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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Salvia fruticosa* Mill., folium

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Salvia fruticosa</i> Mill., folium
Herbal preparation(s)	Not applicable
Pharmaceutical form(s)	Not applicable
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Note: This draft assessment report is published to support the public consultation of the draft public statement on *Salvia fruticosa* Mill., folium. It is a working document, not yet edited, and shall be further developed after the release for consultation of the public statement. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft public statement.



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# 1. Introduction

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

- Herbal substance(s)

*Salvia fruticosa* folium consists of the whole or cut, dried leaves of *Salvia fruticosa* Mill. containing not less than 18mL/kg or 12mL/kg of essential oil in the whole or in the cut drug respectively (calculated with reference to the dried drug).(Ph.Eur. 8<sup>th</sup> Edition 2014 (8.2); Ref. 01/2008:1561).

*Salvia fruticosa* Mill. (syn. *Salvia triloba* L.f.) is an evergreen shrub growing up to 1 m. Flowers hermaphrodite, calyx not accrescent, upper lip of corolla more or less straight and gynostegium present. Clearly differentiated from *S. officinalis* due its trifoliate ovate-lanceolate or ovate leaves with typical hairy or tomentose coverings. Leaf blade measures about 8 to 50 mm long and 4 mm to 20 mm wide. The leaf is oval to oblong-lanceolate. The margin is finely crenate and wavy, though indistinctly due to strong pubescence on both pages. The base is obtuse and has sometimes one or two lobes more or less developed. Both pages are tomentose with gray pubescence on the upper side and strong white pubescence beneath. The veining is indistinct. The petiole is strongly tomentose pubescence white and measures about 1 mm in diameter (Goñalons, 1993).

### Principal constituents of the herbal substance:

The following constituents have been reported (Al-Kalaldehy et al., 2010; Dincer et al., 2012; El-Sayed et al., 2001; Shaiq Ali et al., 2000; Kaliora et al., 2014; Proença da Cunha and Roque, 2008; Gruenwald et al., 2000):

Volatile compounds: The essential oil isolated from leaves is predominately composed of oxygen containing monoterpenes, [1,8-cineole (40 - 67%), camphor (2-25%),  $\alpha$ - and  $\beta$ -thujone (< 5,0%)], monoterpene and sesquiterpene hydrocarbons (camphene, myrcene,  $\alpha$ -pinene,  $\beta$ -pinene, *E*-caryophyllene).

Flavonoids: including 7-O-gIucosides and 7-O-glucuronides of apigenin, chrysoeriol, hispidulin, luteolin, 6-methyl luteolin, salvigenin, jaceosidin.

Phenolic acids: rosmarinic acid (1.0 to 2.5%)

Diterpenes: including carnosic acid and carnosol (0.5%)

Triterpenes: ursolic acid, oleanolic acid, etc.

Bitter constituents: picrosalvine

- Herbal preparation(s)

Comminuted herbal substance.

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

Not applicable.

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

Databases and other sources used to research available pharmaceutical, non-clinical and clinical data on *Salvia fruticosa* Mill. or its relevant constituents:

- Relevant articles and references retrieved from databases:
  - PubMed. Search terms:
    - *Salvia triloba*. Publication year: June 1968-January 2014 (28 publications were listed)
    - *Salvia fruticosa*. Publication year: March/April 1987- July 2014. (49 publications listed)
    - Greek sage: (8 relevant publications listed)
  - ISI Web of Science. Search terms:
    - *Salvia triloba*. Publication year: June1968-January 2014. (28 publications listed)
    - *Salvia fruticosa*. Publication year: March/April 1987- July 2014 ( 49 publications listed)
    - Greek sage:(11 relevant publications listed)
    - Three-lobed sage (1 relevant publication)
  - The Cochrane Library
    - *Salvia triloba*: no entries listed
    - *Salvia fruticosa*: no entries listed.
    - Greek sage: no entries listed
    - Three-lobed sage: no entries listed
- Book collections from the following libraries:
  - Biblioteca das Ciências da Saúde da Universidade de Coimbra;
  - Biblioteca Geral Universidade de Coimbra.
- Pharmacopoeias and monographs.

Information on *Salvia fruticosa* Mill was carefully analysed and only articles considered of interest to this Assessment Report were selected.

## **2. Data on medicinal use**

### **2.1. Information about products on the market**

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

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

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Comminuted herbal substance	Herbal medicinal product in increased secretion of sweat	Infusion for oral use as a tea. Not specified posology	Marketed in Denmark from 1996 to 2001

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

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

Not applicable

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

Not applicable

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

Not applicable

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

Archeologic evidences support that *Salvia fruticosa*, concealed among the ancient authors under the general name "*elelisphakon*," has probably been used for medicinal purposes since 1400 b.c. However, translations mistakes of that term in the restrictive sense of the garden sage (*S. officinalis* L.) are probably related with the loss of reputation as a medicinal herb and with the assignment to *S. officinalis* of uses most likely attributed for *S. fruticosa*.

*Salvia fruticosa* is an endemic species of the Eastern Mediterranean basin, extending its native range from Sicily and Southern Italy, Cyrenaica, the Southern part of the Balkan Peninsula, Greece to West Syria. Furthermore, it is found as a naturalized plant in the Western Mediterranean region, especially in Spain and Portugal, where it was probably introduced by ancient navigators. In all these regions *S. fruticosa* has been used over time in traditional medicine practices (Rivera *et al.*, 1994; Karousou *et al.*, 2000).

A systematic inventory of the medicinal uses of *Salvia fruticosa*, abridging literature, was published by Rivera *et al.* (1994). Authors testify its traditional use in southern E.U. countries, particularly in Spain and Portugal: the infusion of the leaves is used at Madeira, Portugal for relieving headache (before 1990) and as a blood depurative recommended for circulatory troubles. In Spain, the infusions and decoctions of leaves or flowering shoots are reputed as stomachic (taken during two or nine consecutive days), blood depurative, recommended for circulatory troubles and as a tranquilizer. In other non EU Mediterranean countries the infusions or decoctions are used as carminative and stomachic and the juice is used for poor appetite. Application as a vulnerary and cicatrizing has also been recorded in Spain.

An ethno pharmacological survey (Dokos *et al.*, 2009) of endemic medicinal plants in Paphos district of Cyprus reports other positive uses of *Salvia fruticosa* to help digestion - as herbal tea is offered to help digestion after heavy meals and as hypoglycaemic for the beneficial effects on the pancreatic function experienced by diabetic patients that consume a daily drink of sage as a breakfast tea. Infusion is also mentioned to reduce coughs, colds, sore throats and tonsillitis. Effects against sweating, anti-diarrhoeic, antipyretic, spasmolytic and tonic were often reported (Dokos *et al.*, 2009).

Proença da Cunha *et al.* (2008) reports the topical use of the infusion (3 to 4 g / 100 ml of water) as a mouthwash or gargle for relief of inflammations and infections of the mouth and throat or as washes, irrigations or cataplasms for relief of mucosal inflammations and infections. Consistently the ESCOP monograph of trilobed sage (2014) [quoting Stahl-Biskup (2008) and Benedum (2006)] also express the beneficial topical use of the infusion (3 g of dried drug in 125 ml of water as a mouthwash or gargle) for relief of inflammations and infections of the mouth and throat.

The ESCOP monograph [quoting Stahl-Biskup 2008; Böhme 2010] also reports the oral use of the infusion (1 to 1.5 g of dried drug in 150 ml of water, once or several times daily) for relief of digestive disorders such as dyspepsia.

Table 2: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
a) Comminuted herbal substance	Digestive disorders Dyspepsia	Infusion or decoction for oral use as a tea. A cup after heavy meals. 1-1.5 g of dried drug as an infusion in 150 ml of water, once or several times daily	Rivera <i>et al.</i> , 1994; Dokos <i>et al.</i> , 2009; ESCOP 2014 (quoting Stahl-Biskup, 2008 and Böhme, 2010)
	Inflammations and infections of the mouth and throat	Infusion, 3 -4 g / 100 ml of water as a mouthwash or gargle	ESCOP 2014 (quoting Stahl-Biskup, 2008 and Böhme, 2010); Proença da Cunha, 2008
	Mucosal inflammations and infections	Infusion or decoction, 3 to 4 g / 100 ml of water. Topical application as washes, irrigations or cataplasms.	Proença da Cunha, 2008
	Headache relief	Infusion for oral use as a tea not specified posology	Rivera <i>et al.</i> , 1994
	Diuretic	Infusion or decoction for oral use as a tea not specified posology	Rivera <i>et al.</i> , 1994
	Tranquilizer	Infusion or decoction for oral use as a tea not specified posology	Rivera <i>et al.</i> , 1994
	Hypoglycaemic (beneficial effects, restoring pancreatic dysfunction)	infusion for oral use as a tea. A cup at breakfast (daily) not specified posology	Dokos <i>et al.</i> , 2009

### 2.3. Overall conclusions on medicinal use

From data it is clear the popularity of *Salvia fruticosa* (leaves) in the traditional medicines of several Mediterranean regions. However, the earliest literature (such as Rivera *et al.*, 1994) only reports the indications of medicinal use and doesn't reports full data on strength, posology and duration of use. This kind of information only could be found in books and monographs published after 2008, so unsuitable and insufficient to prove the circumstances of a long-standing traditional use in accordance

with Directive 2004/24/EC (i.e. more than 30 years including at least 15 years within EU). It comes also clear that the scarcity of complete specific and unequivocal historical information on the long term traditional medicinal usage of trilobed-sage is probably due to the fact that medicinal applications of *Salvia fruticosa* have been improperly included in the repertory of usages of *S. officinalis*.

### 3. Non-Clinical Data

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

##### 3.1.1. Primary pharmacodynamics

Several non-clinical studies have been conducted with extracts, essential oil and isolated constituents of *Salvia fruticosa* Mill. *in vivo* and *in vitro*.

In this section, were considered studies putatively related to the most consistent indications attributed to *Salvia fruticosa*, namely the relief of mucosal inflammations and infections of mouth and throat (by topical use of the infusions) and for relief of dyspepsia and digestive disorders.

##### Anti-inflammatory activity

El-Sayed *et al.* (2006) investigated, *in vivo*, the anti-inflammatory activity of *Salvia triloba* chloroform dry extract (yield: 6.75%), ethanol dry extract (yield: 4%), butanol dry extract (yield: 1%) and water fluid extract (yield: > 20%). Chloroform extract, by oral administration in rats at 25 mg/kg b.w. showed the highest anti-inflammatory activity in acute and chronic inflammation: carrageenan-induced rat paw oedema was inhibited by 17% ( $p < 0.01$ ) compared to 47% by diclofenac at 10 mg/kg as positive control; in the cotton pellet granuloma assay, the chloroform extract inhibited chronic mean gain in pellet weight by 18 mg compared to 29 mg by diclofenac.

##### Antimicrobial and antiviral activity

Sokovic *et al.* (2002) tested the antifungal activity of the essential oil of *S. triloba*, 1,8-cineole and camphor against 13 fungal species (type cultures and isolates), such as *Aspergillus* sp., *Penicillium* sp., *Phomopsis*, *Alternaria*, *Microsporum* and *Epidermophyton* sp.. Minimum inhibitory concentrations (MIC) and minimum fungicidal concentrations (MFC) were found to be, respectively: 5.0-15.0 µl/ml and 5.0-20.0 µl/ml for the essential oil, 4.0-9.0 µl/ml and 5.0-15.0 µl/ml for 1,8-cineole, and 3.0-5.0 µl/ml and 3.0-10.0 µl/ml for camphor.

Sivropoulou *et al.* (1997), using the disk diffusion assay in the essential oil of *S. fruticosa*, noticed that the essential oil was bactericidal against *Staphylococcus aureus* at 1/4000 dilution, while dilutions up to 1/10000 caused a considerable decrease in bacterial growth rates.

The essential oil of *S. fruticosa* and its main components exhibited virucidal activity against *Herpes simplex* virus 1 at a concentration of 0.2% inactivated 80% of infectious virus within 30 minutes and thujone at 0.1% inactivated 95%, whereas 1,8-cineole and camphor at 0.1% inactivated 35% and 0%, respectively (Sivropoulou *et al.*, 1997).

Al-Bakri *et al.* (2010) study the antibacterial and antifungal activities of ethanol extracts of seven *Salvia* species, as well as of the hydrodistilled volatile oil of *S. triloba* against *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) in planktonic and biofilm cultures. Activity was assessed using the agar diffusion method and broth microdilution method for determination of minimal inhibitory concentration (MIC) value. *S. triloba* ethanol extract exhibited the highest antimicrobial activity and was the only active against *S. aureus* (minimal biocidal concentration:  $1.0 \pm 0.35$  mg/ml). The activity of *S. triloba* volatile oil was



higher than that of the ethanol extract, both in the extent and spectrum. Both *S. triloba* ethanol extract (2,5 µg/ml) and volatile oil (0,1%) demonstrated dose-dependent anti-adhesion activities against *E. coli* (66.7% and 76.0%, respectively), but no activity was observed against *P. aeruginosa* and *C. albicans*. The ethanol extract demonstrated anti-adhesive effect against *S. aureus* (60.9%) and one of the MRSA strains (37.2%).

### Spasmolytic activity

Todorov et al. (1984) studied the effects on the tone and phasic contractile activity of isolated segments from guinea pig ileum *in vivo* of extracts isolated from *Salvia officinalis*, *Salvia triloba* and *Salvia verbenaca*. From three-lobed sage leaf a fluid extract (1:2, 70% ethanol), a decoction an infusion and fractions of these obtained by partitioning between benzene and water were prepared and tested. The decoction, and the aqueous fraction from the infusion, caused contraction of the smooth muscle preparation without affecting phasic contractions. The aqueous fraction of the decoction decreased the tone and caused relaxation. The fluid extract potentiated phasic activity but did not affect the tone. The infusion caused contraction of the intestinal segments and intensified phasic contractions. All the extracts inhibited contractions induced by acetylcholine (10<sup>-7</sup> M), barium chloride (10<sup>-4</sup> M), histamine (10<sup>-5</sup> M) and serotonin (10<sup>-5</sup> M) by 20-90%.

Table 3: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
fluid extract (1:2, 70% ethanol)		<i>In vitro</i> tests	Todorov et al. (1984)	Spasmolytic activity
Decoction / infusion		<i>In vitro</i> tests	Todorov et al. (1984)	Spasmolytic activity
Essential oil		<i>In vitro</i> tests	Al-Bakri et al. (2010) Sivropoulou et al. (1997) Sokovic et al. (2002)	Antifungal and antibacterial activities; Antiadhesive effect against <i>S. aureus</i> and other MRSA
1,8-cineole		<i>In vitro</i> tests	Sokovic et al. (2002)	Antifungal activity
camphor		<i>In vitro</i> tests	Sokovic et al. (2002)	Antifungal activity
chloroform dry extract (yield: 6.75%)	oral administration in rats at 25 mg/kg b.w.	<i>In vivo</i> carrageenan-induced rat paw oedema was inhibited	El-Sayed et al. (2006)	anti-inflammatory

### 3.1.2. Secondary pharmacodynamics

#### Antihypertensive activity

Todorov et al. (1984) explored the antihypertensive activity of *Salvia triloba* using an *in vivo* rat model. A dry extract (decoction, DER not available), administered intraperitoneally to nembutal-anaesthetized, spontaneously hypertensive rats as a single dose of 50 mg/kg b.w., reduced blood pressure by 31% compared to saline controls after 120 minutes.

## Central Nervous System (CNS) effects

Todorov *et al.* (1984) studied the central effects of *Salvia fruticosa*. A dry decoction and the dry benzene fraction from an infusion and administered subcutaneously to mice at 100 mg/kg b.w. 10 minutes before administration of hexobarbital (80 mg/kg b.w.), delayed the onset of sleep. Relatively to sedative and hypnotic effects, compounds isolated from *S. triloba* prolonged hexobarbital sleep in the rat.

Orhan and Aslan (2009) showed that a 75% hydroethanolic dry extract (1g/60 ml; total phenolic content: 10.9 mg/g, expressed as gallic acid equivalent) exerted dose-dependent anti-amnesic activity in mice. A passive avoidance apparatus (step-through type) was used to investigate long-term memory; amnesia was induced by scopolamine (1 mg/kg, given intra-peritoneal 30 minutes after oral administration of the extract) and donepezil was used as a positive control. The extract had a relative memory-enhancing effect of 57.1 and 71.4% at 200 and 400 mg/kg b.w. respectively (control group 0%, donepezil group set to 100%).

Mahdy *et al.* (2012) studied the effect of *Salvia triloba* methanol extracts on the oxidative stress status in Alzheimer's disease (AD) induced in rats. [70 male rats were distributed by 7 groups: control group, AD induced rats (positive control), AD group treated with Rivastigmine in a dose of 0,3 mg/kg b.w.t., AD induced rats treated with total extract of *S. triloba* in a dose of 750 or 375 mg/kg b.w.t. After three months of exposure to this treatment oxidative stress markers, malondialdehyde (MDA) and nitric oxide (NO); total antioxidant capacity (TAC) and superoxide dismutase activities (SOD), acetylcholine (Ach) and acetylcholinesterase (AChE) were assessed. Both doses of Greek-sage extracts demonstrated significant increase in Ach (12.4% - *S. triloba*), serum TAC and SOD. Brain AChE, MDA and NO showed significant decrease in AD induced rats. *S. triloba* reduces the oxidative stress status and improves the neurodegeneration characteristic of Alzheimer's disease in rats. *S. triloba* treatments inhibit AChE, retarding the catabolism of Ach, which have been shown to improve memory functions.

Salah and Jager (2004) studied the *in vitro* inhibition of acetylcholinesterase, the affinity to the GABA A-benzodiazepine site and to the serotonin transporter of aqueous, ethanol and ethyl acetate extracts of *S. triloba* and other six plants traditionally used for treatment of neurological disorders. In what concerns to *S. triloba* the ethyl acetate extract showed a weak inhibitory activity by 28% at 1.0 mg/ml and 11% at 0.25 mg/ml, while a dry aqueous extract (1 g/20 ml) was inactive (Ellman's method). Aqueous and ethanol extracts were tested for their binding affinity at the benzodiazepine site, an action that enhances the receptor sensitivity endogenous GABA. The aqueous extracts showed little effect, whereas the ethanol extract of *S. triloba* has moderate activity. In what concerns to serotonin reuptake binding assay, results showed no significant activity.

Senol *et al.* (2010) studied the inhibition of acetylcholin-esterase activity of a dichloromethane dry extract of *S. fruticosa* (13.4:1) to. Results showed 27% of inhibition at 25 µg/ml and 51% at 100 µg/ml.

Orhan *et al.* (2009) tested the potential of 75% hydroethanol dry extract (1 g/60 ml; 1% total phenols) to inhibit acetylcholinesterase activity, obtaining an IC<sub>50</sub> of 0.71 mg/ml.

Savelev *et al.* (2004) assessed the inhibition of the human cholinesterases by *S. triloba* leaf essential oil. Results were inconsistent concerning to butyrylcholinesterase. However, IC<sub>50</sub> values of 0.04-0.06 mg/mL were reported regarding the inhibition of acetylcholinesterase. The major constituents of the essential oil were also tested individually. The most pronounced acetylcholin-esterase inhibition was observed for 1,8-cineole (IC<sub>50</sub>: 0.06 mg/ml), β-caryophyllene (IC<sub>50</sub>: 0.03 mg/ml), α-pinene (IC<sub>50</sub>: 0.1 mg/ml) and β-pinene (IC<sub>50</sub>: 0.2 mg/ml); α-thujone and camphor at 0.5 mg/ml inhibited the enzyme by 37% and 13%, respectively. None or low butyrylcholinesterase inhibition was observed.

### **Ulcerogenicity**

El-Sayed *et al.* (2006) studied *in vivo* the ulcerogenic potential of the oral administration to rats of 25 mg/kg b.w of several extracts of *Salvia triloba* [Chloroform (dry yield: 6.75%), ethanol (4%), butanol (1%) and water (> 20%, viscous extract)]. The ulcer indices were 0 for the ethanol extract, 1.2 for the water extract ( $p < 0.01$ ) and 1.3 for the chloroform extract ( $p < 0.01$ ), compared to the positive control 12.3 (acetylsalicylic acid at 1 mg/kg).

### **Oestrogenic activity**

There are reports of the oestrogenic activity of *Salvia* species (*S. officinalis*, *S. sclarea* and *S. lavandulaefolia*) and some of them are components of preparations used to treat gynaecological disorders particularly in Spain (Duke, 1985). According Rivera *et al.*, (1994) *S. fruticosa* may be in the origin of such reports.

### **3.1.3. Safety pharmacology**

No data available

### **3.1.4. Pharmacodynamic interactions**

No data available

### **3.1.5. Conclusions**

Results of non-clinical pharmacological studies are compatible or not contradictory with the plausibility of the beneficial effects of *Salvia fruticosa* infusions or decoctions for relief of mucosal inflammations and infections and digestive spasms. These effects are probably related with the tannin content, as well as of the predominant volatile compounds, 1,8-cineole and camphor.

None of the reported results constitute any cause for safety concern.

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

No data available

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

No data available

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

No data available

### **3.3.2. Repeat dose toxicity**

No data available

### **3.3.3. Genotoxicity**

No data available

### 3.3.4. Carcinogenicity

No data available

### 3.3.5. Reproductive and developmental toxicity

Elbetieha *et al.* (1998) studied the reproductive toxicity potential of *Salvia fruticosa* in rats. Ingestion of an aqueous dry extract by female rats at 200, 400 and 800 mg/kg b.w. from days 1 to day 6 of pregnancy had no significant effects on the number of pregnancies, implantations, viable fetuses or resorptions when compared to the control. Intra-gastric administration of a 95%-ethanolic dry extract at 400 mg/kg also had no effect on the number of pregnancies or implantations, but the number of viable fetuses decreased ( $p < 0.005$ ) and the number of resorptions increased ( $p < 0.005$ ). In contrast, intra-gastric administration of the aqueous dry extract at 800 mg/kg or the ethanolic dry extract at 400 mg/kg to adult female rats for 30 consecutive days had no effect on the occurrence of pregnancy, but the number of implantations ( $p < 0.05$ ) and viable fetuses ( $p < 0.01$ ) decreased and the number of resorptions increased ( $p < 0.01$  for aqueous dry extract,  $p < 0.005$  for ethanolic dry extract). Ingestion of the same extracts at the same dosage levels for 30 consecutive days by adult male rats had no effect on the final number of pregnant females impregnated by these males. On the other hand, the number of implantations and viable fetuses were reduced in such females ( $p < 0.01$  for aqueous dry extract,  $p < 0.001$  for ethanolic dry extract), whereas the number of resorptions increased ( $p < 0.005$ ). Prenatal exposure of male and female rat offspring to the ethanolic dry extract at 400 mg/kg showed no effect on the timing of testicular descent or vaginal opening.

### 3.3.6. Local tolerance

No data available

### 3.3.7. Other special studies

$\alpha$ - and  $\beta$ -Thujones are known to be abortifacient and emmenagogic (Barnes *et al.*, 2007).

### 3.3.8. Conclusions

Data are insufficient to state the safety of the use of *Salvia fruticosa* during pregnancy and lactation.

Although the little concentration of  $\alpha$ - and  $\beta$ -thujones expected in water extracts of *Salvia fruticosa* (relative amount of  $\alpha$ - and  $\beta$ -thujones in the essential oil of *Salvia fruticosa* doesn't exceed 5.0%) reproductive and developmental toxicity of these compounds should not be neglected.

## 3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional indications of use.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety is scarce.

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

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

## **4. Clinical Data**

### **4.1. Clinical pharmacology**

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

No data available

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

No data available

### **4.2. Clinical efficacy**

No data available

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

No data available

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

No data available

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

No data available

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

There are insufficient data on clinical pharmacology or efficacy available for *Salvia fruticosa* to support a well-established use indication.

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

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

No data available

### **5.2. Patient exposure**

No data available

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

No data available

### **5.4. Laboratory findings**

No data available

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

No data available

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

No data available to support safety in children and adolescents.

### **5.5.2. Contraindications**

No data available

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

No data available

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

No data available

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

No data available to support safety by the use of woman during pregnancy and lactation.

### **5.5.6. Overdose**

No data available

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

No data available

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

No data available

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

Conventional clinical safety data for *Salvia fruticosa* are absent.

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

The use of *Salvia fruticosa* should not be recommended during pregnancy and lactation due to insufficient data. No data on fertility is available.

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

There is no suitable documentation to support the indication of long-stand use or the well-established use of *Salvia fruticosa*, folium as laid down in Article 16a(1)(e) of Directive 2001/83/EC.

Herbal preparations of the *Salvia fruticosa* folium are in medicinal use within the European Union since more than 15 years but less than 30 years. Information regarding the medicinal use outside the European Union for more than 30 years is also insufficient.

There are no clinical data supporting efficacy and safety and the experimental toxicological data are limited.

Genotoxicity, carcinogenicity, reproductive and developmental toxicology of *Salvia fruticosa* folium have not been evaluated.

In conclusion, the HMPC is of the opinion that a European Union herbal monograph on *Salvia fruticosa* folium cannot be established at present.

The HMPC/MLWP will welcome the provision of the necessary data to allow continuation of the assessment work at present.

## **Annex**

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