European Medicines Agency
*Post-authorisation Evaluation of Medicines for Human Use*



London, 21 February 2008
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# OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *MELISSA OFFICINALIS* L., FOLIUM' EMEA/HMPC/5341/2007

Table 1: Organisations that commented on the draft 'Community herbal monograph on *Melissa officinalis* L., folium' as released for consultation on 8 May 2007 until 15 August 2007

| | Name of organisation or individual |
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| 1. | Association of the European Self-Medication Industry (AESGP) |
| 2. | Italian Medicines Agency |
| 3. | Kooperation Phytopharmaka, Germany |
| 4. | European Scientific Cooperative on Phytotherapy (ESCOP) |

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*Table 2: Discussion of comments*

| GENERAL COMMENTS TO DRAFT DOCUMENT | Outcome |
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| Well-established medicinal use<br>Experimental and clinical data and existing official herbal monographs (German Commission E, ESCOP and WHO) have shown evidence of the well-established use of *Melissa officinalis* containing preparations and should be reflected accordingly in the monograph.<br>This applies to mono preparations, and even more so, to fixed combinations of Melissa extracts, which have been used over decades and are one of the leading herbal preparations in their respective indications, with proven efficacy and safety. | Published clinical data are insufficient to support a well-established use. References mentioned rather reinforce the plausibility of the traditional use. This monograph does not address fixed combinations. No changes. |
| We suggest to include a well-established use for topical application into the monograph as clinical data are available supporting the efficacy of extracts from Melissae folium in *Herpes labialis* infections | Available data on herpes infections are connected to one specific product which contains an unusually highly refined extract. Insufficient data on this extract are available in the public domain. The HMPC does not consider the clinical data for this specific product transferable to other products in the form of a well-established use-monograph. No changes. |
| We would like to inform you that from our point of view the scope of the monograph, i.e. the qualitative and quantitative composition, should be described in a more precise manner. Particularly for the so-called "other herbal preparations" information on the drug extract ratio and on the extraction solvent is of utmost importance as well as - if possible - a reference to the respective pharmacopoeia. We would like to recommend to add such information in accordance with the Note for Guidance on the declaration of herbal substances and herbal preparations in medicinal products/traditional products in the SPC. Thus dosage information can be interpreted unambiguously. | We agree that the requested detailed information on the quantitative and qualitative composition would be desirable. Unfortunately it is not available. No changes. |

| SPECIFIC COMMENTS ON TEXT | | |
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| **SECTION TITLE** | | |
| **Paragraph no.** | **Comment and Rationale** | **Outcome** |
| **2. Qualitative and quantitative composition** | Well-established use<br>With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended<br>*Melissa officinalis* L., folium (Melissa leaf)<br>i) Herbal preparations<br>– Liquid extracts (30 - 60% ethanol or methanol) also in fixed combinations with other herbal preparations<br>ii) Aqueous or aqueous-ethanolic dry extracts, also in fixed combinations with other herbal preparations | Published clinical data are insufficient to support a well-established use. No changes. |
| **2. Qualitative and quantitative composition** | Well-established use<br>Dry extracts (70:1, prepared with water) | Available data on herpes infections are connected to one specific product which contains an unusually highly refined extract. Insufficient data on this extract are available in the public domain. The HMPC does not consider the clinical data for this specific product transferable to other products in the form of a well-established use-monograph. No changes. |

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| **2. Qualitative and quantitative composition** | Traditional use<br>i) Herbal preparations<br>- Distillates<br>also in fixed combinations with other herbal preparations<br>iv) Pressed juice from fresh plants<br><br>The modifications reflect the composition of Melissa containing medicinal products currently on the market in Europe.<br><br>For example, in Germany, some examples of medicines containing Melissa are :<br>• Gastrovegetalin solution, Gastrovegetalin 225 (aqueous extract / dry extract for the treatment of gastrointestinal complaints)<br>• Lomaherpan cream (aqueous dry extract for the topical treatment of Herpes simplex)<br>• Sedinfant Lösung (aqueous extract)<br>• Me-Sabona Kapseln<br>• Schoenenberger naturreiner Heilpflanzensaft Melisse, Kneipp Melissen-Pflanzensaft (pressed juice)<br>• Melissengeist (distillate)<br><br>Melissa is also present in a number of combination medicines. Melissa is commonly used with other herbal extracts, e.g. with Valerian, Passiflora or Hops for nervous sleep disorders, or with extracts from Peppermint leaf, Angelica root or other herbs in preparations for gastrointestinal disorders. It is also used in combination with St. John's wort (Me-Sabona plus Kapseln) or with many other herbal ingredients in the “Melissengeist”, obtained by distillation. | This monograph only addresses monopreparations.<br><br>Documentation of 30 years of medicinal use of pressed juice from fresh plants has not been found in the literature. Unless such documentation is provided, this herbal preparation cannot be included in the monograph.<br><br>No changes. |

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| **2. Qualitative and quantitative composition** | "liquid extract 1:1 in 45% ethanol" and a dosage of 2-4 ml up to 3 times per day. We are wondering whether there is a Pharmacopoeia available describing the production of this extract and particularly of the corresponding dry extracts. Furthermore it is not clear whether "in 45% ethanol" means the concentration of ethanol in the herbal medicinal product or the concentration of the extraction solvent. | No reference to an official Pharmacopoeia is available. Information in the monograph stems from the British Herbal Pharmacopoeia (1976). "in 45% ethanol" is interpreted as "use 45% ethanol/water (v/v or W/W) as extraction solvent". No changes. |
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| **3. Pharmaceutical form** | Well-established use<br>Herbal preparations in liquid and solid dosage forms for oral use.<br>The pharmaceutical form should be described by the European Pharmacopoeia full standard term. | See response above. No changes. |
| **3. Pharmaceutical form** | Well-established use<br>For the use in *Herpes labialis* infections the inclusion of semi-solid dosage forms is necessary | See response above. No changes. |
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| **4.1. Therapeutic indications** | Well-established use<br>a) Nervous sleep disorders, tenseness, restlessness and irritability<br>b) Treatment of functional gastro-intestinal disorders and digestive complaints such as minor spasms.<br>Topical treatment of Herpes labialis (cold sores).<br>Background:<br>The well-established indications which we propose to add have been described in the ESCOP monograph (ESCOP 2003), the Hager monograph (Stahl-Biskup 2006), the WHO monograph (WHO 2002) and (except for the antiviral effects) the German Commission E monograph (Commission E 1990). They also correspond to the indications of medicines containing Melissa extracts which are on the market. | See response above. No changes. |

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| **4.1. Therapeutic indications** | Well-established use<br>External use *Herpes labialis* (cold sores)<br>The indication "*Herpes labialis*" is supported by the clinical study of Koytchev at al. 1999 as well as recent in vitro data (Nolkemper et al. 2006) | See response above. No changes. |
| **4.1 Therapeutic indications** | Traditional use<br>c) Nervous sleep disorders, tenseness, restlessness and irritability<br>d) Treatment of functional gastro-intestinal disorders and digestive complaints such as minor spasms.<br>Topical treatment of Herpes labialis (cold sores).<br>Background:<br>For the traditional use, besides the symptomatic treatment of gastrointestinal complaints, a supportive action should be added. This is in line with the indications for Melissa preparations registered as traditional medicinal products under section 109a of the German Medicines Law. | See response above. No changes. |
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| **4.2. Posology and method of administration** | Well-established use<br>**Posology**<br>Liquid extract: 2-4 ml up to 3 times per day<br>Tincture: 2-6 ml up to 3 times per day<br>Fluid or dry extract: 1.5 – 4.5g drug up to 3 times a day<br>External use: Cream containing 1% of aqueous dry extract 2-4 times daily. | Use in children under 12 years of age is not contraindicated. Use in children is not recommended because insufficient data are available. If such severe symptoms occur that medication is considered necessary in this patient group, then medical advice should be sought. This is also in line with the WHO monograph on Melissa. No change.<br>The proposal to delete the limit of 2 weeks duration of use is endorsed. |

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| **4.2. Posology and method of administration** | *Duration of use*<br>No restriction.<br>If the symptoms persist during the use of the medicinal product, medical advice should be sought.<br><br>*Method of administration*<br>Extracts and tinctures for oral use; extracts for topical application.<br>Background:<br>- Posology<br>The indicated dose schemes correspond to the WHO monograph (WHO 2002) and to the doses used in clinical studies of mono preparations.<br><br>The warning against the use in children is neither supported by the ESCOP monograph (ESCOP 2003) nor by traditional or well-established use. The WHO monograph has a general disclaimer pointing to the necessity of medical supervision when Melissa preparations are used in children. Such a disclaimer is not a contraindication.<br><br>A contraindication for children under 12 years of age is not justified, as there is no sign of hazards associated with the use of Melissa preparations. In addition, Melissa leaves are commonly used in food, which reinforces the inappropriateness of a formal warning against the use in children <12 years. | |

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| **4.2 Posology and method of administration** | Herbal combinations with Melissa were explicitly tested and found well tolerable in an open study in 918 children <12 years (Müller and Klement 2006), and in a placebo-controlled study in breast-fed infants (Savino et al. 2005), as well as in a retrospective study in 1.042 children between 0 and 12 years (Gundermann et al. 2004). Hence, the statement indicating that experience in children is lacking is not founded.<br>- Duration of use<br>Some monographs restrict the duration of application of topical Melissa products in the treatment of Herpes Simplex Virus (HSV) infections to 2 weeks. However, this restriction can be explained by the usual duration of the Herpes episode, not by pharmacological/toxicological properties of Melissae folium extract. | |
| **4.2 Posology and method of administration** | <u>Well-established use</u><br>Topical application<br>Cream containing 1% of a lyophilised aqueus extract (70:1) two to four times daily. | |

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| **4.2 Posology and method of administration** | Traditional use<br><br>**Posology**<br>**After corre**<br>~~Adolescents over 12 years of age, adults, elderly~~<br>Herbal substance as a herbal tea: 1.5-4.5 g up to 3 times per day.<br>Liquid extract: 2-4 ml up to 3 times per day<br>Tincture: 2-6 ml up to 3 times per day<br>Corresponding doses of dry extracts.<br>Fresh plant juice: 10 ml 3 times per day<br>~~The use is not recommended in children under 12 years of age (see 4.4. Special warnings and precautions for use).~~<br>Medical supervision is recommended when Melissae folium is applied to children. **Dosage in children according to age[1]).**<br><br>**Duration of use**<br>~~Indication a)~~<br>~~Not to be taken for more than 2 weeks.~~<br>**No restriction.**<br>If the symptoms persist during the use of the medicinal product, ~~a doctor or a qualified health care practitioner should be consulted~~ medical advice should be sought.<br><br>Background:<br>[1] Comment on the dosage recommendation for children:<br>As an example, a preparation in the German market (viscous extract from Melissa leaf (2,3 - 3,0 :1), extraction solvent: water has the following dosage recommendation:<br>Children less than 1 year of age: 1 ml 1 - 2 times daily<br>Children from 1 - 4 years of age: 1 ml 2 - 3 times daily<br>Children from 4 - 12 years of age: 2 ml 3 times daily<br>Children more than 12 years of age and adults: 3 - 6 ml 3 times daily | Detailed information on traditional use (30/15 years) of fresh plant juice has not been provided. No changes.<br><br>Medical supervision cannot be required for a traditional herbal medicinal product. No changes.<br><br>The data on use in children refers to a combination product, which is not addressed in this monograph. No changes. |

[1] Comment on the dosage recommendation for children:

As an example, a preparation in the German market (viscous extract from Melissa leaf (2,3 - 3,0 :1), extraction solvent: water has the following dosage recommendation:

Children less than 1 year of age: 1 ml 1 - 2 times daily

Children from 1 - 4 years of age: 1 ml 2 - 3 times daily

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| **4.3. Contraindications** | Well-established use<br>Hypersensitivity to Melissa officinalis<br>Traditional use<br>Hypersensitivity to ~~the active substance~~ Melissa officinalis.<br>Background:<br>The various monographs do not state any other contraindication (ESCOP 2002; WHO 2003; Mills and Bone 2005; Stahl-Biskup 2006). | Standard text “active substance”. No changes. |
| **4.3. Contraindications** | Well-established use<br>Should contain the text of the column “traditional use” | See comment above. No changes. |
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Children from 4 - 12 years of age: 2 ml 3 times daily
Children more than 12 years of age and adults: 3 - 6 ml 3 times daily

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| **4.4. Special warnings and precautions for use** | Well-established use<br>**None known.**<br>Traditional use<br>~~The use is not recommended in children under 12 years of age due to lack of adequate data.~~<br><br>~~As a precautionary measure, concomitant use with sedatives is not recommended unless advised by a doctor.~~<br><br>For tinctures and extracts, the appropriate labelling for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use", must be included.<br>Background:<br>The WHO monograph does not indicate any specific warnings (WHO 2002). According to the review of Mills and Bone (2005), none are required.<br><br>Melissa preparations have been tested in clinical trials involving breast-fed infants and children (Müller and Klement 2006; Savino et al. 2005). The corresponding trials were performed with combination products and no risks were reported. The warning concerning children should be removed.<br><br>The precautionary measure not to recommend concomitant use with sedatives, unless advised by a doctor, is also not found in the WHO (2002), ESCOP (2003), Commission E and Hager (Stahl-Biskup 2006) monographs. There are no reports of any pharmacodynamic interactions between sedatives and Melissa preparations or their combinations. Melissa does not have sedative effects per se but rather induces sleep by its anxiolytic effect. | The data on use in children refers to a combination product, which is not addressed in this monograph. No changes.<br><br>The information on concomitant use with synthetic sedatives has been removed. |

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| **4.5. Interactions with other medicinal products and other forms of interactions** | Well-established use<br>**None reported.**<br>Background:<br>Corresponds to the WHO, ESCOP and Hager monograph (WHO 2002; ESCOP 2003; Stahl-Biskup 2006), and to the review of Mills and Bone (2005). | See comment above. |
| **4.5 Interactions with other medicinal products and other forms of interactions** | Well-established use<br>Should contain the text of the column “traditional use” | No well-established use indication is accepted. No changes. |
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| **4.6. Pregnancy and lactation** | Well-established use<br>No indications of risks in pregnancy and lactation have appeared from the widespread use of Melissa as a medicinal product.<br>Results of sufficient studies are not available.<br>In accordance with general medical practice, the products should not be used during pregnancy and lactation without medical advice.<br>Traditional use<br>Safety during pregnancy and lactation has not been established.<br>No adverse effects have been reported from the use of Melissa leaf as a medicinal product during pregnancy and lactation.<br>In the absence of sufficient data, the use during pregnancy and lactation is not recommended.<br>Background:<br>The statements are in line with ESCOP and WHO monographs (WHO 2002; ESCOP 2003). A combination preparation containing Melissae folium has been shown to be non toxic in reproductive toxicology testing according to ICH (Rösch et al., 2006). According to the review of Mills and Bone (2005), no harmful effects on the foetus are known, and Melissa is compatible with breastfeeding. Although the constituents of the essential oil of Melissa may pass into breast milk, adverse effects are not to be expected. | In case of absence of sufficient data, the standard wording in this section is used. No changes. |
| **4.6. Pregnancy and lactation** | Well-established use<br>No data available. In accordance with general medical practice the product should not be used orally during pregnancy and lactation without medical advice. | No well-established use indication is accepted. No changes. |

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| **4.6. Pregnancy and lactation** | Traditional use<br>No data available. In accordance with general medical practice the product should not be used orally during pregnancy and lactation without medical advice. | In case of absence of sufficient data, the standard wording in this section is used. No changes. |
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| **4.7. Effects on ability to drive and use machines** | Well-established use<br>**None known.**<br>Traditional use<br>**None known.**<br>~~May impair ability to drive and use machines. Affected patients should not drive or operate machinery.~~<br>Background:<br>The ESCOP monograph does not point to a specific problem with driving or operating machinery (ESCOP 2003). The review of Mills and Bone (2005) explicitly states that no adverse effect on the ability to drive or operate machinery is to be expected. Melissa does not have hypnotic effects, but has an anxiolytic action. We consequently suggest to delete this warning. | It remains unclear whether Melissa has sedative effects or not. The warning simply says that if you are affected, do not drive or operate machinery. No changes. |
| **4.7. Effects on ability to drive and use machines** | Well-established use<br>Not relevant | No well-established use indication is accepted. No changes. |

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| **4.7. Effects on ability to drive and use machines** | We suggest to change the text to "As with most sedatives, taking Melissa officinalis L., folium preparations immediately (up to 2 hours) before driving a car or operating hazardous machinery is not recommended.<br>Reason: No data are available which prove an impairment | It remains unclear whether Melissa has sedative effects or not. The warning simply says that if you are affected, do not drive. No changes. |
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| **4.8 Undesirable effects** | Well-established use<br>None known.<br>Background:<br>This is in line with ESCOP, WHO and Hager monographs (WHO 2002; ESCOP 2003; Stahl-Biskup 2006), and to published reviews of herbal safety (Mills and Bone 2005). | No well-established use indication is accepted. No changes. |
| **4.8 Undesirable effects** | Well-established use<br>Should contain the text of the column "traditional use" | No well-established use indication is accepted. No changes. |
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| **4.9 Overdose** | Well-established use<br>No case of overdose has been reported. | No well-established use indication is accepted. No changes. |
| **4.9 Overdose** | Well-established use<br>Should contain the text of the column "traditional use" | No well-established use indication is accepted. No changes. |
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| **5.1. Pharmacodynamic properties** | Well-established use<br>Preparations from Melissae folium have been shown to affect gastro-intestinal motility, (e.g. spasmolytic effects) in vitro and to have gastric anti-inflammatory effects and sedative effects in vivo.<br>Different combinations with Melissae folium were shown to be efficacious for treatment of functional gastrointestinal diseases and nervous tenseness in a number of randomized controlled double blind clinical trials.<br>Mono-preparations were found to have calming effects in randomized placebo-controlled double blind trials.<br>Antiviral effects were observed in vitro, and confirmed in clinical trials in patients with Herpes labialis.<br>Background:<br><br>▪ *Spasmolytic effects*<br>The essential oil of Melissae folium has been shown to possess spasmolytic properties in ileal preparations *ex vivo* (Debelmas and Rochat 1967; Reiter and Brandt 1985; Wagner and Sprinkmeyer 1973).<br>A 30% ethanolic extract had a significant effect in histamine-induced ileal spasms in vitro (Heinle et al 2006, Itokawa et al 1983) and KCl-induced ileal spasms in vitro (Sadraei et al. 2003) and showed a tendential effect in a fourth study (Forster et al. 1980). This is in accordance with the slight decreasing effect on the slow waves in small intestinal muscle in vitro, which was observed in an electrophysiological study (30 % ethanolic fluid extract, Liu et al 2004).<br>A 30% ethanolic extract of Melissae folium showed a strong binding affinity to the serotonin receptor 5-$HT_4$, but not in the receptors 5-$HT_3$ and muscarinic $M_3$ from the small intestine rats in vitro (Simmen et al. 2006). | No well-established use indication is accepted. No changes. |

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| | A 30% ethanolic fluid extract exerted a significant and dose-dependent tonicising effect on gastric muscle without pre-contraction with a spasmogen, as well as in gastric fundus, corpus and antrum (Schemann et al. 2006). This points to a prokinetic effect in the stomach.<br>In a study of upper gastrointestinal transit time in mice, a Melissa officinalis extract significantly reduced motility which may be the possible mechanism of action in functional gastrointestinal disturbances (Capasso et al. 2007).<br>In a model of gastric hyperacidity and gastric ulcer, a 30 % ethanolic Melissa fluid extract simultaneously inhibited significant the secretion of acid, stimulated the secretion of gastro-protective gastric mucus and played a protective role against indometacin-induced ulcer in vivo in rats (Khayyal et al. 2001). This was connected to a significant increase of the concentration of the anti-inflammatory prostaglandin $E_2$ in the gastric wall (Khayyal et al. 2001).<br>Anti-inflammatory effects were also observed for the same extract in leucocytes (Germann et al. 2006) and in whole blood (Schempp et al. 2004) in vitro. This also points, in addition to the effects in functional gastro-intestinal diseases, to gastro-intestinal anti-inflammatory effects. The Hager monograph also mentions a choleretic action (Stahl-Biskup 2006).<br>Three placebo- and one reference-controlled clinical trials in 926 patients have shown that Melissa extract (30 % ethanolic fluid extract, DER 1:2.5-3.5) in a herbal combination was clinically effective in functional dyspepsia (Rösch et al. 2006). This conclusion was confirmed by meta-analyses (Gundermann et al. 2004, Melzer et al. 2004) and observational and open studies with 2554 patients (Rösch et al. 2006). Efficacy as part of the same herbal combination has also been demonstrated in irritable bowel syndrome by a randomized, placebo-controlled | |

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| | double blind study (Madisch et al. 2004) and retrospective data (Holtmann et al. 2004).<br>Melissa, in another combination, was also effective in abdominal pain and bloating according to a randomized, double blind, placebo controlled study involving 32 patients with irritable bowel syndrome (Vejdani R. et al. 2006).<br>Spasmolytic effects were demonstrated in breast-fed infants with intestinal colic with a combination of chamomile, Melissa and fennel in a randomized double-blind trial (Savino et al. 2005).<br><br>▪ *Soothing effects*<br>Calming effects were described in mice after intraperitoneal application of a 30% ethanolic dry extract (Soulimani et al. 1991; Soulimani et al. 1993), after oral intake of essential oil (Wagner and Sprinkmeyer 1973), and after inhalation of essential oil (Ammon 1989; Buchbauer et al. 1993). Anxiolytic effects of rosmarinic acid (from Melissae extract) were observed in behavioural models in rats (Pereira et al. 2005).<br>A 30% methanolic dry extract of Melissa leaves was tested for its central nervous effects in a placebo-controlled double-blind cross-over trial involving 20 healthy volunteers who received doses of 300, 600 and 900 mg of extract for 4 days in separate study phases. The intake of 300 mg of a 30 % methanolic dry extract per day led to a significantly higher degree of calmness, which points to relaxing effects (Kennedy et al. 2002).<br>Encapsulated dried leaf (1600 mg) led to an acute improvement of cognitive performance and mood in a double-blind, randomised, placebo-controlled study (Kennedy et. al 2003).<br>Anxiolytic/calming effects of Melissae folium have also been observed in an earlier trial with an ethanolic preparation (Buchner et al. 1974). A calming effect of a 45 % ethanolic fluid extract in agitation was observed in a placebo controlled open study in | |

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| | Altzheimer patients (Akhondzadeh et al. 2003).<br>A lozenge containing a herbal combination including Melissa extract was found to have an anxiolytic-like effect in a randomized clinical double blind study in healthy volunteers (Dimpfel et al. 2004).<br>Application of a topical lotion containing Melissa essential oil significantly reduced agitation in patients with dementia in a 4 week double-blind, placebo-controlled study in 72 patients (Ballard et al. 2002).<br>A hydroethanolic extract of Melissa in combination with valerian produced higher sleep quality in volunteers and patients with light insomnia (Cerny and Schmid 1999; Dreßing et al. 1992; Dreßing et al. 1996; Kennedy et al. 2006), and in children <12 years (Müller and Klement 2006).<br><br>▪ *Antiviral effects*<br>Antiviral effects including effects against Herpes simplex virus were found with aqueous extracts from Melissa leaf (Nolkemper et al. 2006, Allahverdiyev et al. 2004, Chlabicz and Galasinski 1986; Cohen et al. 1964; Herrmann, Jr. and Kucera 1967; König and Dustmann 1985; Kucera et al. 1965; Kucera and Herrmann, Jr. 1967; May and Willuhn 1978; Vanden Berghe et al. 1985; Yamasaki et al. 1998).<br>The antiviral effects of a 1% aqueous extract in a topical preparation against HSV were confirmed in an open study ivolving 115 patients (Wöbling and Leonhardt 1994; Wöbling and Milbradt 1984), and confirmed in a double-blind, placebo-controlled studies (Koytchev et al. 1999; Vogt et al. 1991; Wöbling and Leonhardt 1994) | |

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| **5.1. Pharmacodynamic properties** | Well-established use<br>We refer to the ESCOP monograph. The level of evidence for *Herpes labialis*: 1b (see clinical study). The ATC code for *Herpes labialis* (D11AX99) should be added. | No well-established use indication is accepted. No changes. |
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| **5.2. Pharmacokinetic properties** | Well-established use<br>**The uptake of rosmarinic acid from Melissae folium extract was shown in small intestine ex vivo and in vivo.**<br>Background:<br>The uptake of rosmarinic acid from Melissae folium fluid extract (30 % ethanol) was shown in small intestine *ex vivo* (Kelber et al 2006). *In vitro* and *in vivo* data from rat (Konishi et al. 2005) as well as from the Caco-2 model (Konishi and Kobayashi 2005) pointed to paracellular absorption of rosmarinic acid. It can be assumed that rosmarinic acid is metabolised in the intestinum into m-coumaric acid and hydroxylated phenylpropionic acids, which are then more efficiently taken by the specific intestinal monocarboxylic acid transporter (MCT). Furthermore, human data with Perilla frutescens extract also showed an efficient absorption of rosmarinic acid in vivo (Baba et al. 2004, 2005). These data were not included in earlier monographs, as e.g. the ESCOP monograph (2003). | No well-established use indication is accepted. No changes. |
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| **5.3. Pre-clinical safety data** | Well-established use<br>Melissa tincture and ethanolic extract did not show any mutagenic effects in mutagenicity and genotoxicity studies.<br>A complete battery of toxicity tests (including acute, chronic and reproductive toxicity) has been performed for a combination product containing an ethanolic Melissae extract. No relevant toxic effects were shown.<br>Traditional use<br>Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended~~, unless necessary for the safe use of the product~~.<br>~~Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.~~<br>Mutagenic effects could be excluded in studies on mutagenicity and genotoxicity.<br>Directive 2001/83/EC does not require pre-clinical safety data. Safety of traditionally applied products is sufficiently characterized by long-standing experience. Thus, the restriction "unless necessary for the safe use of the product" is misleading in the case of *Melissa*, as there is no evidence of unsafe use.<br><br>Directive 2001/83/EC does not require testing for reproductive toxicity, genotoxicity or carcinogenicity. As the requirement for such tests is a relatively recent development, it cannot be expected that such tests have been performed with traditional products. Again, the 15 year rule of the Directive 201/83/2001 was made to ensure the lack of a corresponding risk through long-term experience with safe application. Since there is no suspicion of genotoxic or carcinogenic risk related to the use of *Melissa* preparations, the call for additional data to this regards would not be appropriate. | No well-established use indication is accepted. No changes.<br><br>"unless necessary for the safe use of the product" is a standard text used in all monographs on traditional herbal substances/preparations. No changes.<br><br>The data concerning mutagenicity in Schimmer et al. (1994) concerned a 70% ethanol extract which is not covered by the monograph. The data concerning mutagenicity in Ramos Ruiz et al. (1996) were derived from tests on *Aspergillus nidulans*, which are not considered sufficiently reliable (Ames' test minimum requirement according to guideline). |

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| **5.3. Pre-clinical safety data** | However, data on Melissa tincture and ethanolic extract exist and have shown a lack of mutagenic effects (Ramos Ruiz et al. 1996; Saigusa and et al. 1982; Schimmer et al. 1994). Further on, a complete range of toxicological tests including acute, chronic and reproductive toxicity testing has been performed with a combination preparation containing Melissa extract (Rösch et al. 2004). Correspondingly, the statement that tests on genotoxicity have not been performed is not correct. | |
| **5.3. Pre-clinical safety data** | Well-established use<br>We suggest to add as a reference: Ruiz et al. | No well-established use indication is accepted. No changes. |
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| **5.3. Pre-clinical safety data** | Inhibition of the thyroid stimulating hormone (TSH) deriving from in vitro studies as well from studies in animals has been described, as reported in the following references:<br>1) Santini F, et al., In vitro assay of thyroid disruptors affecting TSH-stimulated adenylate cyclase activity. J Endocrinol Invest. 2003 Oct;26(10):950-5.<br>2) Benvenga S. Assault on the thyroid by xenobiotics: another attack on G-protein coupled. J Endocrinol Invest. 2003 Oct;26(10):948-9.<br>3) Auf'mkolk M, et al., Extracts and auto-oxidized constituents of certain plants inhibit the receptor-binding and the biological activity of Graves' immunoglobulins. Endocrinology. 1985 May;116(5):1687-93.<br>4) Auf'mkolk M, et al., Inhibition by certain plant extracts of binding and adenylate cyclase stimulatory effect of bovine thyrotropin in human thyroid membranes. Endocrinology. 1984 Aug;115(2):527-34.<br>5) Sourgens H, et al., Antihormonal effects of plant extracts. Planta Med. 1982 Jun;45(6):78-86.<br>Therefore, according to the numerous evidences, we think that this should be reported at least in the preclinical section, because it is relevant for the safe use of the product, particularly for people affected by thyroid diseases. | Endorsed. The following text has been added to the monograph: “Data from *in vitro* and animal studies indicate that the water extract of *Melissa officinalis* may inhibit the activity of thyroid stimulating hormone (TSH). The clinical relevance of these findings is not known.” |