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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

COMMUNITY HERBAL MONOGRAPH ON *MENTHA x PIPERITA* L., AETHEROLEUM

DISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	January 2007 March 2007 May 2007
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ADOPTION BY HMPC	

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KEYWORDS	Herbal medicinal products; HMPC; Community herbal monographs; well-established medicinal use; traditional use; *Mentha x piperita* L.; Menthae piperitae aetheroleum; peppermint oil

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COMMUNITY HERBAL MONOGRAPH ON
***MENTHA x PIPERITA* L., AETHEROLEUM**

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished product.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1, 2]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(1)(a)(ii) of Directive 2001/83/EC as amended	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended
Mentha x piperita L., aetheroleum (peppermint oil)	*Mentha x piperita* L., aetheroleum (peppermint oil)
i) Herbal substance not applicable	i) Herbal substance not applicable
ii) Herbal preparation	ii) Herbal preparation
Essential oil obtained by steam distillation from the fresh aerial parts of the flowering plant.	Essential oil obtained by steam distillation from the fresh aerial parts of the flowering plant.

3. PHARMACEUTICAL FORM

Well-established use	Traditional use
In gastro–resistant capsules (for oral use). In liquid or semi-solid preparations (for cutaneous use).	In liquid or semi-solid preparations • For cutaneous and transdermal use • For inhalation. • For oromucosal use
The pharmaceutical form should be described by the European Pharmacopeia full standard term.	The pharmaceutical form should be described by the European Pharmacopeia full standard term.

[1] The material complies with the Ph. Eur. monograph (ref. 01/2005:0405)
[2] The declaration of the active substance(s) for an individual finished product should be done in accordance with relevant herbal quality guidance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Well-established use	Traditional use
• Oral use 1. Herbal medicinal product for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome. • Cutaneous use 2. Herbal medicinal product for the symptomatic relief of mild tension type headache.	Traditional herbal medicinal product • Cutaneous and transdermal use 1. For the relief of symptoms in coughs and colds 2. For the symptomatic relief of localised muscle pain 3. For the symptomatic relief of localised pruritic conditions in intact skin • Inhalation 4. For the relief of symptoms in coughs and colds • Oromucosal use 5. For the relief of symptoms in coughs and colds The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

4.2 Posology and method of administration

Well-established use	Traditional use
Posology • Oral use The use is not recommended in children under 8 years of age (see 4.4 Special warnings and precautions for use). *Adolescents over 12 years of age, adults, elderly* 0.2 - 0.4 ml in gastro-resistant capsules up to three times daily. *Children between 8 to 12 years of age* 0.2 ml in gastro resistant capsules, up to three times daily. • Cutaneous use The use is not recommended in children and adolescents under 18 years of age (see 4.4 Special warnings and precautions for use).	**Posology** The use in children under 2 years of age is contraindicated (see 4.3 Contraindications). The use is not recommended in children between 2 to 4 years of age (see 4.4 Special warnings and precautions for use). • Cutaneous and transdermal use - Indications 1, 2 and 3 Single dose *Children between 4 to 10 years of age* Semi-solid preparations 2 - 10% Hydroethanolic preparations 2 - 4%

Adults, elderly In liquid or semi-solid preparations 10% in ethanol, up to three times daily. **Duration of use** • Oral use The gastro-resistant capsules should be taken until symptoms resolve, usually within one or two weeks. At times when the symptoms are more persistent, the intake of gastro-resistant capsules can be continued for periods of no longer than 3 months per course. • Cutaneous use If symptoms persist or worsen after 2 weeks, a physician should be consulted. **Method of administration** • Oral use The capsule must be taken before meals. • Cutaneous use The solution should be rubbed on the skin of the forehead and temples, every 15 minutes.	*Children between 10 to 12 years of age, adolescents between 12 to 16 years of age* Semi-solid preparations 5 - 15% Hydroethanolic preparations 3 - 6% up to three times daily *Adolescents over 16 years of age, adults* Semi-solid and oily preparations 5 - 20% In aqueous-ethanol preparations 5 - 10% In nasal ointments 1 - 5% essential oil. • Inhalation - <u>Indication 4</u> *Adolescents over 12 years of age, adults* 2 - 4 drops up to three times daily • Oromucosal use - <u>Indication 5</u> 2 - 3 drops (0.08 - 0.12 ml), 3 - 4 times per day (0.2 - 0.5 ml) **Duration of use** - <u>Indications 1, 4 and 5</u> Not to be used for more than 2 weeks. - <u>Indications 2 and 3</u> It is not recommended to use the medicinal product continuously for more than 3 months. If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Method of administration** • Cutaneous and transdermal use - <u>Indication 1</u> Application on the chest or on the back - <u>Indications 2 and 3</u> Application on the affected area

	• Inhalation The essential oil is added to hot water and the vapour is inhaled. Alternatively, the essential oil can be added on an appropriate support/material and the vapour is inhaled. • Oromucosal use In lozenges or oral spray.

4.3 Contraindications

Well-established use	Traditional use
• Oral use Hypersensitivity to peppermint oil or menthol. Patients with liver disease, cholangitis, achlorhydria, gallstones and any other biliary disorders. • Cutaneous use Hypersensitivity to peppermint oil or menthol.	Children under 2 years of age, because menthol can induce reflex apnoea and laryngospasm. Children with history of seizures (febrile or not). Hypersensitivity to peppermint oil or menthol.

4.4 Special warnings and precautions for use

Well-established use	Traditional use
• Oral use The use is not recommended in children under 8 years of age, as there is no sufficient experience available. The capsules should be swallowed whole, i.e. not broken or chewed, because this would release the peppermint oil prematurely, possibly causing local irritation of the mouth and oesophagus. Patients, who already suffer from heartburn have sometimes an exacerbation of this symptom after taking peppermint oil. Treatment should be discontinued in these patients. • Cutaneous use The use is not recommended in children and adolescents under 18 years of age. Eye contact with unwashed hands after the application of peppermint oil may potentially cause irritation.	The use is not recommended in children between 2 to 4 years of age, as there is no sufficient experience available. • Cutaneous and transdermal use Eye contact with unwashed hands after the application of peppermint oil, may potentially cause irritation. Peppermint oil should not be applied on broken or irritated skin. • Oromucosal use Patients, who already suffer from heartburn have sometimes an exacerbation of this symptom after taking peppermint oil. Treatment should be discontinued in these patients. Peppermint oil should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract.

4.5 Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
• Oral use Use of food or antacids administered at the same time could cause early release of capsule content. Other medicinal products used to decrease stomach acid, like histamine-2 blockers and proton pump inhibitors may cause premature dissolution of the enteric coating and should be avoided.	None reported.

4.6 Pregnancy and lactation

Well-established use	Traditional use
• Oral use Studies in animals have shown no teratogenic effects. It is unknown if peppermint constituents are excreted in human breast milk. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. • Cutaneous use Data on the use during pregnancy and lactation is not available. As a general precaution, the use is not recommended, unless medical advice proposed benefit is higher than the potential risk.	• Cutaneous and transdermal use • Inhalation • Oromucosal use In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

4.7 Effects on the ability to drive and use machines

Well-established use	Traditional use
No studies on the effect on the ability to drive and use machines have been performed.	No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Well-established use	Traditional use
• Oral use Urine and stools with an odour to menthol were observed; dysuria and inflammation of the glans of the penis have been reported. The frequency is not known.	• Cutaneous and transdermal use Hypersensitivity reactions such as skin rash, contact dermatitis, and eye irritation have been reported. These reactions are most of the time mild and transient. The frequency is not known. Irritation of the skin and mucosa of the nose is possible, after local application. The frequency is not known.

Allergic reactions to menthol were reported, with headache, bradycardia, muscle tremor, ataxia, anaphylactic shock and erythematous skin rash. The frequency is not known. Heartburn, perianal burning, blurred vision, nausea and vomiting were reported. The frequency is not known. • Cutaneous use Hypersensitivity reactions such as skin rash, contact dermatitis, and eye irritation have been reported. These reactions are the most of the time mild and transient. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	• Inhalation Apnoea, broncho- and laryngoconstriction in hypersensitive patients have been reported. The frequency is not known. • Oromucosal use Contact sensitivity to menthol and peppermint oil in patients presenting with intra-oral symptoms in association with burning mouth syndrome, recurrent oral ulceration or a lichenoid reaction, were reported. The frequency is not known. Allergic reactions to menthol were reported, with headache, bradycardia, muscle tremor, ataxia, anaphylactic shock and erythematous skin rash. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care professional should be consulted.

4.9 Overdose

Well-established use	Traditional use
• Oral use Overdose may cause severe gastro-intestinal symptoms, diarrhoea, rectal ulceration, epileptic convulsions, loss of consciousness, apnoea, nausea, disturbances in cardiac rhythms, ataxia and other CNS problems, probably due to the presence of menthol. In the event of overdose, the stomach should be emptied by gastric lavage. Observation should be carried out with symptomatic treatment if necessary.	• Cutaneous and transdermal use No case of overdose has been reported. • Inhalation Inhalation of large doses of menthol may lead to dizziness, confusion, muscle weakness, nausea and double vision. • Oromucosal use Overdose may cause severe gastro-intestinal symptoms, diarrhoea, rectal ulceration, epileptic convulsions, loss of consciousness, apnoea, nausea, disturbances in cardiac rhythms, ataxia and other CNS problems, probably due to the presence of menthol. In the event of overdose, the stomach should be emptied by gastric lavage. Observation should be carried out with symptomatic treatment if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Well-established use	Traditional use
• Oral use Pharmacotherapeutic group: *Other drugs for functional bowel disorders* ATC code: *AO3AX* *In vitro* studies The principal pharmacodynamic effect of peppermint oil relevant to the gastrointestinal tract is a dose-related antispasmodic effect on the smooth musculature, due to the interference of menthol with the movement of calcium across the cell membrane. Peppermint oil showed antifoaming and carminative activity *in vitro.* Reductions in gastric and intestinal foam volume were observed *in vitro* studies with peppermint oil. *In vivo* studies In several studies in healthy subjects or patients, who underwent exposure to peppermint oil either by topical intraluminal (stomach or colon) or oral administration by single doses, result in effects, indicating a substantial spasmolytic action of peppermint oil on the smooth muscles of the gastrointestinal tract. The enteric coating delays the release of the product until it reaches the distal small bowel, exerting local effects of colonic relaxation. Peppermint appears to enhance production of bile. The choleretic and antifoaming effects of peppermint oil play an additional role to the antispasmodic action, decreasing the abdominal distension, as the discomfort and abdominal pain.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

• Cutaneous use Pharmacotherapeutic group: *Other local anesthetics* ATC code: *N01BX* The topical application of peppermint oil, produces a prolonged cold sensation at the local of application, by the stimulation of the cold-sensitive receptors, giving an analgesic effect. The application to the forehead showed on the EMG activity, a significant reduction of the M temporalis wave, as a pronounced increase in blood flow through the capillaries of the skin.	

5.2 Pharmacokinetic properties

Well-established use	Traditional use
• Oral use Menthol and other terpene constituents of peppermint oil are fat soluble and rapidly absorbed at the proximal small intestinal tract. To some extent, they are excreted in the form of glucoronide. The peak menthol urinary excretion levels were lower and secretion delayed with the modified-release preparations, than with the immediate release preparations. In one clinical study with peppermint oil and one clinical study with menthol, some inhibition of CYP3A4 activity has been described. Further investigations are necessary. On a preliminary report, peppermint oil, when administered orally, may interfere with felodipine, increasing their blood levels. In animals (rats), peppermint oil increases levels of cyclosporine in the blood, but this is not clear in humans. • Cutaneous use The systemic absorption after dermal application was examined and concentration time profiles were erratic and variable and the half-lives relatively shorts.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended • Cutaneous and transdermal use The absorption rate for Peppermint oil was measured after the application of eserine in a peppermint oil vehicle, to a 2.2cm^2 shaved area on the abdomen of mice. The latent period between application and the eserine-induced signs, gave the absorption rate of peppermint oil, which was of 58 minutes. The systemic absorption after dermal application was examined and concentration time profiles were erratic and variable and the half-lives relatively shorts. • Inhalation After inhalation, pulmonary absorption depends on various factors, like the type of compound. Their release depends on the water temperature. The rapid elimination indicates that there should be no accumulation during long-term application.

5.3 Preclinical safety data

Well-established use	Traditional use
Peppermint oil was negative in two validated tests of genotoxicity, the Ames test and the mouse lymphoma assay. There is more evidence for genotoxicity potential of menthol and there seems to be a discrepancy between peppermint oil and its most important constituent menthol. However, the present evidence points to a very weak or totally absent genotoxicity of peppermint oil. The highest recommended daily dose in EU is 1.2 ml peppermint oil i.e. 1,080 mg peppermint oil, which contains maximum 140 mg pulegone + menthofuran (Ph Eur). For a 60 kg person this would correspond to a daily intake of 2.3 mg/kg bw. No cases of liver damage caused by peppermint oil or mint oil were reported under that posology (see SCF report referred to in the HMPC 'Public statement on the use of herbal medicinal products containing pulegone and menthofurane' (EMEA/HMPC/138386/2005)). The oral toxicity of menthone was evaluated in an animal model. The decrease in plasma creatinine and the increase in phosphatase alkaline and bilirrubin were dose dependent, after levels of 0, 200, 400 and 800 mg/kg bw/day. The non-observable-effect-level (NOEL) for menthone in this study was lower than 200 mg/kg bw/day. A NOEL of 400 mg/kg bw/day was reported in a 28 day toxicity study in rats. In 2000, the FAO/WHO Joint Expert Committee on Foods Additives established an acceptable daily intake (ADI) of 0 - 4 mg/kg bw/day for menthol.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product. Peppermint oil was negative in two validated tests of genotoxicity, the Ames test and the mouse lymphoma assay. Weak and inconsistent genotoxic responses in other non-validated tests are probably toxicologically inconsequential. There is more evidence for genotoxicity potential of menthol and there seems to be a discrepancy between peppermint oil and its most important constituent menthol. However, the present evidence points to a very weak or totally absent genotoxicity of peppermint oil.

6. PHARMACEUTICAL PARTICULARS

Well-established use	Traditional use
Not applicable.	Not applicable.

7. DATE OF COMPILATION/LAST REVISION

8 May 2007