EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

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

Final – Revision 1

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)		*Rosmarinus officinalis* L., folium *Rosmarinus officinalis* L., aetheroleum
Herbal preparation(s)		Comminuted herbal substance Essential oil
Pharmaceutical form(s)		Leaf Comminuted herbal substance as herbal tea for oral use and as a bath additive. Essential oil Herbal preparations in semi-solid dosage forms for cutaneous use.
First assessment	Rapporteur	H. Pinto-Ferreira
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1. Introduction

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

- Herbal substance(s)

According to the European Pharmacopoeia (Ph. Eur., 01/2013:1560), Rosemary leaf is defined as whole, dried leaf of *R. officinalis* L. It contents a minimum of 12 ml/kg of essential oil and 3% of total hydroxycinnamic derivatives expressed as rosmarinic acid ($C_{18}H_{16}O_8$; M_T360.3).

The plant is native to the Mediterranean regions but has spread to all parts of the world. The leaves are sessile, tough, linear to linear-lanceolate, 10 mm to 40 mm long and 2 mm to 4 mm wide and have recurved edges. The upper surface is dark green and glabrous, the lower surface is greyish-green and densely tomentose with a prominent midrib.

In the last years, a revision of *Salvia* genus based in phylogenetic, taxonomic, morphological and practical factors offered the transfer of *R. officinalis* L. to *Salvia rosmarinus* (L.) Schleid. Thus, *S. rosmarinus* (L.) Schleid. is included as a synonym of *R. officinalis* L. (Drew *et al*., 2017).

Rosemary leaves contain 1,2-cineole, α-pinene, apigenin, betulin, betulinic acid, caffeic acid, camphor, carnosic acid, carnosol, carnosol isomer, methyl carnosate, cirsimaritin, diosmin, hesperidin, limonene, luteolin 3'-O-beta-D-glucuronide, luteolin 3'-O-(3"-O-acetyl)-beta-D-glucuronide, oleanolic acid, rosmadial, rosmanol, rosmarinic acid, scutellarein, thymol, ursolic acid (Senorans *et al*., 2000; Okamura *et al*., 1994). The diterpene rosmariquinone has been isolated from a methanolic extract of *Rosmarinus officinalis* L. (Houlihan *et al.*, 1985).

The leaves contain 0.5 to 2.5% of a volatile oil, consisting of 0.8-6% esters and 8-20% free alcohols (Chandler, 1995). Methanolic extracts from the leaves of *Rosmarinus officinalis* harvested from different locations of Turkey at four different times of the year were analyzed by HPLC. The amounts of carnosol, carnosic acid and rosmarinic acid, varied in different geographical regions of growth, and showed a seasonal variation. The levels of the constituents were higher in the warm months of June 2004 and September 2004 (Yesil-Celiktas *et al*., 2007).

- Herbal preparation(s)

No pharmacopoeia monographs are available for preparations for extracts from the leafs.

Rosemary oil (Ph. Eur., 01/2008: 1846) is defined as the essential oil obtained by steam distillation from the aerial parts of *R. officinalis* L.; it is clear, mobile, colourless or pale-yellow liquid with a characteristic odour. Its chemical composition is complex.

The structure of the carbon skeleton of the main constituents of the essential oil point to three biogenetic types: the eucalyptol type (Italy, Morocco and Tunisia), the camphor-borneol type (Spain) and the alpha-pinene-verbenone type (France, Corsica). Bog rosemary (Andromeda species) and wild or March rosemary (Ledum palustre L.) are members of the family Ericacea and not related to rosemary (Chandler, 1985).

For rosemary oil, the percentages are within the following ranges to comply with Ph. Eur. (Ph. Eur., 01/2008: 1846):

	Spanish type	Moroccan and Tunisian type
α-pinene	18-26%	9.0-14.0%
camphene	8.0-12.0%	2.5-6.0%
β-pinene	2.0-6.0%	4.0-9.0%
β-myrcene	1.5-5.0%	1.0-2.0%

limonene	2.5-5.0%	1.5-4.0%
cineole	16.0-25.0%	38.0-55.0%
ρ-cymene	1.0-2.2%	0.8-2.5%
camphor	13.0-21.0%	5.0-15.0%
bornyl-acetate	0.5-2.5%	0.1-1.5%
α-terpineol	1.0-3.5%	1.0-2.6%
borneol	2.0-4.5%	1.5-5.0%
verbenone	0.7-2.5%	max 0.4%

- 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

This Assessment Report resulted from a revision of that previously issued (EMA/HMPC/13631/2009) considering the decision of HMPC (July 2021) on the need of revision following relevant updates from data published in the literature between 2010 and 2021.

Search web engines used: Google, Google Scholar

Search terms for every database: "Rosmarinus officinalis", "Rosemary" (2010-2021).

Scientific databases: Web of Science; PubMed; Science Direct; Clinical Key; Cochrane Database of Systematic Reviews

Medical or Toxicological databases: Toxline

Pharmacovigilance resources: Data from Eudravigilance. Search terms: "Rosmarinus officinalis", "Rosemary" (2010-2021).

No data were provided by the interested parties during the Call for data regarding the First revision of the monograph.

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** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory Status**
Rosemary essential oil			
Rosemary oil	Traditional use to support the function of	As bath additive • 1.35 g /100 l water	1976, DE, TU

	the skin	for 10-20 min at 34-37ºC, if necessary 1 x daily • 0.39 g / 150 l water for 10-30 min at 35-39ºC, every 2-3 days	
Rosemary oil	Auxiliary treatment in conditions of exhaustion	If necessary 3-4 x / weekly • 4 g rosemary oil / 150 l water for 10-20 min at 34-37ºC; if necessary 3-4 x / weekly • 2.08 g rosemary oil / 100 l water for 10-20 min at 34-37ºC; if necessary 3-4 x / weekly • 2 g rosemary oil / 100 l water for 10-20 min at 34-37ºC; if necessary 3-4 x / weekly • 5 g rosemary oil / 150 l water for 10-20 min at 35-38ºC; max. 1 x daily	1976, DE, WEU 1990, DE, WEU
Rosemary oil	For the symptomatic treatment of muscle and joint pain and in circulatory disturbance.	Ointment 6 g rosemary oil/ 100 g ointment; approx. 3 cm of ointment 2-3 x daily	1976, DE, WEU
Rosemary oil	Stimulation of circulation	100 g solution contain 5 g essential oil as bath additive For a full bath 30 ml	1994, AT, TU
Rosemary oil	Inflammation of the skin; small superficial wounds; strain trauma	Suspension (0.1%) for cutaneous use: 100g contain 0.1g rosemary oil Adults and adolescents > 12 years Diluted or undiluted as poultice Duration: 7 days	2010, AT, TU
Rosemary oil	Minor muscular and articular pain and minor peripheral circulatory disorders	Cream with 10% rosemary oil 3-6 cm of cream 2-3 times daily Adults Duration: 4 weeks	2016, AT, CZ, ES, HR, HU, PL, SE, SI, SK, UK, TU
Rosemary leaf			
Comminuted herbal substance for herbal tea	Improvement of digestion	1-2 g/250 ml, 2-3 times/day (2-4 g/day)	1976, ES, TU
Powdered herbal	Dispepsia, improvement of	2 caps (250 mg) 3 times/day	1990, ES, TU

substance (capsules)	digestion		
Infusion	Dyspeptic complaints Improvement of hepatic and biliary function and in dyspeptic complaints	2 g, 1-2 times/day	1990, PL, TU
Decoction (External use)	Adjuvant therapy in rheumatic conditions and peripheral circulatory disorders. Adjuvant therapy in rheumatic conditions, myalgia and peripheral circulatory disorders	1 liter of decoction (1:20) added to bath water (twice weekly)	1990, PL, TU
fluid extract (1:17.5-18.9), extraction solvent: liqueur wine	Traditional use to support the cardiac and circulatory function.	2-3 x daily 20 ml; 100 g liquid contain 94.816 g extract; 700 ml = 721 g liquid 2-3 x daily 10 ml	1976, DE, TU
fluid extract (1:12.5-13.5), extraction solvent: liqueur wine		1-2 x daily 20 ml	
Expressed juice (1:1.8-2.2) - Rosemary herba recens		2-3 x/daily, 5 ml containing 100% expressed juice	

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

Rosemary (*Rosmarinus officinalis* L.) belongs to the family Lamiaceae (Labiatae) and has been an important medicinal plant since earliest times. It is also a commonly used spice and flavouring agent. Its essential oil is used therapeutically, in particular in balneology (Morton, 1978).

Rosmary oil was recognised for its medicinal and cosmetic properties in ancient Greece and by the Romans, where it was used as a tonic, stimulant, and carminative for dyspepsia, headache, and nervous tension, and also to strengthen the memory. In the middle-ages, it was distilled for medical purposes (Puerto, 2005).

In different regions of the world, the medical use varies. In the Indian Materia Medica (Nadkarni's, 1999), rosemary oil it is described to have a carminative and stimulant action.

The Eclectic physicians used the oil of rosemary in 2 to 10 drop doses for colic, nervous disorders, and painful or delayed menses (Felter and Lloyd, 1983).

Women have used rosemary for minor menstrual complaints and an abortive agent in Brazilian folk medicine. It is traditionally referred to as an emmenagogue and is generally avoided during pregnancy (Lemonica *et al*., 1996). It is claimed to stimulate bile. Rosemary is said to prevent baldness when used as a hair tonic (de Oliveira *et al*., 2019).

The following uses are reported in the literature: as an antiseptic, diuretic, antidepressant and antispasmodic, as well as for cold, influenza, rheumatic pain. The oil is reported to have antimicrobial properties and to have a relaxing effect on tracheal smooth muscles (Erenmemisoglu *et al*., 1997; Chandler, 1995).

In folk medicine, rosemary is put on dressings for healing wounds and for eczema. It is also used as an insecticide, as a preservative and antioxidant for meals and fats (Bisset and Wichtl, 1994).

Rosemary oil was notified for Generally Recognized as Safe (GRAS) status by the Fragrance and Essence Manufacturers Association of the USA (FEMA) in 1965 and has been listed by the U.S. Food and Drug Administration (FDA) for food use (GRAS). In 1970, the Council of Europe included rosemary oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principles in the final product (EFSA, 2008a, EFSA 2008b, citing Opdyke, 1974).

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form Strength (where relevant) Posology Duration of use**	**Reference**
Rosemary essential oil			
Essential oil	<u>*Cutaneous use*</u> Antiseptic and wound healing	Alcoholic solution 2% V/V	Ph. Fr., 1980
Essential oil	<u>Cutaneous use</u> Adjuvant therapy in rheumatic conditions and in peripheral circulatory disorders. Promotion of wound healing and as a mild antiseptic	Essential oil (2% V/V) in ethanol, as an antiseptic	ESCOP, 1997 [citing: Stahl-Biskup, 1994; Bisset and Wichtl, 1994; Paris and Mouse, 1971; Hänsel, 1991; Velasco Negueruela *et al*., 1992; del Rio Hijas, 1992; Rulffs, 1984]
Essential oil	Dyspeptic complaints	10-20 drops essential oil[a]	Bisset and Wichtl, 1989
	<u>External use</u> Supportive treatment for rheumatic diseases; Circulatory problems	6-10% essential oil in semi-solid preparations	Blumenthal *et al.,* 1998
Rosemary leaf			
Herbal substance for Infusion or decoction	Spasmolytic	5 to 10 g/l; Infusion for 15 m. Decoction for 30 min 200 to 400 ml/day	Ph. Fr., 1980
Liquid extract		3 to 5 g/day	

Dried leaves and twigs	Flatulent dyspepsia associated with pathogenic tension. Headaches, migranous or hypertensive. Topically: mylagia, sciatica, intercostal myalgia	2-4 g or by infusion, 3 times per day 2-4 ml of liquid extract 1:1 in 45% alcohol, 3 times per day	British Herbal Pharmacopoeia, 1983
Dried flowering tops	Improvement of hepatic and biliary function and in dyspeptic complaints.	Infusion: 2-4 g of rosemary daily Fluid extracts (1:1, 45% ethanol v/v): 1.5-3 ml daily Tincture (1:5, 70% ethanol): 3-8.5 ml daily	ESCOP, 1997 [citing: citing: Stahl-Biskup, 1994; Bisset and Wichtl, 1994; Paris and Mouse, 1971; Hänsel, 1991; Weiß, 1991]
	<u>Cutaneous use</u> Adjuvant therapy in rheumatic conditions and in peripheral circulatory disorders. Promotion of wound healing and as a mild antiseptic.	Ethanolic extract (1:20) 1 litre of decoction (1:20) added to bath water (twice weekly)	
Herbal substance	Dyspeptic complaints	4-6 g drug	Bisset and Wichtl, 1989; Blumenthal *et al*., 1998
	<u>Cutaneous use</u> Supportive treatment for rheumatic diseases; Circulatory problems	50 g to a full bath	

[a] *<u>Assessor's comments during the 5 years revision concerning the essential oil</u>*
While the Posology for the essential oil is 10-20 drops in Blumenthal et al., 1998, the Ph. Fr. posology was only 3-4 drops. Nevertheless, this posology has been deleted from the current use. Also the reference from the British Herbal Pharmacopoeia refers to the oral use of Rosemary herbal substance and not the pure essential oil.
In summary, there is no real bibliographic reference confirming the posology for the oral use and there are no marketed products containing rosemary essential oil.

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Essential oil			
Rosemary oil	For the symptomatic treatment of muscle and joint pain and in circulatory disturbance.	<u>Cutaneous use</u> Ointment 6 g rosemary oil/ 100 g ointment; approx. 3 cm of ointment 2-3 x daily	since 1976

Rosemary oil	Minor muscular and articular pain and minor peripheral circulatory disorders	Cutaneous use 10% rosemary oil 3-6 cm of cream 2-3 times daily Adults Duration: 4 weeks	since 2016 since 1989 (Bisset and Wichtl)
Rosemary leaf			
Comminuted herbal substance	Improvement of digestion	Oral use 1-2 g/250 ml, 2-3 times/day (2-6 g/day) as infusion	since 1976
Comminuted herbal substance	Dyspeptic complaints Improvement of hepatic and biliary function and in dyspeptic complaints	Oral use 2 g, 1-2 times/day as infusion	since 1990
Comminuted herbal substance	Adjuvant therapy in rheumatic conditions and peripheral circulatory disorders. Adjuvant therapy in rheumatic conditions, myalgia and peripheral circulatory disorders.	As bath additive 1 liter of decoction (1:20) added to bath water (twice weekly)	since 1990
Comminuted herbal substance	Spasmolytic	Oral use 5 to 10 g/l; Infusion for 15 min. Decoction for 30 min 200 to 400 ml/day	since 1980 (Ph. Fr.)

Historical data and documented period of use in the EU support the evidence of traditional use for:

- Rosemary leaf: Oral administration for the symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract.
- Rosemary leaf: Use as a bath additive for the relief of minor muscular and articular pain and in minor peripheral circulatory disorders.
- Rosemary oil: cutaneous use of preparations containing 6-10% essential oil in semi-solid dosage forms for the relief of minor muscular and articular pain and in minor peripheral circulatory disorders

The uses as "auxiliary treatment in conditions of exhaustion", "to support the cardiac and circulatory function" and "for depressive states with general debility" and indications of "cardiovascular weakness" cannot be accepted for traditional use as they are not suitable for use without the need for medical diagnosis, prescription and supervision. The use "to support the function of the skin" cannot be considered as a therapeutic indication.

The reference from the BHP can not be considered for the monograph, as the herbal material does not comply with the Ph.Eur. definition.

The topical use of the liquid extract can not be accepted for traditional use as no data regarding the preparation and dosage for this indication are found. The cutaneous use of rosemary oil as antiseptic and wound healing based in the French Pharmacopoeia is not considered as this reference has been deleted and not in use anymore. Moreover, there are no products in the EU market with this preparation and therapeutic indication.

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

- **Spasmolytic/relaxant activity**

***Ex vivo* studies**

Rosemary leaf extracts

A study was performed to test the antispasmodic activity of 2.5 and 10.0 ml/l of alcoholic extracts (not further specified) of some medicinal plants, including Rosemary, prepared from 1 part of the plant and 3.3 parts of ethanol (31% w/w). The guinea pig ileum was employed and acetylcholine and histamine were used as spasmogens. In histamine–induced contractions all plants, except Melissa exhibited a significant increase of the Effective Dose-50 (DE_{50}) and decreased the maximal possible contractility induced by histamine (Forster and Niklas, 1980).

Essential oil

Three essential oils (*Mentha piperita* L.*, Salvia officinalis* L.*, Rosmarinus officinalis* L.) were investigated for their spasmolytic action on the longitudinal musculature of guinea-pig ileum. The concentration of the components of the oils influences their action. The three essential oils show a spasmolytic action. According to the authors, the stimulating action of pinene, which is present at a higher content in rosemary (21.4%), could be observed (Taddei *et al*., 1988).

In another study, these three plant emulsions were tested in doses between 0.1 and 1 mg/kg i.v., in male guinea pig, using the experimental method of Boissier and Chivot's. Oddi's sphincter, contracted by morphine hydrochloride (1 mg/kg i.v.) prolapses following injection of the three plants. The time to return to normal of Oddi's sphincter is accelerated in relation to the dose of the various essences (Giachetti *et al*., 1988).

The effects of the volatile oil of *R. officinalis* on the tracheal smooth muscle of rabbit and guinea pig were tested in vitro using tracheal strips. The contractions of rabbit tracheal smooth muscles induced by acetylcholine were inhibited as well the contractions of guinea pig tracheal muscle, induced by histamine stimulation. The oil also inhibited contractions of both tracheal muscles induced by high potassium solution, which was dose dependent and reversible. It inhibited the contractions of both tracheal muscles induced by acetylcholine and histamine in Ca^{2+} free solution. This result suggests possible calcium antagonistic properties of rosemary oil (Aqel, 1991).

A study has been performed to investigate if rosemary and its constituents affect the contractility of isolated guinea pig atria and if there are quantitative differences when compared with the guinea pig ileum. The rosemary oil used consisted of 40.9% 1,8-cineole, 5.2% bornyl acetate, 13.9% α-pinene and 7.1% β-pinene. Due to this composition, the essential oil does not comply with the Ph. Eur. monograph (Ph. Eur., 01/2008: 1846). The method consisted of a modification of the one of Magnus. In guinea pig ileum, half-maximal inhibition of acetylcholine–induced contractions was achieved by 465

nl/ml 1,8-cineole (2.5 x 10-3 M), 112 nl/ml bornyl acetate (5.7 x 10-4 M). Half maximal inhibition of contractility of the non-stimulated atria was observed at 250 nl/ml rosemary oil, 100 nl/ml 1,8-cineole (6 x 10-4 M), 400 nl/ml bornyl acetate (2 x 10-3 M). α-pinene and β-pinene increased contractility of the isolated guinea pig ileum. The contractility of the heart was not influenced up to 300 nl/ml, for both substances. The authors concluded that rosemary oil, 1,8-cineole and bornyl acetate depress contractility of the cardiac muscle and inhibit acetylcholine–induced contractions of guinea pig ileum (Hof and Ammon, 1989).

In another study, the effect of the oil was investigated on the vascular smooth muscle of rabbit, using isolated aortic segments (rings). The oil inhibited the contractions induced by norepinephrine stimulation in Ca^{2+} containing and free solution and high K^{+} solutions. The effects were shown to be dose-dependent and reversible. It suggests that the oil has a direct vascular smooth muscle relaxant effect (Aqel, 1992).

Isolated compounds

The spasmolytic activity (against $BaCl_2$ and acetylcholine) of the major components of the essential oils of several aromatic plants was studied. Camphor revealed no agonistic activity against either of the two spasmogen agents studied (Cabo *et al*., 1986).

3.1.2. Secondary pharmacodynamics

- **Antimicrobial activity**

***In vitro* studies**

Essential oils from *Rosmarinus officinalis* L. were evaluated on their antimicrobial and fungicide activities by several authors. It was seen active against a broad spectrum of microorganisms and also insecticidal activity at different concentrations (Benjilali et al., 1986; Héthelyi *et al*., 1989; Konstantopoulou *et a*l., 1992; Panizzi *et al*., 1993; Boatto *et al*., 1994). Larrondo and Calvo (1991) could not detect activity against *Candida albicans*.

- **Cardiovascular activity**

***Ex vivo* studies**

The potential effects of an aqueous extract of the leaves of *R. officinalis* on certain cardiovascular parameters on isolated rabbit heart, such as left ventricular pressure, coronary flow and heart rate, were investigated. In conclusion, some of the active constituents were shown to be associated with coronary vasodilatation and positive inotropic effects (Khatib *et al*., 1998).

- **Antioxidative effect**

***In vivo* studies**

The study by Asai *et al.* (1999) was aimed to investigate the antioxidative properties *in vivo* of several extracts; the phospholipid peroxides (PLOOH) as key products of oxidative injury in membranous phospholipid layers in the plasma, red blood cells (RBC) and livers were determined in mice by chemiluminescence's-high performance liquid chromatography. The hexane extract of rosemary (containing about 1.5% carnosol) was fed to a group of 18 mice. Another 18 mice (eating a normal diet) served as controls. At the end of one week, the animals were fasted overnight and heparinized blood was withdrawn from 6 mice in each group. The animal's livers were weighed and homogenized. The addition of rosemary did not affect food intake or liver weight and did not change the *in vitro* liver lipid peroxidizability compared to controls. However, the α-tocopherol concentrations in plasma, RBC, and liver were significantly lower in mice fed rosemary. Rosemary resulted in a lower level of PLOOH in

RBC but did not affect PLOOH levels in plasma or the liver compared to controls. The authors stated that the decrease in α-tocopherol concentrations was unexpected and is unexplained; however, the PLOOH levels remained similar to that of controls, suggesting that some component in rosemary had an antioxidant effect in the liver and partially made up for the loss of α-tocopherol (Asai *et al*., 1999).

Male rats were fed an experimental diet for 8 weeks. Test diets contained either 10% or 20% casein with rosemary (0, 100, 200, or 400 parts per million (ppm)) or BHT, 400 ppm, as a positive control. The mitogenic reactivity of isolated splenic mononuclear cells from the test animals against concanavalin A (Con A), phytohemagglutinin (PHA), and lipopolysaccharide (LPS) were assessed as were plasma uric acid and tocopherol levels in blood and liver. Rosemary treatment had no effect on feed consumption or growth of the animals and did not affect uric acid or tocopherol levels. Rosemary only had a significant effect on mitogenic reactivity to Con A and PHA in rats fed a 10% casein diet with 200 ppm rosemary ($p<0.05$ compared to controls). Rosemary had no impact on mitogenic reactivity to LPS. The authors conclude that rosemary may not have any significant immunopotentiation in healthy situations but that its effectiveness in more related to its antioxidant potential (Babu *et al.*, 1998).

- **Hepatoprotective effect**

***In vivo* studies**

Administration of rosemary ethanolic extract (0.15 g/100 g body weight) (no further information) to rats for 3 weeks produced a hepatoprotective effect, using carbon tetrachloride and cyclophosphamide as mutagenic and hepatotoxic compounds. There were amelioration of the serum and liver parameters, confirmed by histopathological examination of the liver tissue. Rosemary oil (1.1 mg/g BW) used as pre-treatment for 7 days, followed by *i.p.* injection with cyclophosphamide reduced the mitodepression in the bone marrow. According to the author, this effect is due to the high percentage of phenolic compounds with antioxidant activity (Fahim *et al*., 1999).

An extract of rosemary (no further information) was given to female A/J mice for 4 weeks at concentrations of 0.3-0.6% (by weight) prior to determination of the activities of detoxification enzymes glutathione S-transferase (GST) and NAD(P)H:quinone reductase (QR) in lung, liver and stomach. Liver activities of GST and QR, and stomach GST activity were significantly increased in animals fed diets containing rosemary extract but did not affect lung GST and QR activities (Singletary and Rokusek, 1997).

A study was performed to evaluate the hepatoprotective effect of the aqueous extracts from the whole plant and young sprouts. The authors concluded that the extract obtained from young sprouts exerted an hepatoprotectrive activity in rat when administered orally at 1000, 150O and 2000 mg/Kg (Fleurentin *et al*., 1986).

Tert-butyl hydroperoxide induces in freshly isolated rat hepatocytes malonaldehyde formation and lacticodehydrogenase and aspartate aminotransferase leakage. The results showed the antihepatotoxic action of an extract of *Rosmarinus officinalis* young sprouts (no further information) on carbon tetrachloride-induced toxicity in rats (Joyeux *et al*., 1990).

The protective effect of the oral administration of the isolated essential oil after CCl_4-induced injury was tested in rats. The administration of 5 and 10 mg/kg bw during 7 days showed a hepatoprotective effect. Interestingly, pre-treatment with the studied essential oil during 7 days significantly reversed the activities of antioxidant enzymes catalase, peroxidase, glutathione peroxidase and glutathione reductase in liver homogenates, especially in the dose of 10 mg/kg (Rašković *et al*., 2014).

- **Choleretic and diuretic activity**

***In vivo* studies**

Rosmarinus officinalis L. was tested for its diuretic effect. An aqueous extract was administered orally to Wistar rats for 1 week. The urinary volume, the excretion of sodium, potassium and chloride were determined, as well the concentration of electrolytes and urea in plasma and creatinine clearance. The dose of 10 mg/kg of 8 or 16% extract in distilled water enhanced diuresis in rats compared with the control group from the day five. *R. officinalis* at the dose of 8% reached at the day six the peak of urinary excretion of sodium, potassium and chloride ($p<0.01$). At 16%, it induced slight increases of sodium and chloride excretion on day seven and potassium on day six ($p<0.05$) (Haloui *et al.*, 2000).

For the evaluation of the choleretic and protective activities in the rat, lyophilised and aqueous extracts of *Rosmarinus officinalis* young sprouts and total plant were tested. *R. officinalis* ethanol extracts prepared from young sprouts and total plant show a significant dose-related choleretic activity and are more active than the total plant extract. Aqueous extract of young sprouts show a significant hepatoprotective effect on plasma GTP levels when given as pre-treatment before tetrachloride intoxication, while the whole plant extract was inactive (Hoefler *et al*., 1987).

An aqueous alcoholic extract (15%) of *R. officinalis* in blossom has been investigated by experimental biliary fistula in guinea pig. The increase of the biliary flux happens because of a rapid cholagogic activity and a slowest choleretic activity. An acute toxicity in mice and rats did not reveal any signs of toxicity at the dose used (2 g/kg i.p.) (Mongold *et al*., 1991).

After the administration of the essential oil, the increase of the secreted bile and of the cholates present in it did not produce in rats the expected dose-effect linearity (Taddei and Giachetti, 1993).

- **Antiulcerogenic effect**

***In vivo* studies**

The crude hydroalcoholic (70%) extract (CHE) of *Rosmarinus officinalis* L. decreased the ulcerative lesion index in different experimental models in rats, produced by some ulcerogenic products like indomethacin, ethanol and reserpine. The pharmacological mechanism seemed not related with nitric oxide, or with prostaglandins. The results of the experiments suggested that the CHE increases the mucosal nonprotein sulphydryl group's content or, as another hypothesis, the activity of the antioxidant compounds of the CHE react with N-ethyl-maleimide (Dias *et al*., 2000).

- **Hypoglycaemic effect**

Some reviews summarize the positive effect in lipidic and glucemic profiles of essential oil, leaf extracts and leaf (Hasani *et al*., 2016; Andrade *et al*., 2018; de Oliveira *et al*, 2019; Bao *et al*., 2020).

In vivo studies

A leaf extract was obtained from the fresh leaves (5 g) in 50 ml of boiled water with 1 h of stirring at room temperature. Then, the supernatant was decanted and the residue was macerated for two more days with distilled water. The pooled supernatants were combined and filtered. Diabetic rats received 200 mg of the rosemary extract/kg bw for 21 days. An hypoglycemic effect, together with restoration of elevated liver enzymes function close to normal levels was observed (Ramadan *et al*., 2013).

In a study on normo- and hyperglycaemic mice, the effect of a hot infusion of *R. officinalis* leaves (two handful of leaves in 1 l of boiling water) was investigated, as well the chronic toxicity. The mixture was cooled to the temperature room and 200 ml was given orally 30-60 min before each meal. The normo- and alloxan-induced hyperglycaemic group taking the infusion presented lower levels of glucose plasma levels than the control ($p<0.05$, 0.01 respectively). The author mention the hyperglycaemic and insulin release inhibitory results in alloxan-diabetic rabbits, using the volatile oil, from the study of

Al-Hader *et al*. The interpretation of the author about this controversial effect is the small content of volatile oil on the leaves infusion and the presence of other components (Erenmemisoglu *et al*., 1997).

In alloxan diabetic rabbits, *R. officinalis* volatile oil increased fasting plasma glucose levels by 17 % ($p<0.05$) above those of untreated animals 6 h after administration. The author concludes that these data suggest that the volatile oil of R. officinalis has hyperglycaemic and insulin inhibitory effects in rabbits (Al-Hader *et al*., 1994).

- **Antitumorigenic activity**

***In vivo* studies**

A study was performed to evaluate the activity of rosemary extract (no further information), carnosol and ursolic acid in inhibiting the *in vivo* formation of mammary 7, 12-dimethylbenz[α]anthracene (DMBA)-DNA adducts and the initiation of DMBA-induced mammary tumorigenesis in female rats. A significant decrease in the in vivo formation of rat mammary DMBA-DNA adducts, compared to controls resulted after the supplementation of diets for two weeks with rosemary extract (0.5% by weight), but not with carnosol (1.0%) or ursolic acid (0.5%). After injecting intraperitoneally for 5 days at 200 mg/kg BW, rosemary and carnosol, but not ursolic acids, significantly inhibited adduct formation by 44% and 40%, respectively, compared to controls. A significant decrease of 74% and 65% in the number of DMBA-induced mammary adenocarcinomas per rat was associated with injection of this dose of rosemary and carnosol, respectively. Ursolic acid had no effect (Singletary *et al*., 1986).

A methanol extract of the leaves of *Rosmarinus officinalis* L. (no further information) was evaluated for its effects on promotion and initiation of mouse skin tumour. (Ho *et al*., 1994). According to the authors studies of the effects of an extract of leaves of rosemary and the pure phytochemicals on the carcinogenic process in short-term animal studies (biochemical markers) and long term animal tumour studies, indicate that they have potent inhibitory effects on biochemical marker changes associated with tumour initiation and promotion, and anticarcinogenic activity in several animal models. Topical application of carnosol or ursolic acid isolated from rosemary inhibited TPA-induced ear inflammation, ornithine decarboxylase activity and tumour promotion (Huang *et al*., 1994).

After 13 weeks, post-DMBA tumour incidence for rats fed the 1.0% rosemary diet (33.3%) was significantly lower than for rats fed the control diet (53.6%). But by 20 weeks, incidence for rats fed 0, 0.5 and 1.0% rosemary was 72.2, 69.6 and 58.3% respectively ($p<0.5$). Rosemary extract can inhibit DMBA-induced mammary tumorigenesis when fed prior to and after DMBA dosing (Singletary, 1992).

- **Anticonvulsivant activity**

***In vivo* studies**

Effects of the aqueous extract of leaves and stems of *Rosmarinus officinalis* on the Picrotoxon-induced seizures in mice was performed. The mortality rate, onset of convulsion and GABA content were monitored. The extract was found to delay the onset of picrotoxin-induced seizures and to decrease the mortality rate (Abdul-Ghani *et al*., 1987).

- **Antinociceptive activity**

***In vivo* studies**

The effect of the aqueous and ethanol extracts of *Rosmarinus officinalis* aerial parts on morphine withdrawal syndrome was investigated in mice. The aqueous and ethanol extracts induced a significant antinociceptive activity in the writhing test. This activity was inhibited by naloxone pretreatment. Phytochemical study indicated that only the aqueous extract of *R. officinalis* has an alkaloid

component. The authors concluded that the aqueous and ethanol extracts of *R. officinalis* aerial parts could diminish morphine withdrawal syndrome (Hosseinzadeh and Nourbakhsh, 2003).

Effects on fertility or reproduction*In vivo* studies

A methanolic extract (2%) from the leaves of *Rosmarinus officinalis* was given to female CD-1 mice, in AIN-76A diet for 3 weeks. The liver microsomal 2-hydroxylation of estradiol and estrone were increased 140-180%, 6-hydroxylation was increased by 30% and 16α-hydroxylation of estradiol was inhibited by 50%. It also stimulated the liver microsomal glucoronidation of estradiol by 54-67% and estrone by 37-56%. In ovariectomized CD-1 mice, it inhibited the uterotropic action of estradiol and estrone by 30-50% compared with the group control (Zhu *et al*., 1998).

- **Other studies**

The results from the study of the action of rosemary essential oil, eucalyptol and camphor on the cortex of mice *in vitro* showed an inhibition of O_2 consumption and the lost of electrolytic gradient of Na^+ and K^+ (Steinmetz *et al*., 1987).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

None reported.

3.1.5. Conclusions

The data obtained with some herbal preparations and pure secondary metabolites show spasmolytic effects *ex-vivo* and *in-vitro*, respectively. The data available allow only very limited conclusions on the plausibility of the therapeutic effects of the traditional use preparations of the monograph.

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

There are no data available on the pharmacokinetics of Rosemary preparations. Just some aspects of the pharmacokinetics of rosmarinic acid, rosemary oil and camphor are known, depending on the preparation used.

Rosemary extracts

Rodent studies suggest the possibility of the induction of CYP1A, CYP2B, CYP2E1, and CYP3A along with some phase II enzymes (e.g. glutathione S-transferase, UDP-glucuronosyltransferase) by different Rosemary extracts (Barceloux, 2008; Debersac *et al*., 2001).

Rosemary oil

In mice, inhalation of 0.5 ml of volatile oil released into the breathing air resulted in detectable levels of 1,8-cineole in the blood and was biphasic, with a short half-life of about 45 min during a second phase, indicating elimination by a two compartment model (Kovar *et al*., 1987).

There are no data on the transfer into human milk.

Isolated compounds

- Rosmarinic acid

In *ex vivo* experiments, permeation of rosmarinic acid across excised rat skin was about 8 times higher from alcoholic solution than from water. After topical application, rosmarinic acid concentration in

muscle and bone tissue beneath the application site was comparable to those after systemic administration. Upon intravenous administration, the classical two-compartment open pharmacokinetic model is followed, given the indication for extensive peripheral tissue distribution, which becomes 7 to 13 times higher in the soft tissue than in blood concentrations (Ritschel *et al*., 1989).

Rosmarinic acid (i.v.) is rapidly eliminated from the circulation (i.v. $T_{1/2}$=9 min) and has a low toxicity (LD_{50} in mice=561 mg/kg i.v.), transient cardiovascular actions becoming pronounced at ≥ 50 mg/kg i.v. (Parnham and Kesselring, 1985).

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

3.3.1. Single dose toxicity

Rosemary extracts

In a study to evaluate the acute toxicity in Wistar rats, two representative rosemary leaf extracts obtained by supercritical fluid extraction followed by fractionation (not further information) were used, with different concentrations of phenolic diterpenes, representing medium and high values found in commercial supercritical extracts. At a single dose of 2.0 mg/kg of BW, no deaths or negative clinical signs were observed during the 2 weeks observational period, with no significant differences in weight gain, food and water consumption, clinical chemistry parameters or histological changes (Anadón *et al.*, 2008).

A 15% alcoholic extract (no further information) showed no signs of toxicity when *i.p.* administered to rats at doses of 2 g/kg (Bisset and Wichtl, 1994).

Rosemary extract (no further information) showed no mortality at intragastric doses up to 1.2 g/100 g bw in rats, classified as a very low lethality (Fahim *et al*., 1999).

Essential oil

Essential oil of rosemary had a lethal dose 50 (LD_{50}) of 5.5 g/kg bw intragastrically in rats, and a lethal effect on all animals at an intragastric dose of 0.9 g/100 g bw (Fahim *et al*., 1999).

3.3.2. Repeat dose toxicity

Rosemary extracts have shown low sub-chronic (up to 3 months) toxicity in rats (study data not published). Sub-chronic studies on five solvent extracts (rosemary extract produced from dried rosemary leaves by acetone extraction; rosemary extract prepared by extraction of dried rosemary leaves by means of supercritical carbon dioxide; rosemary extract prepared from a partially deodorized ethanolic extract of rosemary; extract prepared from a deodorized ethanolic extract of rosemary; extract which is a decolorized and deodorized rosemary extract obtained by a two-step extraction using hexane and ethanol; no further information) up to 400 mg/kg bw reveal that the only effect at high doses of these rosemary extracts is a slight increase in relative liver weight. This effect has been shown to be reversible and may be the result of Phase I and II enzyme induction. The effect was not accompanied by increases in plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP). Considering the low magnitude, reversibility and the nature of the hepatic changes, and the absence of increases in plasma ALT, AST and AP, the Panel concluded that the minor increase in the liver weight reported, accompanied by minimal centrilobular hypertrophy and microsomal enzyme induction, represent an adaptive response and are not of toxicological concern. Overall, the 90-day feeding studies in rats with the different rosemary extracts tested, reveal NOAEL values in the range of 180 to 400 mg extract/kg bw/day equivalent,

depending on the carnosol and carnosic acid content of the respective extracts, to 20-60 mg/kg bw/day of carnosol plus carnosic acid (EFSA, 2008a).

3.3.3. Genotoxicity

Rosemary extracts, essential oil

No Guideline-conform Tests are available for rosemary extracts or the essential oil from rosemary.

According to EFSA report (EFSA, 2008a) four of the five rosemary extracts considered were tested for genotoxicity (study data not published). Several in vitro genotoxicity studies were performed in both prokaryotic and eukaryotic test systems and an in vivo mouse micronucleus test performed with an extract with a two-step extraction using hexane and ethanol-. The Panel concluded that these do not give rise to safety concerns with respect to genotoxicity of the tested rosemary extracts.

Isolated compounds

Camphor did not show mutagenic activity in *Salmonella typhimurium* strains TA 1535, TA 1538, TA 98 and TA 100 with and without S9 activation. 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).

3.3.4. Carcinogenicity

No carcinogenicity studies are available for rosemary extracts or the essential oil from rosemary.

Isolated compounds

- Camphor

No studies on carcinogenicity from 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 (Stoner *et al*., 1973).

3.3.5. Reproductive and developmental toxicity

Aqueous extract

An aqueous extract of *R. officinalis* was given to pregnant rats (doses of 26 mg of a 30% w/v aqueous extract – 13 mg solids/ml, made with leaves, flowers and stems, administered by gavage during two different periods of Wistar rats pregnancy). One group (N=12) received the extract from days 1 to 6 of pregnancy (preimplantation period) and another group (N=14) received the same extract from days 6 to 15 of pregnancy (organogenic period), against control groups (N=12) which received saline solution. The animals were sacrificed at term. The authors suggested that rosemary extract may present an anti-implantation effect (the difference was not significant compared to the control), without interfering with the normal development of the concept after implantation (Lemonica *et al*., 1996).

Ethanolic extract

Nusier *et al.* (2007) performed a study on the effects of a 70% ethanol: 30% water extract of rosemary on reproductive function in adult male Sprague Dawley rats, ingesting rosemary extracts dissolved in water at levels of 250 and 500 mg/kg bw/day for 63 days. Body weight and absolute and relative testes weights were not affected, but in the highest dose group the average weight of the

epididymides, ventral prostates, seminal vesicles, and preputial glands significantly decreased. A significant decline in spermatogenesis in testes due to a decrease in the number of primary and secondary spermatocytes and spermatids in the high dose group was observed and attributed to a significant decrease in testosterone. In rats of the highest dose group, sperm motility and density were also significantly decreased in the caudal epididymis and in the testes. For the high dose group the treatment also markedly increased the number of foetal resorptions in female rats impregnated by the high dose males, thereby reducing their fertility. For the 250 mg/kg bw dose groups no statistically significant decreases in these parameters were observed and it can therefore be concluded that 250 mg extract/kg bw/day is the NOAEL in this study (human equivalent exposure of 40 mg/kg bw). Analytical details on the extract used in the study were not provided.

Teratogenicity

Aqueous extracts

Rosemary aqueous extract did not interfere with normal foetal development after implantation in rats. Mated female rats were randomly assigned to groups, and treated either during the preimplantation or postimplantation period. Either, 26 mg daily of a 30% (w/v) boiled aqueous extract of rosemary (stems, leaves, and flowers) or an equal amount of saline solution was administered either from the 1st to 6th day (preimplantation) or the 6th to 15th day (organogenic period). On day 21, the rats were sacrificed and the foetuses were examined for external malformations. No differences were noted in the term foetuses and the rate of post-implantation loss was the same in both groups (Lemonica *et al*., 1996).

Isolated compounds

D-Camphor showed no evidence of teratogenicity after oral administration during the foetal period of organogenesis to pregnant rats at doses up to 1000 mg/kg bw/day, and to pregnant rabbits at doses up to 681 mg/kg bw/day (NOEL values). No increased incidence in variations, retardations or malformations was observed at any of the treated dose levels. These values represent Human Equivalent Doses (HED) of 161 and 220mg/kg, respectively. Taking in account that the daily maximum human therapeutic camphor dose is approximately 1.43mg/kg bw (85.8mg for a reference body weight of 60kg), the therapeutic ratio (lowest toxic dose level in the animal experiment [mg/kg bw/day]/maximum therapeutic dose [mg/kg bw/day]) for the endpoint of embryotoxicity is at least 112.6. Thus, the author concluded that the results reflected a wide margin of safety (Leuschner, 1997).

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

None reported.

3.3.8. Conclusions

Studies for the preparations described in the monographs are scarce.

Available test on reproductive toxicity do not suggest harmful effects for the route of application described in the monograph, however, since data with the preparations of the monographs are not available the use is not recommended during pregnancy.
Tests on genotoxicity and carcinogenicity have not been performed for the preparations listed in both monographs.

3.4. Overall conclusions on non-clinical data

Results from *in vitro* and *in vivo* experimental studies on Rosemary leaf and isolated constituents to support the proposed indications are very limited.

Specific data on pharmacokinetics and interactions are not available.
Non-clinical information on the safety of *R. officinalis* leaf and essential oil is scarce.

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

Rosemary extract

The effectiveness of a hydrophilic fraction from an alcoholic extract of rosemary was tested in humans to assess its ability to prevent lipid peroxidation of skin surface lipids with vitamin E used as a control. Three concentrations of the extract were assayed (3 ml of 5% ethanol solution containing 50, 100 or 500 µg/ml of the extract). The rosemary extract dose-dependently protected the skin lipids from oxidative stress *in vitro*. Lipids extracted after the topical treatment showed a significantly higher resistance towards lipoperoxidative chain reactions than did lipids from the controls. The authors suggested that the hydrophilic rosemary extract may be an important natural antioxidant for the skin (Calabrese *et al*., 2000).

Essential oil

A study was performed in 40 adults to assess the EEG activity, the alertness and the mood after 3 min of aromatherapy, with rosemary. The rosemary group showed decreased frontal alpha and beta power, suggesting increased alertness, lower state anxiety scores and was faster but not accurate on the math computations (Diego *et al*., 1998).

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

None reported.

4.2. Clinical efficacy

4.2.1. Dose response studies

None reported.

4.2.2. Clinical studies (case studies and clinical trials)

No clinical studies have been performed in the indications being part of the monograph.
There are some clinical studies performed with preparations from rosemary leafs. The scope of the assessment in this section are the indications mentioned in the monographs. Only studies related to these indications are to be included in the assessment.

Beside these investigations, preparations from Rosemary leaf have been tested for clinical efficacy for instance in the treatment of androgenetic alopecia (Panahi *et al*., 2015; also discussed in Dhariwala

and Ravikumar, 2019), memory performance, anxiety, depression and sleep quality (Nematolahi *et al*., 2018 and acute effect on cognition and cerebrovascular level (Moss *et al*., 2018). There is no information available that preparations of rosemary have been in medicinal use for more than 10 years in EU in these indications (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Thus, these studies will not be considered for a well-establish use monograph.

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

None reported.

4.4. Overall conclusions on clinical pharmacology and efficacy

No clinical studies for the indications of the monographs could be found.

5. Clinical Safety/Pharmacovigilance

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

There are no clinical safety data available from clinical trials.

Serious poisoning by rosemary or its oil is not reported. The potential problems of gastroenteritis and nephritis, after the ingestion of large amounts of the oil are mentioned in the literature, but do not relate to actual cases (Bisset and Wichtl, 1994).

5.2. Patient exposure

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

5.3. Adverse events, serious adverse events and deaths

<u>Rosemary extracts</u>

A rosemary leaf plaster caused contact dermatitis in a 56-year-old man. A man applied a rosemary leaf plaster to treat a pain in his knee. Three days later, he developed an itchy, vesicular exudative dermatitis that improved within 10 days of withdrawing the plasters. Patch tests were only positive for rosemary. The authors note that this is the first report of a rosemary-induced case of contact dermatitis (Fernandez *et al*., 1997).

The report of a hepatic abscess secondary to ingestion of a rosemary twig was considered to be serious (Karamarkovic *et al*., 2007). However, this case is considered to be not relevant for the safety assessment of authorized/registered medicinal products containing rosemary.

Isolated compounds

- Carnosol

A case of contact dermatitis was reported in a 56-year old man on his hands, forearms and face, after it was introduced in a food processing factory where he was working with an extract from Rosemary leaves, rich in carnosol and rosmanol extract. Patch testing showed the contact allergy was due to carnosol (Hjorther *et al*., 1997).

Further case reports related to allergic contact dermatitis show, from patch testing, that carnosol (CAS RN: 5957-80-2) is a major allergen in rosemary. The chronic use of rosemary as a culinary spice in

food was associated with the development of chronic contact cheilitis. Exposure to rosemary extracts also has been associated with occupational asthma (Barceloux, 2008).

Essential oil

Cases of Hypersensitivity (asthma) have been found in the literature. The frequency is not known.

Isolated compounds

- Camphor

Orally, camphor readily causes epileptiform convulsions if taken in sufficient quantity (Barnes *et al*., 2002).

According to EFSA (EFSA, 2008b), in humans, the intoxication of camphor includes central nervous stimulation, oral and gastric irritation, nausea and vomiting, excitement, hallucinations, delirium, muscular excitability, tremors, convulsions and urinary retention. Locally, it can produce irritation of the skin, eyes and mucous membranes of the respiratory tract. In the same report, it is mentioned that the intoxications present in the literature, in general, involve accidental intake of camphorated oil (20% camphor in cottonseed oil).

No acute toxicity was reported after doses lower than 2 mg/kg bw. Clinically insignificant signs of toxicity may be seen in sensitive individuals at doses of 5 mg/kg bw and higher. Clinical manifest signs in these individuals require doses higher than 30 mg/kg bw (EFSA, 2008b).

20 children aged 1 to 4 years became ill with seizures, after ingestion of 1 to 1.5 tablespoons of camphorated oil equivalent to about 3 to 4.5 g of camphor (EFSA, 2008b).

In a literature review of 64 cases, 6 reports of death were found. In a 19-month old child, the ingestion of 1 g of camphor in camphorated oil was fatal (EFSA, 2008b).

In a recent published case report, a 10-year old boy presented at the emergency room with symptoms of lethargy, nausea, vomiting and rigors. 24 h 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, 2008b). Assuming a body weight of 30 kg, this would correspond to 10 mg/kg BW of camphor.

The American Academy of Pediatrics concluded that although adults recovered from ingestion of up to 43 g of camphor, the ingestion of 2 g generally produces dangerous effects. In children, ingestion of 0.7 to 1.0 g of camphor has proved fatal (American Academy of Pediatrics, 1978).

Assessor's comment:
From available published case reports, clinical studies and marketed medicinal products, the following table is added to the monograph, section 4.8 'Undesirable effects': (all symptoms are stated according to MedDRA-terminology and classified according to the most relevant system organ class – SOC- related to the target organ).

Rosmarinus officinalis folium

System organ classes (SOC)	**MedDRA-terms**	
Immune system disorders	Hypersensitivity (contact dermatitis)	Frequency not known

Rosmarinus officinalis aetheroleum

System organ classes (SOC)	MedDRA-terms	
Immune system disorders	Hypersensitivity (contact dermatitis)	Frequency not known
Respiratory, thoracic and mediastinal disorders	Hypersensitivity (asthma)	Frequency not known

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

Rosemary leaf

The use in children under 12 years of age is not recommended due to lack of adequate data (see section 'Special warnings and precautions for use').

Essential oil

The use in children and adolescents under 18 years of age is not recommended due to lack of adequate data (see section 'Special warnings and precautions for use').

5.5.2. Contraindications

Not to be used in cases of hypersensitivity to the active substance.

Essential oil

Cutaneous use:
Caution is needed when applying essential oils to diseased or damaged skin, because it is more prone to allergic reactions, as well as being more permeable to the essential oil (Tisserand and Young, 2014.; Vandersteen, 2017).
Because of this, the following contraindication is included:
Do not apply to broken or irritated skin

Rosemary leaf

Use as bath additive:
Do not apply to broken or irritated skin

5.5.3. Special warnings and precautions for use

Rosemary leaf

Oral use:
The use in children under 12 years of age is not recommended due to lack of adequate data.

Obstruction of bile duct, cholangitis, liver disease, gallstones and any other biliary disorders that require medical supervision.

Use as bath additive:

The use in children under 12 years of age is not recommended due to lack of adequate data and because medical advice should be sought
Articular pain accompanied by swelling of joint, redness or fever should be examined by a doctor.
If there is inflammation of the skin or subcutaneous induration, ulcers, sudden swelling of one or both legs particularly associated with redness and heat, cardiac or renal insufficiency, or a sudden sharp pain in the leg when at rest, a doctor should be consulted.
In cases of hypertension, a full hot bath should be used with caution (Press, 1991).

Essential oil

Cutaneous use:
The use in children and adolescents under 18 years of age has not been established due to the lack of adequate data.
Articular pain accompanied by swelling of joint, redness or fever should be examined by a doctor.
If there is inflammation of the skin or subcutaneous induration, ulcers, sudden swelling of one or both legs particularly associated with redness and heat, cardiac or renal insufficiency, or a sudden sharp pain in the leg when at rest, a doctor should be consulted.
Contact with eyes should be avoided. Should not be applied near mucous membranes.

5.5.4. Drug interactions and other forms of interaction

There are no data available.

5.5.5. Fertility, pregnancy and lactation

The data available are not sufficient to conclude the safety of rosemary preparations used during pregnancy and lactation.

The safety during pregnancy and lactation has not been established and thus rosemary preparations are not recommended.

5.5.6. Overdose

None reported.

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

None reported.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

In general, it can be concluded that rosemary preparations are safe if used in recommended doses.

Due to the lack of data, use is not recommended during pregnancy and lactation, as the safety has not been established.

Rosmary leaf

Rosemary leaf is not recommended for use in children under 12 years of age due to lack of adequate data.

Use is contraindicated in hypersensitive patients. Hot and full baths are contraindicated in cases of open wounds, large skin injuries, acute skin diseases, high fever, severe infections, severe circulatory disturbances and cardiac failure.

Although rosemary preparations contain variable quantities of camphor, there are no human data to support the development of seizures as a complication of the ingestion of rosemary extracts.

With regard to oral use, a special warning is included for rosemary leaf preparations in cases of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary disorders that require medical supervision.

Essential oil

Rosemary aetheroleun is indicated for cutaneous use only; the warning to avoid contact with the eyes and mucous membranes is included in the monograph of *Rosmarinus aetheroleum*, due to potential irritation of the essential oil. As a Contraindication, Do not apply to broken or irritated skin.

The use in children and adolescents under 18 years of age is not recommended due to lack of adequate data.

Where symptoms such as articular pain accompanied by swelling of the joint, redness or fever occur medical advice should be sought.

6. Overall conclusions

Due to the absence the lack of data to recognize efficacy and according to Article 10a of Directive 2001/83/EC in the European Union, well-established use cannot be accepted for both *Rosmarinus officinalis* L-. aetheroleum and *folium*.

Traditional medicinal use of rosemary essential oil and leaves is well documented in several handbooks and it is substantiated by the presence of medicinal products on the European market throughout a period of at least 30 years (15 years in the European Union), according to the requirements laid down in the Directive 2004/24/EC.

The scientific information available on the pharmacological activity is limited. A spasmolytic/relaxant activity was observed in *ex vivo* studies with different extracts not included in the monograph, essential oil and isolated compounds, but which showed a spasmolytic effect consistent with the traditional use.

In conclusion, *Rosmarinus officinalis* L., is recommended with the following indications:

Rosmarinus officinalis L., *folium*

- Oral use
  Traditional herbal medicinal product for the symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract.
- Use as bath additive
  Traditional herbal medicinal product for the relief of minor muscular and articular pain and in minor peripheral circulatory disorders.

Rosmarinus officinalis L., *aetheroleum*

- Cutaneous use

Traditional herbal medicinal product for the relief of minor muscular and articular pain and in minor peripheral circulatory disorders.

Due to the lack of sufficient data to assure the safety, the use in children (*Rosmarini folium* and preparations thereof including *Rosmarini aetheroleum*), in adolescents (*Rosmarini aetheroleum*) and during pregnancy and lactation are not recommended.

As the minimum required data on mutagenicity (Ames' test) are not available for herbal preparations of rosemary leaf and rosemary oil, a European Union list entry cannot be supported due to lack of adequate data.

Annex

List of references