European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *MENTHA X PIPERITA* L., AETHEROLEUM' (EMEA/HMPC/349466/2006)

Table 1: Organisations providing comments on the 'Community herbal monograph on *Mentha x piperita* L., aetheroleum' as released for consultation on 8 May 2007 until 15 August 2007.

	Organisation
1	The Association of the European Self-Medication Industry (AESGP)
2	Kooperation Phytopharmaka, Germany
3	Laboratoire Monin-Chanteaud, France
4	Agenzia Italiana del Farmaco (AIFA), Italy

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SPECIFIC COMMENTS ON TEXT

Paragraph no.	Comment and Rationale	Outcome
4.1. Thera-peutic indication	We appreciate the inclusion of the mentioned two indications, minor spasms of the gastro-intestinal tract and mild tension type headache, under the well-established medicinal use. In addition, we recommend to list the five indications mentioned under traditional use also under well-established medicinal use. This is justified on the basis of the following data: <u>Relief of symptoms in coughs and colds (no. 1, 4 and 5 of the HMPC draft)</u> Reasons: Two actions on secretion in the respiratory tract are reported: secretolytic in the bronchi [Schilcher 1986, Haen 1989] and decongestant in the nose [Reiter and Brandt 1985]. Studies to assess the decongestant action of menthol have been carried out on 62 volunteers with common cold, of whom 30 received a lozenge containing 11 mg of menthol [Eccles 1990]; on 29 healthy subjects breathing through an inhaler containing 125 mg of menthol dissolved in 1 ml of liquid paraffin [Eccles 1989]; and on 31 subjects receiving for 5 minutes menthol-containing air produced by passing the air through a flask containing approximately 1 g of menthol at 80°C [Eccles 1983, Burrow 1983]. These studies all showed that inhalation of menthol causes a subjective sensation of improved nasal air flow or 'easier breathing'. However, in subjects with common cold suffering from nasal congestion, inhalation of menthol produces no objective reduction in nasal airway resistance as measured by rhinomanometry [Eccles 1990, 1994]. The	<u>Relief of symptoms in coughs and colds (no. 1, 4 and 5 of the HMPC draft)</u> Not endorsed. The studies are related to the effects of menthol on nasal congestion of several origins and not to peppermint oil on the relief of symptoms on cough and cold.

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	indication is also described in the ESCOP monograph [ESCOP 2003]. Symptomatic relief of localised pruritic conditions in intact skin (no.3 of the HMPC draft) The well-established medicinal use of this indication can be justified by scientific data from Brown 1972, Osterler 1976, Rajka 1976 and Gilchrest 1982 as well as in the ESCOP monograph [ESCOP 2003].	Not endorsed These old articles are revising the treatment for pain in herpesvirus infections (Ostler, Brown) and for general pruritus (Gilchrest), referring to the effect of a combination of menthol with calamine or with phenol on pain and pruritus.
4.1. Therapeutic indication	Traditional use: Oral use: Prevention and treatment of nausea (indigestion, sea sickness)	It was not indicated any literature. This indication (nausea in general) is found in several articles on their introduction, as an historical indication. The study mentioned in the AR on the postoperative nausea, it was used peppermint oil for inhalation and not for oral use.
4.1. Therapeutic indication	1) Cutaneous use: Herbal medicinal product for the symptomatic relief of mild tension type headache. Comments: We believe that do not exist the evidence for the well established use in this indication. Only two trials report that topical application of peppermint oil is effective in reducing symptoms of tension headache. In the first trial, the analgesic effect with the reduction in sensitivity to headache was produced by a combination of peppermint oil with ethanol (90%), but the real contribution of peppermint oil to the efficacy was unclear (Gobel H, Cephalalgia. 1994 Jun; 14(3): 228-34) because ethanol was not administered in a control group. In the second trial the authors corrected the mistake in the project of the first trial	The first trial was a double blind placebo controlled, randomized, four-fold crossover study, investigating experimental algesimetric parameters, in 32 healthy subjects. Four different preparation tests were used – peppermint oil 10g and eucalyptus oil 5g plus ethanol 90% to 100g; 10g PO and traces of EO plus 90% ethanol; traces of PO and 5g of EO plus ethanol 90%; traces of PO and traces of EO plus ethanol 90% (placebo). On the results, the combination of PO with ethanol had a significant analgesic effect with a reduction in sensitivity of headache, compared to the other preparations. The second was a randomised, placebo-controlled double-blind crossover study, using 10g PO plus 90% ethanol. The placebo was traces of PO plus ethanol 90%. The reference preparation was 500mg acetaminophen. 141 headache attacks (IHS classification) on 41 patients were analysed. The positive result was significant (*P<0, 01*). The number of patients is small, the inclusion criteria are not well defined and the range of ages is very

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	and a solution of ethanol was used as a placebo. However, statistical calculation of sample size was not done in advance and the study recruited only 41 subjects, which were divided into four different treatments, thus indicating that each treatment was investigated on a really too small number of patients. These weak results have not been confirmed by other investigations.	large. We can conclude that there is not strong evidence. Nevertheless, we can find two reasons to include this indication at the WEU: 1. Tension headache is a medical diagnosis and it is not suitable for a traditional indication 2. Besides not having good and large studies, we have some evidence which may be classified at the level IIb.
4.2. Posology	Oral use: Children over 7 years of age, adults: 2 drops up to 3 times daily, on a piece of sugar Not to be used more than 3 days	It was not sent any bibliography to support this posology.
4.3. Special warnings and precautions for use	"Caution has been urged for peppermint oil therapy in patients with gastrointestinal reflux, hiatal hernia or kidney stones" (Diane L. McKay* and Jeffrey B. Blumberg - A Review of the Bioactivity and Potential Health Benefits of Peppermint Tea (*Mentha piperita* L.) *Phytother. Res.* 20, 619–633 (2006)). We suggest to add in this section a recommendation for not using in patients with hiatal hernia or significant gastroesophageal reflux disease	It is already stated on this point that there could be an exacerbation of heartburn which is the major symptom of hiatal hernia and gastro oesophageal reflux. It is also stated that the treatment should be discontinued in these patients. This symptom worsens with the direct action of peppermint oil at the oesophagus and stomach mucosa. As the pharmaceutical form is a gastro resistant capsule, it is recommended that it must not be broken or chewed, because this would release the peppermint oil prematurely, possibly causing local irritation of the mouth and oesophagus.
4.4. Special warnings and precautions for use	We disagree with the statement that the cutaneous use should not be recommended in children and adolescents under 18 years of age. There is no data on risks available, except in children less than 2 years of age (see 4.3).	Not endorsed. The studies performed were on patients above 18 years old, for 10% of peppermint oil in ethanol.

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4.5. Interactions with other medicinal products and other forms of interaction	Peppermint oil has been reported to raise serum levels of simvastatin and felodipine (Plendil) in humans (Dresser GK, et al., Peppermint oil increases the oral bioavailability of felodipine and simvastatin. Amer Soc Clin Pharmacol Ther Ann Meeting, March 24-27, 2002;TPII-95). Potential interactions with these drugs should be mentioned.	See point 5.2
4.9. Overdose	As published by Kooperation Phytopharmaka (1998) there is no data available on oral overdosing of peppermint oil. We therefore suggest saying under "oral use" and "oromucosal use": "No case of overdose has been reported." With regard to the wording on overdose after inhalation, we suggest to take over the wording of the ESCOP monograph: "Excessive inhalation of mentholated products has caused reversible, undesirable effects, such as nausea, anorexia, cardiac problems, ataxia and other CNS problems, probably due to the presence of volatile menthol" [Luke 1962, Thomas 1982, O'Mullana 1982].	Not endorsed. There are some articles describing the symptoms of overdose, not only inhaled but also by ingestion of large doses of peppermint or menthol. We can find this at Eickholt TH, Box RH. Toxicities of peppermint and pycnanthemum albescens oil, fam. *Labiateae*. *J Pharm Sci* 1965; 54:1071-1072. Aspiroz F, Serra J., Treatment of excessive intestinal gas. *Current treatment options in Gastroenterology* 2004, 7:299-305; Soo Hoo GW, Fatal large-volume mouthwash ingestion in an adult: a review and the possible role of phenolic compound toxicity.
5.2. Pharmacokinetic properties	From our point of view, the first three sentences of the second paragraph under "oral use" should be deleted. In the study performed by Gelal et al. (2005, see attachment), a potential influence of menthole on felodipine, a CYP3A4 substrate, was examined in 10 healthy volunteers. It was found that felodipine pharmacokinetics and pharmacodynamics were unaffected by oral administration of 200 mg menthol. For this reason the first and the third sentence should be deleted, and the second sentence as well because further investigations are not justified.	Endorsed The study from Dresser et al. was not confirmed by the other study from Gelal et al. Even Dresser suggested that the results required more studies.