European Medicines Agency
Evaluation of Medicines for Human Use

London, 4 September 2008
Doc. Ref. EMEA/HMPC/101815/2008

OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *MENTHA X PIPERITA* L., FOLIUM' (EMEA/HMPC/193909/2007)

Table 1: Organisations providing comments on the 'Community herbal monograph on *Mentha x piperita* L., folium' as released for consultation on 5 July 2007 until 15 October 2007.

	Organisation
1	The Association of the European Self-Medication Industry (AESGP)
2	Kooperation Phytopharmaka, Germany

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SPECIFIC COMMENTS ON TEXT		
Paragraph no.	**Comment and Rationale**	**Outcome**
2. Qualitative and Quantitative Composition	We suggest to add the following herbal preparations as examples to the list in order to cover the existing variability of preparations: Dry extract (5-7:1, water) Dry extract (3-6:1, ethanol 60 % (V/V)) Liquid extract (1:1, ethanol 35 % (V/V)) Tincture (1:5; ethanol 45% (V/V)) (ESCOP) The following list (from the "Rote Liste 2007") contains preparations in the German market containing peppermint leaves. The "Rote Liste" of 1989 additionally lists various forms of peppermint preparations, mainly in combinations: • as a 1:4-5.5 extracts with 96% ethanol as in Asgocholan Rhein-Pharma or Chelipophyt N • as a 1:4 tincture in Galleb • as a 5:1 extract in 60% ethanol in Hepagallin • as an aqueous dry extract in Knufinke-Leber und Galletee • Plant powder in Hepaton and Lopasan • Leaves (tea) in many preparations such as Gallen-Leber-Tee Cholaflux, Gallen-Leber-Tee Stada, Hacko-Kloster-Kräutertee, Kneipp-Leber und Galletee; Salus Leber-Galle-Tee	Not endorsed This monograph is just related with the single preparation and not with combinations.

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4.1 Therapeutic indication	We agree with the wording of indications which have been attached to the area of traditional use. In addition we suggest including a statement indicating that the well-established medicinal use has been proven for combination products (see 'other comments' section).	See above. The statement related with some combination products is included at the assessment report.
4.2 Posology	WE agree with the wording given under posology and suggest to add the following examples: Dry extract (5-7:1, water) 32.5-65 mg 3 times daily Dry extract (3.5-5:1, ethanol 70 %) 440-570mg 2-3 times daily Liquid extract (1:2, ethanol 37,8 % (m/m)) 640mg 3 times daily Tincture (1:5; ethanol 45% (V/V)); 2-3ml 3times daily (ESCOP) Other preparations equivalent to this liquid extract and tincture and to these dry extracts Thus the preparations being in the market can be covered by the dosage recommendations. For the herbal tea, we propose in accordance with the ESCOP monograph: "4.5 - 9 g of the herbal substance, divided in three single doses. Children between four and twelve years of age 3 - 5 g, adolescents between twelve and 16 years of age 3 - 6 g to be divided in **3 -** single doses." We agree with the wording given under posology and suggest to add the following examples:	These preparations are not covered by this monograph. It is already on the monograph.

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	Background: The original dose recommendations in the section “traditional use” correspond to the indications of the ESCOP monograph (ESCOP 2003). However, the dose indicated for adults appears to relate to traditional use against nausea, not dyspeptic complaints. The mean single dose for herbal infusions is 3 - 6 g, with 3 - 4 doses per day. This amounts to a maximum dose of 24 g of peppermint leaves/day. Furthermore we propose to delete the sentence: "The use is not recommended in children under four years of age (see section 4.4 Special warnings and precautions for use)" because the warning not to use of peppermint leaf preparations in small children is not covered by scientific literature.	There is no references to the use of 24 g of peppermint leaves by day. Not endorsed. It is not recommended because there is no experience and safety available on the use under 4 years of age.
4.3 Contra-indications	We suggest to delete the sentence: "The product must not be used in patients with cholangitis, gallstones and any other biliary disorders that require medical supervision and advice." The ESCOP monograph does not contain these contraindications. They seem overly cautious since peppermint leaf preparations are indicated for the treatment of disorders of the liver-bile-tract. The restriction regarding gall stones does not apply to peppermint alone, but is a general disclaimer of all cholekinetic agents. Peppermint is, however, not a cholekinetic but a choleretic agent.	Endorsed. It should be changed to Special warnings, as this preparation must be used cautiously on inflamed conditions of the GI tract and in case of gallstones, where a medical supervision must exist.

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4.4. Special warnings and precautions for use	We suggest deleting the sentence: "Patients with gastroesophageal reflux (heartburn) should avoid peppermint leaf preparations, because heartburn may increase." The ESCOP monograph has no special warnings ("none required"). The warning against use in gastroesophageal reflux does not apply to peppermint leaf preparations, which contain only small proportions of essential oils, but to the essential oil in non-enteric-coated galenical forms. Adverse effects from the use in children are not to be expected.	Not endorsed. Peppermint leaf extracts reduces the tonus of the oesophageal sphincter (Escop, 2nd ed.), which may increase the gastroesophageal reflux.
4.6 Pregnancy and lactation	We would like to propose the following wording: **No adverse effects have been reported from the use of Peppermint herb as a medicinal product during pregnancy and lactation**. This corresponds to the ESCOP monograph.	Not endorsed.
4.6 Pregnancy and lactation	We would like to propose the following wording: "Safety during pregnancy and lactation has not been established. **No adverse effects have been reported from the use of Peppermint herb as a medicinal product during pregnancy and lactation**. **As a precautionary measure,** in the absence of sufficient data, the use during pregnancy and lactation is not recommended without medical advice**."** This corresponds to ESCOP monograph (ESCOP 2003). Peppermint leaf was reported compatible with breastfeeding (Mills 2005). However, the opinion has been expressed that it may reduce milk flow in breastfeeding women (Mills 2005). Whereas some publications recommend peppermint tea to increase milk flow, others recommend it to alleviate weaning. Peppermint may help activating galactorrhoea after giving birth through its spasmolytic effects.	No change.

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4.8 Undesirable effects	We propose to delete the sentences "The gastroesophageal reflux may worsen and heartburn may increase. See also section 4.4 Special warnings and precautions of use." and insert "None reported." According to the ESCOP monograph, no adverse effects are known. Heartburn as an adverse effect is not related to the application of peppermint leaf preparations, which contain only small proportions of essential oil, but to the use of the essential oil in non-enteric-coated galenical forms.	See 4.4
5.3 Pre-clinical safety data	We suggest deleting the sentences “unless necessary for the safe use of the product. Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.” The following wording might be used instead: “Peppermint essential oil had no mutagenic or DNA-damaging activity in either the AMES or Mouse lymphoma Assay. Aqueous peppermint dry extract did not cause toxicity in acute toxicity testing (LD_{50} >4 g/kg b.w. in mice. Aqueous peppermint extract has no genotoxic effects in rats and does not show nephrotoxicity. Peppermint tea and menthol are neither embryotoxic nor teratogenic in rats.”	No change. Results of the Ames and MLA studies on peppermint oil cannot be reliably extrapolated to leaves preparations or extracts. Aqueous peppermint extract seems protect against some genotoxic insults in rats, but this does not mean that it has been adequately tested for genotoxicity in OECD-accepted genotoxicity tests.

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	Background: Directive 2001/83/EC does not require pre-clinical safety data. Safety of traditionally applied products is sufficiently characterised by long-standing experience. Thus, the restriction "unless necessary for the safe use of the product" is misleading in the case of *Mentha x piperita*, as there is no evidence of unsafe use. The question of carcinogenitiy and reproductive toxicity was addressed in various studies. These experiments were not performed as pivotal toxicity studies and have thus only limited value, but the results still confirmed the safety of peppermint leaf preparations. Peppermint leaf extract has been proven non-toxic up to 4 g/kg in mice over seven days (Della Logia et al. 1990). Aqueous peppermint leaf extract protects from chemically and radiation-induced tumours *in vivo* (Kumar et al. 2004; Samarth et al. 2006a; Samarth et al. 2006b; Samarth et al. 2006c). Infusions of peppermint tea do not show genotoxic properties, but rather protect from genotoxicity of other compounds (Romero-Jimenez et al. 2005). A combination tea with peppermint did not affect postnatal development or demonstrate embryotoxicity or teratogenicity when administered to rats (Mills 2005). Menthol as an isolated compound had no teratogenic effects in mice, rats, hamsters and rabbits at doses of 190, 220, 400 and 430 mg/kg, respectively (Mills 2005).	

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	Slight effects on male reproductive function (segmental maturation arrest in the seminiferous tubules) have been reported based on an experiment in rats with 2% peppermint tea in the drinking water. No signs of nephrotoxicity were found (Akdogan et al. 2004). Peppermint Oil was negative in the Ames test and a mouse lymphoma mutagenesis assay but gave equivocal results in a Chinese hamster fibroblast cell chromosome aberration assay. In a carcinogenicity study of toothpaste and its components, no apparent differences were noted between mice treated with Peppermint Oil and those treated with the toothpaste base (Nair 2001).	