasms in the gastrointestinal tract, feeling of distension, flatulence. Excessive perspiration.</p> <p><u>External:</u> Inflammations of the oral and pharyngeal mucosa</p>	<p>Unless otherwise prescribed, drink one cup of tea infusion 3-4 times daily, prepared as follows: Pour 150 ml boiling water over 1 teaspoonful (about 1.5g) of sage leaves, or over a corresponding amount in one or more teabags. Steep for about 10-15 minutes, strain¹</p> <p>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 1½ teaspoonful (about 2.5g) of sage leaves. Steep for about 10-15 minutes, strain²</p>	<p><u>Method:</u> Oral and Topical Administration</p> <p><u>Duration:</u> In acute cases that last longer than one week or periodically reoccur, it is recommended to seek medical advice</p>	<p><u>Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004) with reference to The German Standard License, 1996</u> ¹ dated 1996 ² dated 1996</p>
<p><u>Internal:</u> Digestive complaints Excessive perspiration.</p>	<p>Unless otherwise prescribed: <u>Internal:</u> Daily dose, 4-6 g dried leaf¹, 0.1- 0,3 g essential oil²,</p>	<p><u>Method:</u> Cut dried leaf for infusion, alcoholic extracts and distillates for gargles, rinses and paints, and for internal</p>	<p><u>Herbal Drugs and Phytopharmaceuticals (Wichtl, 2004) with reference to The German Commission E monograph, 1990)</u></p>

<p><u>External:</u> Inflammations of the oral and pharyngeal mucosa</p>	<p>2.5-7.5 g tincture (as per <i>Erg.B.6</i>)³, 1.5-3 g fluidextract (as per <i>Erg.B.6</i>)⁴</p> <p><u>Externally:</u> 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 water⁵ As a paint: Undiluted alcoholic extract⁶</p>	<p>use and as the pressed juice of fresh plants</p> <p><u>Duration:</u> No information</p>	<p>¹ Dated 1990 ² Dated 1990 ³ Source referred is <i>Ergänzungsbuch zum Deutschen Arzneibuch, 1941</i> ⁴ Source referred is <i>Ergänzungsbuch zum Deutschen Arzneibuch, 1941</i> ⁵ Dated 1990 ⁶ Dated 1990</p>
<p><u>Internal:</u> Dyspeptic symptoms and excessive perspiration.</p> <p><u>External:</u> For inflammations of the mucous membranes of nose and throat.</p>	<p><u>Internal:</u> <i>Dried leaf:</i> 1-3 g, three times daily² <i>Infusion:</i> 1-3 g in 150 ml water, three times daily³ <i>Dry aqueous extract</i> 5.5:1 (w/w): 0.18-0.36 g, three times daily⁴ <i>Fluidextract:</i> 1.5-3 g (<i>Erg.B.6</i>)⁵ <i>Essential oil:</i> 0.1-0.3 ml.⁷ <i>Succus:</i> Pressed juice of fresh plant in 25% alcoholic preservation⁸</p> <p><u>External:</u> <i>Gargle or rinse:</i> Use warm infusion. 2.5 g cut leaf in 100 ml water; or 2 to 3 drops of essential oil in 100 ml water; or use 5 ml of fluidextract diluted in 1 glass water, several times daily⁹ <i>Paint:</i> Apply the undiluted alcoholic fluidextract to the affected area with a brush or swab¹⁰</p>	<p><u>Method:</u> Internal or External Administration</p> <p><u>Duration:</u> No information</p>	<p><u>Herbal Medicine Expanded Commission E Monographs (Blumenthal, 2000)</u> ¹ Blumenthal dated 2000 ² Blumenthal dated 2000 ³ Blumenthal dated 2000 ⁴ Blumenthal dated 2000 ⁵ Source referred is <i>Ergänzungsbuch zum Deutschen Arzneibuch, 1941</i> ⁶ Blumenthal dated 2000 ⁷ Blumenthal dated 2000 ⁸ Blumenthal dated 2000 ⁹ Blumenthal dated 2000 ¹⁰ Blumenthal dated 2000</p>

<p><u>Internal:</u> Flatulent dyspepsia, Hyperhidrosis galactorrhoea</p> <p><u>External:</u> Gargle, mouthwash (pharyngitis, uvulitis, stomatitis, gingivitis, glossitis)</p>	<p><u>Internal:</u> <u>Leaf:</u> 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 daily²</p> <p><u>External:</u> Gargle/ rinses : 2.5 g/100 ml water³</p>	<p><u>Method:</u> Oral administration</p> <p><u>Duration:</u> No information</p>	<p><u>Herbal Medicine,</u> <u>(Barnes et.al., 2002; 2007)</u></p> <p>¹Reference source dated 1983,1998 ² Reference source dated 1983 ³ Reference source dated 1998</p>
<p><u>Internal:</u> Regulate perspiration (during menopause, nightsweat)</p> <p>Lactation inhibition</p> <p>Gastrointestinal complaints</p> <p><u>External:</u> Respiratory diseases and inflammations in mouth and throat</p>	<p><u>Ordinary dose:</u> <u>Internal:</u> Tinctur: 60 drops daily¹ 30-50 drops several times a day² Warm infusion: 2-3 spoonfuls (=3.4-5.1g) of the leaves</p>	<p><u>Method:</u> Internal and external administration</p> <p><u>Duration:</u> No information</p>	<p><u>Lehrbuch der Biologischen Heilmittel,</u> <u>Madaus 1938</u></p> <p>¹Source referred to is Krahn 1896 ² Source referred to is Hager, year not specified</p>
<p><u>Internal</u></p> <p>For symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating</p> <p><u>External</u></p> <p>For symptomatic treatment of inflammations in the mouth or the throat</p>	<p>Tincture (1:10), extraction solvent: ethanol 70% V/V tincture (1:10) 2.5-7.5 g daily, divided in 3 doses.</p> <p>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.</p>	<p><u>Duration</u> <u>No information</u></p>	<p>This tinctur and the ethanol percentage is specified as a separate monograph in Ph. Eur 2008 and the Deutsches Arzneibuch 6. Ausgabe 1926. Spiritus dilutus is Ethanol 68-69% (V/V) = 60-61% (m/m).</p> <p>Information concerning this tincture is documented in earlier German Pharmacopeias (Ergänzungsbuch zum Deutschen Arzneibuch (Erg. B. 6. Stuttgart 1956, 1958</p>

II.4.2.1 Dose response studies

There are no dose response studies available

II.4.2.2 Clinical studies (case studies and clinical trials)

Some clinical studies are performed as specified in II.4.1.1

II.4.2.3 Clinical studies in special populations (e.g. elderly and children)

In a randomized 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).

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. A warning is recommended for the use in children and adolescents because data are not sufficient and medical advice should be sought when children have such symptoms.

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.

II.4.3 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 develop 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.

II.5 CLINICAL SAFETY/PHARMACOVIGILANCE

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

II.5.2 Patient exposure

Products containing *Salvia officinalis* L., folium is widely available. The products have various regulatory status. 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. .

II.5.3 Adverse events and 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).

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

A case of human poisoning has been documented following ingestion of sage oil for acne.

There are several anecdotal and case study reports of the acute effects of essential oils containing thujone causing seizures in humans, indicating that the animal data are of relevance to humans. In most cases, the doses are not well determined but one case was associated with about twelve drops of the essential oil of sage, which caused a generalized tonic-clonic seizure followed by a postictal coma lasting for 15 minutes. However, there are no reliable studies of the long-term effects of sub-convulsive doses either on the nervous system or on the liver (Scientific Committee on Food, 2003).

More than a few drops of the oil can be toxic due to the high thujone content. Thujone is a nervous system stimulant that may cause convulsions at high doses (http://extoxnet.orst.edu/newsletters/n42_83.htm).

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).

II.5.4 Laboratory findings

None known concerning *Salvia officinalis* L.

II.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.

Use in children:

No data about *Salvia officinalis* L. are 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.

Camphor:

The American Academy of Pediatrics concluded that although adults recovered from ingestions of as much as 42 g camphor, the ingestion of 2 g generally produces dangerous effects. In children, ingestions of 0.7 to 1.0 g of camphor have proven fatal (EFSA 2008, with reference to AAP, 1994). In the pediatric population, exposure to as little as 500 mg camphor is cited as a cause of mortality. More commonly, 750 to 1000 mg is associated with the development of seizures and death. Currently available products with 10% camphor contain 500 mg in 5 ml. It is concluded that small doses are dangerous. In children less than 6 years of age, exposure to 500 mg or more requires rapid triage to the closest health care facility.

According to a recently published case report, a 10-year old boy presented at the emergency room with symptoms of lethargy, nausea, vomiting and rigors. Approximately 24 hours previously, he had chewed three over-the-counter cold remedy transdermal patches containing 4.7% (95.4 mg/patch) camphor and 2.6% menthol as active ingredients (EFSA 2008, with reference to Ragucci et al., 2007). On the basis of an assumed body weight of 30 kg, this would correspond to an intake of camphor of approximately 10 mg/kg bw.

1000 mg of camphor is a concerning exposure in the child under 6 years of age (Love et al., 2004). Exposure to camphor should not exceed 2 mg/kg bw on a single day in any age group (EFSA, 2008). According to the extraction rate of 35.4% for camphor shown in the study of Langer et al., 1996, a toxic amount for children and adults will theoretically not be reached in a tea-preparation of 1-9 g sage leaf.

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.

Overdose:

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).

Not many *Lamiaceae* poisonings are known. The essential oils of *Lamiaceae* can be dangerous when ingested in large doses. The most noxious are those, like official sage oil (*Salvia officinalis* L.), that contain monoterpenoid ketones like thujones [(-)-3-isothujone and (+)-3-thujone]. The symptomatology of this type of intoxication is characterized by epileptiform convulsions, sometimes with cyanosis, and interrupted by periods of hypotonus and hyporeflexia.

Thujone:

From the study of Dettling et al. (2004), it can be assumed that at least a concentration of 14.4-16.8 mg thujone per person (60 kg) might lead to changes in attention performances and mood alterations.

Sage can be added to foodstuffs providing the concentration of thujones (α and β) present in the final product does not exceed current Regulatory Status on Thujone (Scientific Committee on Food, 2003)

European Union:

Annex II of Directive 88/388/EEC (EEC, 1988) on flavourings sets the following maximum levels for thujone (α and β) in foodstuffs and beverages to which flavourings or other food ingredients with flavourings properties have been added: 0.5 mg/kg in foodstuffs and beverages

with the exception of

5 mg/kg in alcoholic beverages with not more than 25% volume of alcohol

10 mg/kg in alcoholic beverages with more than 25% volume of alcohol

25 mg/kg in foodstuffs containing preparations based on sage

35 mg/kg in bitters.

Thujone may not be added as such to food.

Thujone is not authorized for use as a flavouring substance in the USA.

Estimates of intakes of thujone have been made in France and the United Kingdom. In France, the mean and 97.5th percentile daily intakes were estimated to be 15.6 and 44.3 $\mu\text{g}/\text{kg}$ bw/day respectively. The intakes in the United Kingdom were estimated to be somewhat lower at 3.9 and 14.2 $\mu\text{g}/\text{kg}$ bw/day respectively. Both estimates were based on the maximum limits proposed by the CoE (Council of Europe, 2000). The major dietary contribution to thujone intake appeared to derive from sage and sage-flavoured products, and alcoholic beverages (Scientific Committee on Food, 2003).

Camphor:

Dietary exposure to camphor arises from the consumption of foods flavoured by using either herbs (e.g. basil, coriander, marjoram, rosemary, sage), their essential oils or the chemically defined flavouring substance *d*-camphor).

The dietary exposure to camphor was estimated to be 1.5 mg/person/day (Council of Europe, 2001).

Assuming an average body weight of 60 kg, this corresponds to an exposure of 25 $\mu\text{g}/\text{kg}$ bw/day

Limits for *d*-camphor, suggested by the Council of Europe were 10 mg/kg in beverages (including alcoholic drinks), 25 mg/kg in food in general, 100 mg/kg in candies, 140 mg/kg in fresh cheese, 150 mg/kg in sauces and condiments. (EFSA, 2008).

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (Panel) have assessed the toxicity risks associated with the exposure to camphor in various food commodities (EFSA 2008).

In humans, signs of camphor intoxication include central nervous stimulation, oral and gastric irritation, nausea and vomiting, excitement, hallucinations, delirium, muscular excitability, tremors, convulsions and urinary retention (EFSA 2008, with reference to Opdyke, 1978). Locally it can produce irritation of skin, eyes and mucous membranes of the respiratory tract (EFSA, 2008)

Intoxications from camphor have been frequently reported in literature, mostly involving the accidental ingestion of camphorated oil (20% camphor in cottonseed oil). For example 20 children aged 1 to 4 years who became ill after ingestion of 1 to 1.5 tablespoons of camphorated oil equivalent to about 3 to 4.5 g camphor. Most of them had seizures, but recovered (EFSA 2008, with reference to Benz, 1919). As little as 1 g camphor ingested in 1 teaspoonful of camphorated oil was fatal in a 19-month-old child (EFSA 2008, with reference to Smith et al., 1954).

“The probable lethal oral bolus dose has been reported to be in the range of 50 to 500 mg/kg bw. No acute toxicity was reported after doses lower than 2 mg/kg bw and clinically insignificant signs of toxicity may be seen in sensitive individuals at doses of 5 mg/kg bw and higher, whereas clinically manifest toxicity in sensitive persons would require doses higher than 30 mg/kg bw.” Although acute exposure estimates via food for children and adults are about 2-5 times and 6-14 times, respectively, lower than the dose of 2 mg/kg bw, the Panel considered dose-response relationship to be robust and to cover also inter-individual variability in sensitivity to camphor, and thus “concluded that that it is unlikely that acute effects may occur in relation to consumption of foods providing less than 2 mg/kg bw in one large portion.”

Limit exposures	Daily doses
2 mg/kg: no acute effects	120 mg/day
5 mg/kg: insignificant effects in sensitive individuals	300 mg/day
30 mg/kg: clinically manifest toxicity in sensitive individuals	1800 mg/day
50-500 mg/kg: a probably lethal oral bolus	3-30 g/day

Assessor’s comment:

Due to variations of thujone and camphor it is difficult to set an exact value on the maximum amount of sage leaves which could result in a overdose based on the available data.

Drug abuse: Only experimental use or abuse due to the reputed effects of another species, *Salvia divinorum* L. (*Lamiaceae*) has been used for centuries by the Mazatecan culture This species has gained popularity due to its potent hallucinogenic effects (Grundmann et al., 2007).

Withdrawal and rebound: No reactions reported.

Ability to drive or operate machinery or impairment of mental ability: No known effects on ability to drive and use machines (ESCOP, 2003), however according to the study performed by Dettling et al. (2004) it was shown that attention performance was changed under the influence of high thujone concentrations.

Thujone:

Dettling et al. (2004), determined if the impacts of thujone (absinthe) on attention performance and mood were different from those experienced with beverages that contain only alcohol. Twenty-two healthy subjects were tested using an attention performance test, which was developed for aptitude diagnostics in the area of performance and which is applied in the diagnostics of alcohol and drug-induced effects on visual orientation performance. Mood was assessed using two questionnaires that test different mood dimensions: the one (Masel Mood test) records the factors vitality, intra-psyche equilibrium, social extraversion and attentiveness, the other (general activation – high activation state scale) records state anxiety and current subjective activation.

The calculated total amount of thujone consumed was 0.28 mg/kg and 0.028 mg/kg for men and 0.24 mg/kg and 0.024 mg/kg for women. The alcohol content was adjusted to 16 g/l in all beverages. The amount of liquid to be consumed depended on the weight of the subject, It was tried to attain a maximum

blood alcohol concentration of 0.05% (= 0.5‰) for each subject. Before drinking every subject received a small standard meal; the beverage had to be drunk then within 10min. All tests were performed before drinking (T0) and 30 (T1) and 90 min (T2) after drinking.

The results between T0-T1 and T0-T2 revealed no significant alterations in attention performance after the consumption of alcohol and low thujone concentration. When the subjects were under the influence of the high thujone concentration the number of correct reactions in the peripheral field of attention decreased significantly and the reaction time in both the peripheral and central fields of attention increased significantly between T0-T1. Furthermore the number of “false alarm” reactions also increased. The changes in performance after 90 min revealed results that show a pattern similar to the results after 30 min but not so pronounced (not significant anymore). No significant differences in attention performance between the three treatments could be found either from T0-T1 or from T0-T2 (ANOVA t-test). It was assumed that the effects of the high thujone condition are quantitative but not qualitative. One possible explanation was given with the theory that the effects of alcohol on attention processing may be an inverted U-shaped function and that thujone shifts the dose-effect to the left. The missing alteration in attention performance, at low thujone concentrations was explained by alcohol antagonizing the effect of thujone. While within the treatment groups the mood state changed either from T0-T1 or from T0-T2, no significant differences (Friedman rank variance analyses) in the alteration of the tested mood dimensions could be found when comparing the treatment groups with each other. Most prominent difference was seen for the point “state anxiety”. High thujone concentrations led to a decrease in state anxiety at T2. This effect was explained with the interaction of thujone with the GABA-receptor. The antagonistic effect of thujone on the GABA-receptor lead to an increase in fear sensations and also have a stimulating and rousing effect, while ethanol acts as a GABA-enhancer (anxiolytic, sedative and amnesic).

Assessors comment: The study by Dettling et al. (2004) showed that approximately 15 mg thujone/person (60 kg) leads to changes in the in attention performance, while intake of approximately 1.5 mg thujone/person gave no such changes in attention performance. Accordingly for safety reasons, 1.5 mg /person in a single dose is suggested as a limit for thujone content in thujone containing herbal medicinal products.

Further clinical studies are needed for assessment of effects on ability to drive or operate machinery or impairment of mental ability, and precautions are included in the monograph.

II.5.6 Overall conclusions on clinical safety

The essential oil of *Salvia officinalis* L. contains constituents like thujone and camphor, which have toxic effect in high doses. Most studies have been performed *in vivo* in animals, and toxicological dose limits have been set based on the available toxicological data, case reports and clinical studies. The toxic effect appears to be of central nervous origin. Maximum apparent doses of rectal or oral preparations regarding the camphor content of sage leaf are up to about 500 mg/day, which may cause insignificant effects in sensitive individuals. Highest estimates of exposure via food are 0.34 mg/kg bw (adults, about 20 mg/day) and 0.83 mg/kg bw (children).

The camphor content in sage leaf preparations for oral and oromucosal use, are not expected to cause safety concern if dose recommendations are followed.

The study by Dettling et al. (2004) showed that approximately 15 mg thujone/person (60 kg) leads to changes in the in attention performance, while intake of approximately 1.5 mg thujone/person gave no such changes in attention performance. Accordingly for safety reasons, 1.5 mg /person in a single dose is suggested as a limit for thujone content in thujone containing herbal medicinal products.

The presence of thujone in sage leaf preparations in the monograph is restricted to a daily intake of 5.0 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 a lack of safety and toxicity data for the long-term effects, hence limitations in duration of use is recommended.

During the meetings of the MLWP after the public consultation, the following points led to amendments in the monograph and the assessment report:

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. An intake of about 0.08 mg thujone/kg bw for a 60 kg adult are assessed as safe when used occasionally in foodstuff and beverages. This exposure level is not a recommended daily intake proven safe. However, as serious side effects on the nervous system and the liver, remains to be shown in clinical studies and in traditional use, we consider that a precautionary approach is taken with a maximum thujone content of 5.0 mg/day and a duration of use of maximum 2 weeks.

Products exceeding the recommended maximum thujone limit cannot be recommended for marketing without supplementary safety studies and a detailed benefit/risk assessment. The MLWP discussion focused on the lack of adverse drug reactions indicating that thujone could be less neurotoxic than thought in the past. The potential danger of the substance is possibly overrated because of the problems encountered with the consumption/misuse of liquors. There are no side effects reported for the *Salviae folium*.

The importance of limiting the exposure of thujone must also be seen together with the background intake of thujone from the use of Sage leaf based spices and other sources of thujone such as alcoholic beverages based on Absinth.

Preparations with less than 5.0 mg thujone/day:

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

Preparations with more than 5.0 mg thujone/day:

These herbal preparations should provide safety studies and a detailed benefit/risk assessment.

The thujone content in sage leaf preparations for oral and oromucosal use, are not expected to cause safety concern if dose recommendations are followed and the specified maximum limits of thujone are not exceeded.

Sage leaf can be recognized 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. However, exposures of children will be limited to be sure that doses causing significant toxic effects are avoided.

The maximum daily dose of 5.0 mg thujone/day is supposed to be divided according to listed posologies in the monograph. Therefore the single dose is always lower than the amount postulated as the lowest described limit of thujone action in the study by Dettling et al., 2004. The content of thujone must be shown for every batch.

II.6 OVERALL CONCLUSIONS

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 symptomatic treatment 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..

Concomitant use of other GABA-acting medicinal products should be avoided. After intake of preparations from sage leaf patients should not drive or operate machinery for safety reasons.

As minimum required data on mutagenicity (Ames' test) are not available, an inclusion to the Community list of traditional herbal substances and preparations can not be recommended.

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 can not 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.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH ON *SALVIA OFFICINALIS* L., FOLIUM^{2,3}

III.2 LITERATURE REFERENCES

² According to the 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMA/HMPC/182320/2005 Rev.2)

³ According to the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMA/HMPC/182352/2005 Rev.2)