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Evaluation of Medicines for Human Use

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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

ASSESSMENT REPORT ON MELISSA OFFICINALIS L., FOLIUM

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1. INTRODUCTION

1.1 Description

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

2. TRADITIONAL MEDICINAL USE

2.1 Information on period of medicinal use in the Community regarding the specified indications

Melissa officinalis L., leaf has been used in Europe internally as a mild sedative and to relieve minor gastrointestinal complaints for a very long time e.g. [Madaus, 1938; Hoppe, 1958; Steinegger and Hänsel, 1972; British Herbal Pharmacopoeia, 1983; Hänsel et al., 1993; ESCOP, 2003]. It is often used in combination products.

2.2 Type of tradition where relevant

European phytotherapy.

2.3 Bibliographic/expert evidence on the medicinal use

A. Indication: For relief of mild symptoms of mental stress and to aid sleep
Medicinal use of *Melissa officinalis* L., leaf has been recorded in the following handbooks:

The Complete German Commission E Monographs [Blumenthal, 1998]. Oral dose: 1.5 – 4.5g of herb per cup of tea, as needed, several times daily. Duration of use: No information.

Lehrbuch der Biologischen Heilmittel [Madaus, 1938]. Daily oral dose: 3.2 – 4.8 g as herbal tea for infusion. Duration of use: No information.

Drogenkunde [Hoppe, 1958]. Daily oral dose: No information. Duration of use: No information.

ESCOP Monograph [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 – 4.5g cut herb several times daily. Infusion: 1.5-4.5 g in 150 ml. Fluidextract 1.1 (g/ml):1.5-4.5ml. 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: 1.5g crude drug for preparation of tea. Duration of use: No information.

Herbal medicine [Weiss and Fintelmann, 2000]. Daily oral dose: 4 teaspoons (≈ 4 g) of the crude drug for preparation of tea. Duration of use: No information.

British Herbal Compendium (Bradley, 2006). Dosage: Three time daily: 2-4g 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 – 4.5g crude drug per cup several times daily as needed; 45% alcohol extract (1:1): 2-4ml 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]. Daily oral dose: 1.5 – 4.5g as tea several times a day. Duration of use: No information.

British Herbal Pharmacopoeia [1983]. Oral dose: thrice daily: 2-4g dried leaves or by infusion. Liquid extract (1:1 in 45% alcohol) 2-4 ml. Tincture (1:5 in 45% alcohol) 2-6ml.

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.

B. Indication: For relief of minor gastrointestinal complaints
Medicinal use of *Melissa officinalis* L., leaf for relief of gastrointestinal complaints is recorded in the handbooks cited above: *The Complete German Commission E Monographs* (relief of functional gastrointestinal complaints)[Blumenthal, 1998], *Lehrbuch der Biologischen Heilmittel* (carminative, indigestion)[Madaus, 1938], D*rogenkunde* (stomachic, carminative)[Hoppe, 1958], *ESCOP Monograph* (symptomatic treatment of digestive disorders such as spasms)[2003], *Herbal Drugs and Phytopharmaceuticals* (gastrointestinal disorders of nervous origin)[Wichtl, 2004], *Pharmakognosie* (spasmolytic)[Steinegger and Hänsel, 1972], *WHO Monographs* (caminative for gastrointestinal disorders)[2002], *Herbal medicines A guide for healthcare professionals* (carminative, gastrointestinal disorders)[Barnes *et al*., 2002], *Encyclopedia of common natural ingredients* (carminative, antispasmodic, stomachic)[Leung and Foster, 1996], *Hagers Handbuch* (functional gastrointestinal disorders)[Hänsel *et al*., 1993], British Herbal Pharmacopoeia, 1983 (carminative, antispasmodic, flatulent dyspepsia, dyspepsia associated with anxiety or depressive states) and British Herbal Compendium (digestive ailments such as dyspepsia, eructation and flatulence)[Bradley, 2006].
The dosage is the same as for indication A. This indication is also described in the review [Koch-Heitzmann and Schultze, 1988].

2.4 Assessor´s overall conclusion on the traditional medicinal use

Traditional medicinal use of *Melissa officinalis* L, leaf, in the form of powdered herbal substance, herbal tea or ethanol extracts, for the relief of mild symptoms of mental stress and to aid sleep is well documented in a number of handbooks.
Traditional medicinal use of *Melissa officinalis* L, leaf, in the form of powdered herbal substance, herbal tea or ethanol extracts, for the symptomatic relief of mild gastrointestinal complaints including bloating and flatulence is well documented in a number of handbooks.
The requirement of medicinal use in these indications for at least 30 years (15 years within the Community) according to Directive 2004/24/EC is considered fulfilled.

In both indications, the following dosages have been recorded:
Herbal substance, cut or powdered: 1.5-4.5 g up to 3 times daily.
Herbal substance as a herbal tea: 1.5-4.5 g up to 3 times per day.
Liquid extract (1:1; extraction solvent 45% ethanol): 2-4 ml up to 3 times per day.
Tincture (1:5; extraction solvent 45% ethanol): 2-6ml up to 3 times per day.

2.5 Bibliographic review of safety data of the traditional herbal medicinal substance

The following two major electronic databases were searched on 14 December 2006 with the search term "melissa OR lemon balm". Results:
PubMed: 157 references obtained.
Toxline: 128 references obtained.
Out of these references, no case reports on adverse reactions or other signals of safety concern in connection with *Melissa officinalis* L., folium were identified.

2.5.1 Patient exposure

Products containing *Melissa officinalis* L., folium, appear to be available in most Member States. The products have various regulatory statuses. A considerable patient/consumer exposure must be anticipated although no exact figures can be given.

The ESCOP Monograph [2003] cites a study which comprised 20 healthy volunteers who were treated with daily single doses of 300, 600 or 900 mg of an extract of Melissa leaf (30 % methanol). No adverse effects were reported.
In another experimental study, 20 healthy volunteers were given 600, 1000 or 1600 mg of dry, powdered leaf as single doses. No adverse effects were reported [Kennedy *et al.*, 2003].
A third experimental study comprised 18 healthy volunteers who received single doses of 300 mg or 600 mg of a 30 % aqueous methanol extract of the leaves. No adverse effects were reported [Kennedy *et al*., 2004].
In a placebo-controlled study, 21 Alzheimer patients were given a daily dose of 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, but here it is said 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].

2.5.2. Adverse effects.

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

2.5.3. Serious events and deaths.

None reported.

2.5.4.1 Intrinsic (including elderly and children)/extrinsic factors

No data available.

2.5.4.2 Drug-drug interactions and other interactions

No data available.

2.5.4.3. Use in pregnancy and lactation

No data available.

2.5.4.4 Overdose

No data available.

2.5.4.5 Drug abuse

No data available.

2.5.4.6 Withdrawal and rebound

No data available.

2.5.4.7 Effects on ability to drive or operate machinery

No data available. Theoretically, 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.

2.5.4.8 Contra-indications

Hypersensitivity to the active substance.

2.5.5. Non-clinical safety data

2.5.5.1 Overview of available data regarding *Melissa officinalis* L., folium, preparation(s) and relevant constituents thereof

Acute toxicity.
No data available.

Repeated dose toxicity.
No data available.

Genotoxicity.
Negative results in the Ames test is reported for a 70 % aqueous ethanolic tincture of Melissa leaf [ESCOP, 2003].
No genotoxic effects were observed from a 20 % tincture in a somatic segregation assay using the diploid strain *Aspergillus nidulans* D-30 [ESCOP, 2003].
No information on carcinogenicity, reproductive or developmental toxicity is available.

2.5.6 Assessor´s overall conclusions on safe use

Both non-clinical and 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. Minimum required data on mutagenicity (Ames' test) are not available for the tea (water extract) or for the traditionally used 45 % ethanol extract (liquid extract or tincture).

Conventional clinical safety data are virtually absent. However, longstanding medicinal use and experience of *Melissa officinalis* L., folium has been documented within the Community. During this time, no clear clinical signals that *Melissa officinalis* L., folium is harmful under normal conditions of use have been identified. As no data on use in children are available, products containing *Melissa officinalis* L., folium cannot be recommended for use in children below the age of 12 years.

3 PHARMACOLOGICAL PROPERTIES

Constituents.
Essential oil. 0.06 – 0.8 % containing monoterpene aldehydes, mainly citral, neral and citronellal [ESCOP, 2003, Hänsel *et al*., 1993].
Sesquiterpene derivatives. β-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 monograph, 2002]. European Pharmacopoeia requires a minimum content of hydroxycinnamic derivatives, expressed as rosmarinic acid, of 4.0 %.
Triterpenes including ursolic and oleanolic acids [ESCOP, 2003].
Tannins [Hänsel *et al.*, 1993].

3.1 Overview of pharmacological effects of *Melissa officinalis* L., folium, preparations and relevant constituents thereof

Pharmacodynamics
The following pharmacodynamic properties have been reported:
The essential oil exhibited spasmolytic activities on isolated guinea pig ileum, rat duodenum and vas deferens, and on the jeujenum and aorta of rabbits. It also had relaxant effects on guinea pig tracheal muscle and inhibited phasic contractions of an electrically stimulated myenteric plexus longitudinal muscle preparation [ESCOP, 2003].
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].
A 30 % aqueous ethanolic extract showed a dose-dependent sedative effect up to a dose of 25 mg/kg bw when administered intraperitoneally to mice. The same extract, at doses of 3 – 6 mg/kg bw, induced sleep in mice treated with an sub-hypnotic dose of pentobarbital and also prolonged pentobarbital-induced sleep [ESCOP, 2003].
Intraperitoneal administration of the essential oil to mice had no sedative effect and did not prolong pentobarbital-induced sleeping time, but when orally administered it showed sedative and narcotic effects at doses of 3.16 mg/kg or higher [ESCOP, 2003].
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 bw. Acid output was reduced and mucin secretion increased. An increase in prostaglandin E_2 release and a decrease in leukotrienes was 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].

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 ESCOP monograph cites an evaluation of human CNS cholinergic receptor binding activity of an ethanolic extract. The extract displaced ^{3}H-(*N*)-nicotine and ^{3}H-(*N*)-scopolamine from muscarinic and nicotinic receptors in homogenates of human cerebral cortical cell membranes at an IC_{50} of < 1 mg/ml. The dry residue of a 30 % methanol extract, mixed with 10 % inert material, displaced ^{3}H-(*N*)-nicotine and ^{3}H-(*N*)-scopolamine from nicotinic and muscarinic receptors in human occipital cortex tissue at an IC_{50} of 11 mg/ml and 4 mg/ml respectively.

An ethanolic extract had no effect on the amplitude and frequency of slow waves in circular smooth muscle of mouse small intestine [Storr *et al*., 2004].

The essential oil of *Melissa officinalis* L. 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_{50} of approximately 20 ng/ml. [Sadraei *et al.*, 2003].

Oral daily doses of 2 g/kg bw of an 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].

Data from *in vitro* and animal studies indicate that the water extract of *Melissa officinalis* 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 finding is not known.

3.1.1 Assessor's comments on pharmacological effects of *Melissa officinalis* L., folium, preparations and relevant constituents

Available pharmacodynamic data on the traditionally used ethanol and water extracts are, at best, inconclusive and cannot be considered to support the traditional indications.

3.2 Clinical studies

The ESCOP Monograph [2003] cites a study which comprised 20 healthy volunteers who were treated with daily single doses of 300, 600 or 900 mg of an extract of Melissa leaf (30 % methanol). Cognitive performance was assessed each day in a pre-dose testing session (baseline) and 1, 2.5, 4 and 6 hours 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 hours after the higher doses ($p = 0.0005$ to $p = 0.05$). Reduction of working memory was more pronounced at 1 and 2.5 hours after the higher doses. Self-rated calmness was elevated significantly after 1 and 2.5 hours 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.*, 2003].

Another experimental study comprised 18 healthy volunteers who received single doses of 300 mg or 600 mg of a 30 % aqueous methanol extract of the leaves. The participants were subjected to mild laboratory-induced psychological stress at 1 hour 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 randomized, 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 ≥ 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 said that the extract was prepared with 45 % ethanol (1:1) and the daily dose was 60 drops for 4 months. The result was the same as in the preceding report. [Akhondzadeh *et al*., 2003a].

3.2.1 Assessor's comments on clinical studies of *Melissa officinalis* L., folium, preparations and relevant constituents

The 2 clinical studies by Kennedy et al [2003; 2004] were performed on a methanol extract which is not covered by the 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.

4 ASSESSOR´S OVERALL CONCLUSIONS

The traditional use of *Melissa officinalis* L., folium for the relief of mild symptoms of mental stress and to aid sleep is well documented in recognised handbooks. For the indication 'symptomatic relief of gastrointestinal complaints such as indigestion, flatulence and minor spasms' there is sufficient evidence of traditional use. Products containing *Melissa officinalis* L., folium, are currently available in most Member States. The requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2004/24/EC is considered fulfilled. Many of the products commercially available are combination products with other herbal substances/preparations.

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 genotoxicity, carcinogenicity, reproductive and developmental toxicity. Use during pregnancy and lactation can thus not be recommended.

Insufficient data on use in children are available therefore products containing *Melissa officinalis* L., folium are not recommended for use in children below the age of 12 years.

Conventional clinical safety data are virtually absent, however, longstanding medicinal use and experience of *Melissa officinalis* L., folium have been documented within the Community. No clinical signals that *Melissa officinalis* L., folium is harmful under normal 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.
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 analyzed by HPLC and contains caffeic acid, chlorogenic acid and rosmarinic acid as major components; no details are given. The extract is standardized 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 a.l*, 1999]. The clinical data for this specific product are not considered transferable to other products in the form of a well-established use-monograph. It is questionable whether this highly purified extract should be considered to be a 'herbal medicinal product' or a (combination) product of chemically defined substance(s).

Sufficient data to develop a Community monograph on the traditional use of *Melissa officinalis* L., folium are available. As the minimum required data on mutagenicity (Ames' test) are not available, an inclusion to the Community list of traditional herbal substances and preparations is not recommended.