



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

14 May 2013  
EMA/HMPC/196746/2012  
Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Melissa officinalis* L., folium

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Melissa officinalis</i> L., folium
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance c) Liquid extract (DER 1: 1), extraction solvent ethanol 45-53% V/V d) Tincture (ratio of herbal substance to extraction solvent 1: 5), extraction solvent ethanol 45-53% V/V e) Dried water or ethanol (45-53% V/V) extracts corresponding to the tea, liquid extract and tincture above.
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid dosage forms for oral use.
Rapporteur	P. Claeson
Assessor(s)	P. Claeson and H. Green



# Table of contents

<b>Table of contents</b> .....	<b>2</b>
<b>1. Introduction</b> .....	<b>3</b>
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof .....	3
1.2. Information about products on the market in the Member States .....	4
1.3. Search and assessment methodology.....	5
<b>2. Historical data on medicinal use</b> .....	<b>6</b>
2.1. Information on period of medicinal use in the Community .....	6
2.2. Information on traditional/current indications and specified substances/preparations .....	9
2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications .....	11
<b>3. Non-Clinical Data</b> .....	<b>12</b>
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	12
3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	14
3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof .....	15
3.4. Overall conclusions on non-clinical data.....	15
<b>4. Clinical Data</b> .....	<b>16</b>
4.1. Clinical Pharmacology .....	16
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents .....	16
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents .....	16
4.2. Clinical Efficacy .....	16
4.2.1. Dose response studies.....	16
4.2.2. Clinical studies (case studies and clinical trials) .....	16
4.2.3. Clinical studies in special populations (e.g. elderly and children).....	17
4.3. Overall conclusions on clinical pharmacology and efficacy.....	17
<b>5. Clinical Safety/Pharmacovigilance</b> .....	<b>18</b>
5.1. Overview of toxicological/safety data from clinical trials in humans.....	18
5.2. Patient exposure .....	18
5.3. Adverse events and serious adverse events and deaths.....	18
5.4. Laboratory findings.....	19
5.5. Safety in special populations and situations .....	19
5.6. Overall conclusions on clinical safety.....	19
<b>6. Overall conclusions</b> .....	<b>19</b>
<b>Annex</b> .....	<b>20</b>
<b>List of references</b> .....	<b>20</b>

# 1. Introduction

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

- **Herbal substance(s)**

*Melissa officinalis* L., folium is the dried leaf of *Melissa officinalis* L. [European Pharmacopoeia, 2013].

*Constituents:*

Essential oil 0.06–0.8% containing monoterpene aldehydes, mainly citral, neral and citronellal [ESCOP, 2003; Hänsel *et al.*, 1993].

Sesquiterpene derivatives  $\beta$ -Caryophyllen and Germacren-D (10% each in the essential oil) [Wichtl, 2004]

Monoterpene glycosides [ESCOP, 2003].

Flavonoids with glycosides of luteolin, quercetin, apigenin and kaempferol [ESCOP, 2003].

Phenylpropanoids including hydroxycinnamic acid derivatives such as caffeic and chlorogenic acids and in particular rosmarinic acid (up to 6%) [ESCOP, 2003; WHO monographs, 2002]. The European Pharmacopoeia requires a minimum content of 1% rosmarinic acid in the dried herbal substance.

Tannins [Hänsel *et al.*, 1993].

Triterpenes including ursolic and oleanolic acids [ESCOP, 2003].

Six new triterpenes (including five sulphated triterpenes) have been isolated from stems and leaves (Mencherini *et al.*, 2007 and 2009).

- **Herbal preparation(s)**

- a) Comminuted herbal substance
- b) Powdered herbal substance
- c) Liquid extract (DER 1:1), extraction solvent ethanol 45-53% V/V
- d) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45-53% V/V
- e) Dried water or ethanol (45-53% V/V) extracts corresponding to the tea, liquid extract and tincture above.

- **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. Information about products on the market in the Member States

### Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Comminuted herbal substance in tea bags is on the market. Extracts are in combination products only
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Czech Republic	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify: Food supplements	Combination product only
Denmark	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify: Food supplements	Only combination products authorised
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Powdered herbal substance in capsules since 1981
Germany	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Several combination products for well-established and traditional use also on the market
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combination products only
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered or authorised
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify: Food supplements	No products authorised/registered
Latvia	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify: Food supplements	The herbal substance is only available in combination products
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market

Member State	Regulatory Status				Comments
The Netherlands	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	A combination product is authorised
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Poland	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Also combination products are authorised and registered. Other combination products on the market
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered products on the market
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Powdered herbal substance in capsules
Sweden	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combination products only
United Kingdom	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

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

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

### 1.3. Search and assessment methodology

The two major electronic databases PubMed and Toxline were searched on 14 December 2006 with the search term "melissa officinalis OR lemon balm". For revision of the monograph, the same databases were searched on 23 February 2012.

Results: PubMed 157 references obtained in 2006 and 97 additional references in 2012.

Toxline: 128 references obtained in 2006 and 45 additional references in 2012.

The abstracts of the references found were screened manually and all articles deemed relevant were accessed and included in the assessment report.

## 2. Historical data on medicinal use

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

A long traditional medicinal use of *Melissa officinalis* L, folium in Europe, in the form of herbal tea, powdered herbal substance or aqueous/ethanolic extracts, for the relief of mild symptoms of mental stress and to aid sleep and for the symptomatic relief of mild gastrointestinal complaints including bloating and flatulence is well documented in a number of handbooks [Madaus, 1938; Hoppe, 1958; Steinegger and Hänsel, 1972; British Herbal Pharmacopoeia, 1983; Hänsel *et al.*, 1993; ESCOP, 2003].

The following information about products currently on the market was obtained from the Member States following a new request.

France

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Powdered herbal substance	Marketed since 1981. Authorised in 1989	Hard capsule (275 mg of powdered herbal substance/ capsule)	Adults: single dose: 0.275 g 3 times daily (daily dose: 0.825 g) Adolescents over 12 years of age: single dose: 0.275 mg 2 times daily (daily dose: 0.55 g)	Traditionally used in the symptomatic treatment of digestive upsets such as: epigastric distension, slow digestion, eructation, flatulence. Traditionally used as an adjuvant treatment for the painful component of functional digestive disorders. Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.

Germany

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Melissae folium, cut	Registered in 2010  On the market	Herbal tea	1 cup of tea from 1 tea sachet (=1.6 g Melissae folium, cut) 1-3 times daily.  3-4 times daily	a) to improve general condition in mental stress b) to aid sleep c) symptomatic treatment of mild dyspeptic complaints like feeling

		since 1993		1.6 g cut herbal substance (prepared as infusion)  For use in adults and adolescents over 12 years.	fullness and flatulence.
2.	Melissae folium, powdered	Registered in 2010  On the market since 1990	Coated tablet	3 tablets (=190 mg Melissae folium, powder), 3 times daily. For use in adults and adolescents over 12 years.  3 times daily 3-4 coated tablets containing 190 mg powdered herbal preparation	a) relief of mild symptoms of mental stress and b) for symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence.
3.	Soft extract from Melissae folium (2.3-3.0:1), extraction solvent water	Registered in 2012	Oral liquid 100 ml (106.95 g) oral liquid contain 10.69 g soft extract	6 ml oral liquid 2-3 times daily. For use in adults and adolescents over 12 years.	a) to improve general condition in mental stress b) to aid sleep c) symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence.
4.	Extract from fresh Melissa leaf (1:5.9-7.8), aqueous	On the market since 1990 at least	Oral liquid	3-4 times daily undefined amount of the oral liquid containing 100% extract. For use in adults and adolescents over 12 years.	Traditional herbal medicinal product for support of mental relaxation, to becalm the bowel.
5.	a) Soft extract (2.3-3:1), aqueous  b) Extract (4-8:1), aqueous  c) Dry extract (5-6.2:1), aqueous	On the market since 1994  On the market since 1994  On the market since 1994	Oral liquid 10g/100g  Capsule 164 mg extract  Soft capsule 225 mg extract	6 ml 3 times daily  2-3 capsules 2-3 times daily  2 soft capsules 3 times daily	a)-d) Well-established use for the symptomatic treatment of dyspeptic complaints such as repletion and flatulence.

	d) Soft extract (2.3-3:1), aqueous	On the market since 1995	Oral liquid 10 g/100 g	6-9 ml 3 times daily  All: For oral use in adults and adolescents over 12 years.	
--	------------------------------------	--------------------------	---------------------------	--	--

#### The Netherlands

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Dried ethanolic (50%) extract (DER 4-6:1)	Registered in 2011	Capsules for oral use containing 171 mg of extract	2 capsules three times daily	In accordance with the HMPC monograph.

#### Poland

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Comminuted herbal substance	Before 1980	Herbal tea in bag	Oral use; adolescents over 12 years of age and adults: 2-3 g in 150 ml of boiling water as a herbal infusion up to 3 times daily	1) Traditionally in mild states of nervous tension as well as to aid sleep  2) Traditionally as symptomatic treatment of moderate gastrointestinal disorders such as flatulence and feeling of fullness.

#### Spain

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Powdered herbal substance	Marketed since 1981  Registered in 2010	Hard capsule containing 275 mg of powdered herbal substance	Adolescents and adults: single dose: 0.55 g 2-3 times daily; daily dose: 1.1-1.65 g	In accordance with the HMPC monograph.



No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Dry extract Extraction solvent: ethanol 50%	Registered in 2011	Hard capsule containing 171 mg of extract equivalent to 684-1026 mg of lemon balm leaf	Adults and elderly: 2 capsules 3 times daily. The use in children or adolescents under 18 years is not recommended.	A traditional herbal medicinal product used for temporary relief of symptoms of mild anxiety, to aid sleep and for mild digestive complaints, such as bloating and flatulence.

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

**Indication 1)** For relief of mild symptoms of mental stress and to aid sleep

Medicinal use of *Melissa officinalis* L., folium has been recorded in the following handbooks:

*The Complete German Commission E Monographs* [Blumenthal, 1998; original monograph published in the German Federal Gazette in 1984]

Oral dose: 1.5–4.5 g of herb per cup of tea, as needed, several times daily. Comminuted herb, herb powder, fluid extracts or dry extracts for teas and other galenical preparations. Ground herb and its preparations for oral use. Duration of use: No information.

*Lehrbuch der Biologischen Heilmittel* [Madaus, 1938]

Daily oral dose: 3.2–4.8 g as herbal tea for infusion. Powdered herbal substance: 0.125 g 3 - 4 times daily. Duration of use: No information.

*Drogenkunde* [Hoppe, 1958]

Daily oral dose: No information. Duration of use: No information.

*ESCOP Monographs* [2003]

Daily oral dose: 2–3 g of the drug as an infusion, two to three times daily. Tincture (1:5 in 45% ethanol), 2-6 ml three times daily. Other equivalent preparations. Duration of use: No restriction.

*Herbal medicine. Expanded Commission E Monographs* [Blumenthal, 2000]

Oral dose: 1.5–4.5 g cut herb several times daily. Infusion: 1.5-4.5 g in 150 ml. Fluid extract 1.1 (g/ml): 1.5-4.5 ml. Native dry extract 5.0-6.0:1 (w/w): 0.3-0.9 g. Duration of use: No information.

*Herbal Drugs and Phytopharmaceuticals* [Wichtl, 2004]

Oral dose: Crude drug 1.5–4.5 g several times daily. Corresponding amount of preparations. Duration of use: No information.

*Lehrbuch der Phytotherapie* [Weiss, 1991]

Daily oral dose: No information. Duration of use: No information.

*Pharmakognosie* [Steinegger and Hänsel, 1992]

Oral dose: 1.5 g crude drug for preparation of tea. Duration of use: No information.

*Herbal medicine* [Weiss and Fintelmann, 2000]

Daily oral dose: 4 teaspoons ( $\approx$  4 g) of the crude drug for preparation of tea. Duration of use: No information.

*British Herbal Compendium* [Bradley, 2006]

Dosage: Three times daily: 2-4 g dried leaf as an infusion; liquid extract (1:1 in 45% alcohol) 2-4 ml; or equivalent preparation.

*WHO Monographs* [2002]

Daily oral dose: Infusion: 1.5–4.5 g crude drug per cup several times daily as needed; 45% alcohol extract (1:1): 2-4 ml three times daily; tincture (1:5 in 45% alcohol): 2-6 ml three times daily.

Duration of use: No information.

*Herbal medicines a guide for healthcare professionals* [Barnes *et al.*, 2002]

Daily oral dose: 1.5–4.5 g dried herb as infusion in 150 ml water several times daily. Duration of use: No information.

*Encyclopedia of common natural ingredients* [Leung and Foster, 1996]

Oral dose: 1.5–4.5 g dried leaves for tea infusion. Duration of use: No information.

*Hagers Handbuch* [Hänsel *et al.*, 1993]

Cut herbal substance. Powdered herbal substance. Liquid extracts or dry extracts and other preparations. Daily oral dose for comminuted herbal substance as well as the corresponding herbal preparations: 1.5–4.5 g as tea several times a day. Duration of use: No information.

*British Herbal Pharmacopoeia* [1983]

Dried leaves: oral dose, 2-4 g thrice daily or by infusion. Liquid extract (1:1 in 45% alcohol): oral dose, 2-4 ml thrice daily. Tincture (1:5 in 45% alcohol): oral dose, 2-6 ml three times daily.

Medicinal and traditional use for treatment of insomnia and nervous restlessness is also described in a review [Koch-Heitzmann and Schultze, 1988]. Dosage: 1.5–2 g crude drug for preparation of tea.

**Indication 2)** For symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence

Medicinal use of *Melissa officinalis* L., folium for gastrointestinal complaints is recorded in the handbooks cited above.

*The Complete German Commission E Monographs* [Blumenthal, 1998] (relief of functional gastrointestinal complaints)

*Lehrbuch der Biologischen Heilmittel* [Madaus, 1938] (carminative, indigestion)

*Drogenkunde* [Hoppe, 1958] (stomachic, carminative)

*ESCOP Monographs* [ESCOP, 2003] (symptomatic treatment of digestive disorders such as spasms)

*Herbal Drugs and Phytopharmaceuticals* [Wichtl, 2004] (gastrointestinal disorders of nervous origin)

*Pharmakognosie* [Steinegger and Hänsel, 1972] (spasmolytic)

*WHO Monographs* [2002] (carminative for gastrointestinal disorders)

*Herbal medicines A guide for healthcare professionals* [Barnes *et al.*, 2002] (carminative, gastrointestinal disorders)

*Encyclopedia of common natural ingredients* [Leung and Foster, 1996] (carminative, antispasmodic, stomachic)

*Hagers Handbuch* [Hänsel *et al.*, 1993] (functional gastrointestinal disorders)

*British Herbal Pharmacopoeia* [1983] (carminative, antispasmodic, flatulent dyspepsia, dyspepsia associated with anxiety or depressive states)

*British Herbal Compendium* [Bradley, 2006] (digestive ailments such as dyspepsia, eructation and flatulence).

The indication 2) is also described in the review by Koch-Heitzmann and Schultze [1988].

The dosages are the same as for the indication 1).

The requirements of medicinal use in these indications for at least 30 years (including at least 15 years within the EU) according to Directive 2004/24/EC is considered fulfilled for the following preparations:

- a) Comminuted herbal substance
- b) Powdered herbal substance
- c) Liquid extract (DER 1:1), extraction solvent ethanol 45-53% V/V
- d) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45-53% V/V
- e) Dried water or ethanol (45-53% V/V) extracts corresponding to the tea, liquid extract and tincture above.

A specific preparation of *Melissa officinalis* L., consisting of a highly purified, dry aqueous extract (70:1) of the leaf, is available in some Member States for treatment of herpes infections. The information on manufacture and constituents is limited. The only information available in the public domain is published in Wölbling and Leonhardt (1994), in which the herbal substance is stated to comply with the monograph in the German Pharmacopoeia. Extraction is performed with water and the extract is further purified by chromatography but no details of this process are available. The dried extract is analysed by HPLC and contains caffeic acid, chlorogenic acid and rosmarinic acid as major components; no details are given. The extract is standardised with respect to antiviral activity using the plaque inhibition test. Some clinical trials have been reported on this product [Vogt *et al.*, 1991; Wölbling and Leonhardt, 1994; Koytchev *et al.*, 1999]. The data for this specific product are not considered transferable to other products in the form of a monograph.

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

For both indications 1) and 2), the following oral dosages for adolescents, adults and elderly (single dose) have been recorded:

Herbal tea: 1.5-4.5 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion, 1-3 times daily.

During the 5-year revision of the monograph, a traditional use of the powdered herbal substance in solid dosage forms for oral use was identified and added to the monograph:

Powdered herbal substance: 0.19-0.55 g, 2-3 times daily.

Liquid extract (DER 1:1; extraction solvent ethanol 45-53% V/V): 2-4 ml, 1- 3 times daily.

Tincture (ratio of herbal substance to extraction solvent 1:5; extraction solvent ethanol 45-53% V/V): 2-6 ml, 1-3 times daily.

Dried water or ethanol (45-53% V/V) extracts in doses corresponding to the posologies for tea, liquid extract and tincture above.

As part of the 5-year revision of the monograph, the percentage of ethanol in the extraction solvents has been stated as % V/V for the sake of consistency with other monographs and following the clarification that all ethanol percentages arising from the British Herbal Pharmacopoeia are expressed in V/V. However, according to the HMPC Q&A document (EMA/HMPC/345132/2010), 45% m/m ethanol (=53% V/V) preparations are considered to be corresponding products and are thus also covered by the monograph.

### 3. Non-Clinical Data

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

##### **Primary Pharmacodynamics (related to the indication "relief of mild symptoms of mental stress and to aid sleep")**

###### Aqueous or ethanolic extracts

###### *In vitro*

In an *in vitro* study (rat brain homogenate assay), a freeze dried aqueous extract of the aerial parts of *Melissa officinalis* inhibited GABA transaminase activity ( $IC_{50}=0.35$  mg/ml), resulting in elevated GABA levels, possibly related to an anxiolytic activity [Awad *et al.*, 2007].

In evaluations of human CNS cholinergic receptor binding activity, an ethanolic extract (80% ethanol) displaced 3H-(*N*)-nicotine and 3H-(*N*)-scopolamine from muscarinic and nicotinic receptors in homogenates of human cerebral cortical cell membranes with  $IC_{50}$ -values in the range of 0.08-4.3 mg plant material/ml [Wake *et al.*, 2000; Kennedy *et al.*, 2003].

In a similar study, the dry residue of a 30% methanol extract, mixed with 10% inert material, displaced 3H-(*N*)-nicotine and 3H-(*N*)-scopolamine from nicotinic and muscarinic receptors in human occipital cortex tissue with  $IC_{50}$ -values of 11 mg/ml and 4 mg/ml respectively [Kennedy *et al.*, 2002].

###### *In vivo*

A freeze-dried aqueous ethanolic (20%) extract of *Melissa officinalis* L., folium at doses of 50-200 mg/kg once a day for 3 weeks increased GABA levels, cell proliferation and neuroblast differentiation dose-dependently in the mouse hippocampal dentate gyrus (DG) with reduction of corticosterone levels in serum [Yoo *et al.*, 2011].

An ethanolic extract (30%) showed a dose-dependent sedative effect up to a dose of 25 mg/kg body weight (b.w.) when administered intraperitoneally to mice. The same extract, at doses of 3–6 mg/kg b.w., induced sleep in mice treated with a sub-hypnotic dose of pentobarbital and also prolonged pentobarbital-induced sleep [ESCOP, 2003].

Administration of Cyracos® (a 30% ethanolic extract of *Melissa officinalis* L., folium that has been standardized to consist of more than 7% rosmarinic acid and greater than 15% hydroxycinnamic acid derivatives) to mice orally (120, 240 and 360 mg/kg) for 15 days significantly reduced anxiety-like

reactivity dose-dependently in an elevated plus maze task. In an open field task, no significant effect was observed. Parallel experiments in independent groups of mice showed that the Cyracos<sup>®</sup> dose at which it exerted anxiolytic-like effects did not alter exploratory or circadian activities [Ibarra *et al.*, 2010].

#### Essential oil

##### *In vitro*

The effects of *Melissa officinalis* essential oil were investigated *in vitro* using a range of radioligands targeting the major binding sites of the GABA<sub>A</sub> receptor. Melissa inhibited binding of TBPS to the rat forebrain GABA<sub>A</sub> receptor channel (IC<sub>50</sub>=0.040 mg/ml), but had no effect on NMDA, AMPA or nicotinic acetylcholine receptors [Abuhamdah *et al.*, 2008].

##### *In vivo*

Intraperitoneal administration of the essential oil to mice had no sedative effect and did not prolong pentobarbital-induced sleeping time. However, when administered orally, the oil showed sedative and narcotic effects at doses of 3.16 mg/kg or higher [ESCOP, 2003].

#### **Primary Pharmacodynamics (related to the indication “symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence”)**

##### Aqueous or ethanolic extracts

##### *In vitro*

A 30% aqueous ethanolic extract (1:3.5) at concentrations of 2.5 ml/l and 10 ml/l did not show any significant antispasmodic activity when tested on contractions of the guinea pig ileum induced by acetylcholine and histamine [ESCOP, 2003].

An ethanolic extract (information on concentration not reported) had no effect on the amplitude and frequency of slow waves in circular smooth muscle of mouse small intestine [Storr *et al.*, 2004].

##### Essential oil and isolated compounds

##### *In vivo*

Isolated components of the essential oil exhibited spasmolytic activities on isolated guinea pig ileum, rat duodenum and vas deferens, and on the jejunum and aorta of rabbits. The essential oil also had relaxant effects on guinea pig tracheal muscle (EC<sub>50</sub>: 22 mg/l) and inhibited phasic contractions of an electrically stimulated myenteric plexus longitudinal muscle preparation (EC<sub>50</sub>: 7.8 mg/l) [ESCOP, 2003].

The essential oil and its main component citral inhibited contractions of isolated rat ileum caused by KCl (80 mM), acetylcholine (320 nM) and 5-HT (1.28 µM) in a concentration-dependent manner with an IC<sub>50</sub> of approximately 20 ng/ml [Sadraei *et al.*, 2003].

#### **Secondary Pharmacodynamics**

##### Aqueous or ethanolic extracts

Oral daily doses of 2 g/kg b.w. of a dried aqueous extract of *Melissa officinalis* L., folium, were given to hyperlipidemic rats for 28 days. Total cholesterol, total lipid, alanine transaminase, aspartate transaminase and alkaline phosphatase in blood serum were reduced. The levels of lipid peroxidation in the liver tissue were also reduced but the levels of glutathione in this tissue increased. Morphological

studies of the liver showed a decrease of hyperlipidemia-derived degenerative changes such as vacuolization, picnotic nuclei, mononuclear cell infiltration and rupturing in the endothelium of the central veins in the hepatocytes. The extract thus exerted a hypolipidemic effect and showed a protective effect on the liver [Bolkent *et al.*, 2005].

An ethanolic extract (information on concentration not reported) from *Melissa officinalis* L., folium given orally (3-1,000 mg/kg) produced dose-related antinociceptive action in chemical (acetic acid-induced visceral pain, formalin- or glutamate-induced nociception) models of nociception in mice. The antinociception caused by the extract in the glutamate test was significantly attenuated by intraperitoneal treatment of mice with atropine, mecamylamine or L-arginine. In contrast, the antinociception effect of the extract was not affected by intraperitoneal treatment with naloxone. The results suggest that the extract produced antinociception in several models of chemical pain through mechanisms that involved cholinergic systems (i.e. through muscarinic and nicotinic acetylcholine receptors) and the L-arginine-nitric oxide pathway [Guginski *et al.*, 2009].

Data from *in vitro* and animal studies indicate that the water extract of *Melissa officinalis* L., folium may inhibit the activity of thyroid stimulating hormone [Santini *et al.*, 2003; Benvenga 2003; Auf'molk *et al.*, 1985; Auf'molk *et al.*, 1984; Sourgens *et al.*, 1982]. The clinical relevance of these findings is not known.

An aqueous extract of the aerial parts of *Melissa officinalis* showed antioxidant and neuroprotective properties against Mn-induced neurotoxicity (oxidative stress), especially in the hippocampus and striatum, in mice at a dose corresponding to 100 mg plant material/kg/day for 90 days [Martins *et al.*, 2011].

An ethanolic liquid extract was tested for its potential anti-ulcerogenic activity against indometacin-induced ulcers in rats. It showed dose-dependent anti-ulcerogenic activity at oral doses of 2.5–10 ml/kg b.w. Acid output was reduced and mucin secretion increased. An increase in prostaglandin E2 release and a decrease in leukotrienes were observed. The anti-ulcerogenic effect was also confirmed histologically. The results were interpreted as due to the flavonoid content of the plant and to its free radical scavenging activity [ESCOP, 2003].

#### Essential oil

Antiviral activity, anti-inflammatory activity of rosmarinic acid, antimicrobial activity of the essential oil and free radical scavenging properties have also been reported [ESCOP, 2003].

The hypoglycaemic effects of *Melissa officinalis* essential oil were investigated in type 2 diabetic mice following oral administration for 6 weeks (0.0015 mg/d). The results showed significantly reduced blood glucose and TAG concentrations, improved glucose tolerance and significantly higher serum insulin levels compared with the control group [Chung *et al.*, 2010].

#### **Safety Pharmacology**

No data available.

#### **Pharmacodynamic Interactions**

No data available.

### **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**

#### Acute toxicity

No data available.

#### Repeated dose toxicity

No data available.

#### Genotoxicity

Negative results in the Ames test are reported for a 70% aqueous ethanolic tincture of *Melissa officinalis* L., folium [ESCOP, 2003].

No genotoxic effects were observed from a 20% tincture (information on concentration not reported) in a somatic segregation assay using the diploid strain *Aspergillus nidulans* D-30 [ESCOP, 2003].

In *in vivo* micronucleus and comet assays, CF-1 male mice (5 animals per group) were treated orally with ethanolic (extraction solvent ethanol 45%; 250 or 500 mg/kg) or aqueous (100 mg/kg) solutions of extracts from the aerial parts of *Melissa officinalis* for 2 weeks, prior to treatment with saline or methylmethanesulfonate (MMS) doses by intraperitoneal injection (40 mg/kg b.w.). The mice were killed by cervical dislocation, 24 h after treatment, for evaluation of 1,000 micronucleated polychromatic erythrocytes (MNPCE) in the bone-marrow per mouse. The proportion of PCE and NCE in 200 erythrocytes/animal was calculated to detect possible cytotoxic effects. For COMET assaying, samples of peripheral blood were collected from mouse tail-tips 4 h after MMS treatment. To assess the extent of DNA damage, the visual classification method of Collins *et al.* was applied.

No statistically significant difference in the frequency of MNPCE or the ratio of PCE to NCE, between the negative control and the groups that ingested extracts could be detected.

When evaluating antimutagenicity a significant decrease in the frequency of MMS-induced MNPCE was observed only in mice that had received 500 mg/kg of the ethanolic extract. For the aqueous extract, there was no statistically significant reduction in the frequency of MNPCE.

According to COMET assay results, DNA damage in both parameters (damage index and frequency) following ingestion of 500 mg/kg of an ethanol extract and 100 mg/kg of an aqueous extract during the 15 days treatment presented no statistically significant difference to the negative control. The analysis of DNA damage after pre-treatment with the ethanolic and aqueous extracts indicated no diminution in MMS-induced DNA damage [de Carvalho *et al.*, 2011].

No information on carcinogenicity, reproductive or developmental toxicity is available.

### **3.4. Overall conclusions on non-clinical data**

Results from relevant experimental studies on *Melissa officinalis* L., folium to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

Non-clinical information on the safety of *Melissa officinalis* L., folium is scarce. As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended. An *in vivo* micronucleus test and COMET assay in mice with a 45% ethanol extract and a water extract of the aerial parts of *Melissa officinalis* revealed no mutagenicity. However, due to a number of shortcomings in both studies (e.g. only males included, doses too low, number of cells counted and only a weak response of the positive control) it is not possible to finally conclude on the genotoxic potential of *Melissa officinalis*.



## 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

#### 4.2.1. Dose response studies

No data available.

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

The ESCOP monograph [ESCOP, 2003] cites a study in 20 healthy volunteers treated with daily single doses of 300, 600 or 900 mg of an extract of *Melissa officinalis* L., folium (30% methanol). Cognitive performance was assessed each day in a pre-dose testing session (baseline) and 1, 2.5, 4 and 6 h after treatment. The Cognitive Drug Research computerized test battery was used supplemented by two serial subtraction tasks. Subjective mood was measured by Bond-Lader visual analogue scales. Significant improvement of quality of attention was observed at all times after a dose of 600 mg of the extract ( $p=0.0001$  to  $p=0.049$ ). Significant decreases in the quality of working memory and secondary memory were seen 2.5 and 4 h after the higher doses ( $p=0.0005$  to  $p=0.05$ ). Reduction of working memory was more pronounced at 1 and 2.5 h after the higher doses. Self-rated calmness was elevated significantly after 1 and 2.5 h by the lowest dose ( $p=0.01$  to  $p=0.05$ ) while alertness was significantly reduced at all time points ( $p=0.001$  to  $p=0.05$ ) [Kennedy *et al.*, 2002].

Another experimental study comprised 18 healthy volunteers who received single doses of 300 mg or 600 mg of an extract of *Melissa officinalis* L., folium (30% methanol). The participants were subjected to mild laboratory-induced psychological stress at 1 h after treatment and the effect on mood and cognitive performance assessed as in the previous tests. The 600 mg dose ameliorated the negative mood effects of the stress, with significantly increased self-ratings of calmness and reduced self-ratings of alertness. In addition, a significant increase in the speed of mathematical processing with no reduction in accuracy was observed after ingestion of the 300 mg dose [Kennedy *et al.*, 2004].

In a randomised, placebo-controlled study, 21 Alzheimer patients were given a daily dose of 60 drops of a 50% ethanolic extract (1:4) for 16 weeks. The patients were  $\geq 65$  years of age with a score of 12 on the cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS-cog) and 2 on the Clinical Dementia Rating (CDR). At the end of the test, the Melissa extract produced a significantly better outcome on cognitive functions than placebo (ADAS-cog = 1.  $F = 6.93$ ,  $p=0.01$ . CDR = 1.  $F = 16.78$ .  $p<0.0001$ ) [Akhondzadeh *et al.*, 2003b].



This study was also published in another journal, but here it was stated that the extract was prepared with 45% ethanol (1:1) and the daily dose was 60 drops for 4 months. The results were the same as in the preceding report [Akhondzadeh *et al.*, 2003a].

In a prospective, single-centre, open-label, 15-day study, 20 stressed volunteers (outpatients; 6 male, 14 female) between the ages of 18 and 70 years who were affected by mild to moderate anxiety disorders and sleep disturbances were treated with 600 mg of Cyracos<sup>®</sup> per day, divided into two doses. Cyracos<sup>®</sup> is a 30% ethanolic extract of *Melissa officinalis* L., folium that has been standardised to consist of more than 7% rosmarinic acid and greater than 15% hydroxycinnamic acid derivatives. The volunteers were interviewed using a test based on the Free rating Scale for Anxiety to evaluate anxiety and its associated symptoms and on the Hamilton Rating Scale for Depression to assess insomnia. Cyracos<sup>®</sup> reduced anxiety manifestations by 18% ( $p < 0.01$ ), ameliorated anxiety-associated symptoms by 15% ( $p < 0.01$ ) and lowered insomnia by 42% ( $p < 0.01$ ). 95% of subjects (19/20) responded to treatment, of which 70% (14/20) achieved full remission for anxiety, 85% (17/20) for insomnia and 70% (14/20) for both [Cases *et al.*, 2011].

In a double-blind placebo-controlled randomised trial of *Melissa officinalis* oil and donepezil, there was no evidence that Melissa aromatherapy (external application to hands and upper arms) is superior to placebo or donepezil in the treatment of agitation in people with Alzheimer's disease [Burns *et al.*, 2011]

The effect of an infusion of *Melissa officinalis* L., folium on oxidative stress status was investigated in 55 radiology staff members. The infusion was prepared from one tea bag and taken twice daily (1.5 g/100 ml). Use of Melissa infusion resulted in a significant improvement in plasma levels of catalase, superoxide dismutase and glutathione peroxidase and a marked reduction in plasma DNA damage, myeloperoxidase and lipid peroxidation, reflecting improved oxidative stress condition and DNA damage [Zeraatpishe *et al.*, 2011].

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

No data available.

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

The two clinical studies in healthy volunteers by Kennedy *et al.* [2002; 2004] were performed using a methanol extract, which is not covered by the HMPC monograph. The studies of effects on cognitive functions are of questionable relevance for the traditional medicinal use and considered insufficient to support a well-established use monograph.

The study by Akhonzadeh *et al.* [2003a] on 21 Alzheimer patients is considered insufficient to support a well-established use monograph in this indication and use in Alzheimer patients is outside the scope of traditional use.

The clinical study by Cases *et al.* [2011] on 20 volunteers suffering from mild to moderate anxiety disorders and sleep disturbances treated with a standardised extract of *Melissa officinalis* L., folium resulted in improvements in anxiety symptoms and insomnia. However, the study was an open label design, did not include a control group, no physiological stress markers were investigated and the sample size was too small. The study is considered insufficient to support a well-established use monograph.

## 5. Clinical Safety/Pharmacovigilance

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

In the study, which comprised 20 healthy volunteers treated with daily single doses of 300, 600 or 900 mg of an extract of *Melissa officinalis* L., folium (30% methanol), no adverse effects were reported [Kennedy *et al.*, 2002].

In the study in 20 healthy volunteers 600, 1000 or 1,600 mg of dry, powdered leaf as single doses, no adverse effects were reported [Kennedy *et al.*, 2003].

In the study comprising 18 healthy volunteers, who received single doses of 300 mg or 600 mg of an extract of *Melissa officinalis* L., folium (30% methanol), no adverse effects were reported [Kennedy *et al.*, 2004].

In the placebo-controlled study in 21 Alzheimer patients given daily 60 drops of a 50% ethanolic extract (1:4) for 16 weeks, there was no statistically significant difference between the treated group and the placebo group with respect to adverse effects, with the exception of agitation which was more frequent in the placebo group [Akhondzadeh *et al.*, 2003a].

This study was also published in another journal, indicating that the extract was prepared with 45% ethanol (1:1) and the daily dose was 60 drops for 4 months. The following adverse effects were observed: vomiting (3), dizziness (1), wheezing (2), agitation (1), nausea (1) and abdominal pain (2). Agitation was more frequent in the placebo group than in the verum group (6 vs. 1) [Akhondzadeh *et al.*, 2003b].

In the prospective, single-centre, open-label, 15-day study in 20 stressed volunteers (affected by mild to moderate anxiety disorders and sleep disturbances, 600 mg of Cyracos<sup>®</sup> per day in 2 doses), no adverse effects were observed and all volunteers complied with the treatment until the end of the study [Cases *et al.*, 2011].

### 5.2. Patient exposure

Products containing *Melissa officinalis* L., folium, appear to be available in most EU Member States. Many of the products commercially available are combination products with other herbal substances/herbal preparations. The products fall within a number of regulatory categories depending on usage. *Melissa officinalis* L., folium is used to give fragrance to wine, tea and beer and is listed by the Council of Europe as a natural source of food flavouring in category N2, indicating that lemon balm can be added to foodstuffs in small quantities. Lemon balm is also listed as GRAS (Generally Recognised As Safe) by the US Food and Drug Administration [Barnes *et al.*, 2002].

A considerable patient/consumer exposure must be anticipated although no exact figures can be given.

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

Adverse effects have been reported in the clinical study by Akhondzadeh *et al.* [2003b] (see section 5.1),. No other reports have been identified.

No case reports on adverse reactions or other signals of safety concern in connection with *Melissa officinalis* L., folium were identified in the literature or in the WHO database.

No serious events or deaths are reported.

#### **5.4. Laboratory findings**

No data available.

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

No data available. Theoretically, based on the indication, products containing *Melissa officinalis* L., folium, may cause drowsiness. This risk may increase in combination with alcohol or other sedatives or if excessive doses are taken.

#### **Contra-indications**

Hypersensitivity to the active substance.

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

Conventional clinical safety data are absent. However, long-standing medicinal use and experience of *Melissa officinalis* L., folium has been documented within the EU. During this time, no clinical signals that *Melissa officinalis* L., folium is harmful under the specified conditions of use have been identified. Products intended for adults and adolescents over 12 years of age have been on the market in Member States for more than 30 years. As no data are available, products containing *Melissa officinalis* L., folium cannot be recommended for use in children below the age of 12 years. No data to recommend a specific limit to the duration of use for Melissa products are available, however as a general precaution, if symptoms persist longer than 2 weeks during the use, a doctor or a qualified health care practitioner should be consulted.

### **6. Overall conclusions**

The information available is insufficient to establish that *Melissa officinalis* L., folium has a recognised efficacy and a 'well-established' medicinal use as defined in Article 10a of Directive 2001/83/EC.

However, the traditional uses of *Melissa officinalis* L., folium:

- for relief of mild symptoms of mental stress and to aid sleep and
- for symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence

are well documented in recognised handbooks and serve as the basis for the HMPC monograph based on traditional usage.

Products containing *Melissa officinalis* L., folium are currently available in most EU Member States. Many of the products commercially available are combination products with other herbal substances/herbal preparations.

The requirement of medicinal use for at least 30 years (including at least 15 years within the EU) according to Directive 2004/24/EC is considered fulfilled for the following herbal preparations:

- a) Comminuted herbal substance
- b) Powdered herbal substance
- c) Liquid extract (DER 1: 1), extraction solvent ethanol 45-53% V/V
- d) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45-53% V/V

- e) Dried water or ethanol (45-53% V/V) extracts corresponding to the tea, liquid extract and tincture above.

There is very little information on toxicity and only a few clinical studies have been published, all comprising a small number of participants. There is insufficient information on carcinogenicity, reproductive and developmental toxicity. Use during pregnancy and lactation can thus not be recommended. The available data on mutagenicity (micronucleus test and COMET assay in mice) are not considered adequate, therefore inclusion of *Melissa officinalis* L., folium in the 'Community list of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products' is not recommended at this stage.

Sufficient data on use in children under 12 years of age are unavailable, therefore products containing *Melissa officinalis* L., folium are not recommended for use in this age group.

Conventional clinical safety data are absent. However, long-standing medicinal use and experience of *Melissa officinalis* L., folium have been documented within the EU and no clinical signals that *Melissa officinalis* L., folium is harmful under the specified conditions of use have been identified.

In view of the empirically acknowledged sedative properties of *Melissa officinalis* L., folium, a warning for use in connection with driving of cars and operation of machinery is advisable.

## **Annex**

### **List of references**