15 January 2020
EMA/HMPC/522410/2013
Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Mentha x piperita* L., aetheroleum

Final – Revision 1

Initial assessment	
Discussion in Working Party on European Union monographs and European Union list (MLWP)	January 2007 March 2007 May 2007
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Adoption by HMPC Monograph (EMEA/HMPC/349466/2006) AR (EMEA/HMPC/349465/2006) List of references (EMEA/HMPC/199469/2007) Overview of comments received during the public consultation (EMEA/HMPC/494410/2007) HMPC Opinion (EMEA/HMPC/453712/2007)	31 October 2007

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First systematic review	
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Keywords	Herbal medicinal products; HMPC; European Union herbal monographs; well-established medicinal use; traditional use; *Mentha x piperita* L., aetheroleum; *Menthae piperitae* aetheroleum; peppermint oil

BG (bălgarski): Лютива мента, масло CS (čeština): silice máty peprné DA (dansk): Pebermynteolie DE (Deutsch): Pfefferminzöl EL (elliniká): αιθέριο έλαιο μίνθης EN (English): peppermint oil ES (espanol): menta piperita, aceite esencial de ET (eesti keel): piparmündiõli FI (suomi): piparminttuöljy FR (français): menthe poivrée (huile essentielle de) HR (hrvatski): eterično ulje paprene metvice HU (magyar): borsosmentaolaj IT (italiano): Menta piperita essenza	LT (lietuvių kalba): Pipirmėčių eterinis aliejus LV (latviešu valoda): Piparmētras ēteriskā eļļa MT (malti): żejt tal-menta NL (nederlands): Pepermuntolie PL (polski): Olejek eteryczny mietowy PT (português): óleo essencial de hortelã-pimenta RO (română): ulei volatil de izmă bună; ulei volatil de mentă SK (slovenčina): silica mäty piepornej SL (slovenščina): eterično olje poprove mete SV (svenska): pepparmyntolja IS (íslenska): NO (norsk): peppermynteolje

European Union 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(a) of Directive 2001/83/EC *Mentha x piperit*a L., aetheroleum (peppermint oil) i) Herbal substance Not applicable ii) Herbal preparation Essential oil	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC *Mentha x piperit*a L., aetheroleum (peppermint oil) i) Herbal substance Not applicable ii) Herbal preparation Essential oil

3. Pharmaceutical form

Well-established use	**Traditional use**
Herbal preparations in solid gastro-resistant dosage forms for oral use. Herbal preparations in liquid or semi-solid dosage forms for cutaneous use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	Herbal preparations in liquid or solid dosage forms for oral and oromucosal use. Herbal preparations in liquid dosage forms for inhalation. Herbal preparations in liquid or semi-solid dosage forms for cutaneous or transdermal use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

[1] The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance.

[2] The material complies with the Ph. Eur. monograph (ref.: 0405)

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	**Traditional use**
Indication 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. Indication 2) Herbal medicinal product for the symptomatic relief of mild tension type headache.	Indication 1) Traditional herbal medicinal product used for the relief of symptoms in coughs and colds. Indication 2) Traditional herbal medicinal product used for the symptomatic relief of localised muscle pain. Indication 3) Traditional herbal medicinal product used for the symptomatic relief of localised pruritic conditions in intact skin. 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 Indication 1) *Adolescents, adults and elderly* 0.2–0.4 ml in solid gastro–resistant dosage forms. Daily dose 0.6–1.2 ml divided in two or three times daily. *Children between 8 to 11 years of age* 0.2 ml solid gastro–resistant dosage forms three times daily. Daily dose 0.6 ml. The use is not recommended in children under 8 years of age (see section 4.4 'Special warnings and precautions for use'). See section 6 for content of pulegone and menthofuran Indication 2) *Adults and elderly* In liquid or semi-solid preparations 10% in	**Posology** Indication 1) <u>Inhalation</u> *Adolescents, adults and elderly* 0.08-0.16 ml of essential oil up to three times daily. Daily dose 0.08-0.48 ml. The use in children under 2 years of age is contraindicated (see section 4.3 'Contraindications'). The use is not recommended in children between 2 years to 11 years of age (see 4.4 'Special warnings and precautions for use'). <u>Oral or oromucosal use</u> *Adolescents, adults and elderly* 0.08-0.12 ml essential oil, 3-4 times per day. Daily dose 0.24-0.48 ml. The use in children under 2 years of age is contraindicated (see section 4.3

Well-established use	Traditional use
ethanol. The treatment consists of one application, which can be repeated two times at 15 minutes intervals. One treatment daily. The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use'). **Duration of use** Indication 1) The gastro-resistant dosage forms 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 dosage forms can be continued for periods of no longer than 3 months per course. Indication 2) If the symptoms persist or worsen during the use of the medicinal product, a doctor should be consulted. **Method of administration** Indication 1) Oral use The gastro-resistant dosage forms must be taken 30 minutes before meals and taken whole (see section 4.4 'Special warnings and precautions for use'). Indication 2) Cutaneous use The preparation should be rubbed on the skin of the forehead and temples.	'Contraindications'). The use is not recommended in children between 2 to 11 years of age (see 4.4 Special warnings and precautions for use). Cutaneous use *Adolescents, adults and elderly* Nasal ointments 1-5%. Up to three times daily The use in children under 2 years of age is contraindicated (see section 4.3 'Contraindications'). The use is not recommended in children between 2 to 11 years of age (see 4.4 Special warnings and precautions for use). Indication 1, 2 and 3) Cutaneous and transdermal use *Adults and elderly* Semi-solid and oily preparations 5-20% Hydroethanolic preparations 5-10% Up to three times daily *Adolescents* Semi-solid preparations 5-15% Hydroethanolic preparations 3-6% Up to three times daily *Children 4 to 11 years of age* Semi-solid preparations 2-10% Hydroethanolic preparations 2-4% Up to three times daily See section 6 for content of pulegone and menthofuran The use in children under 2 years of age is contraindicated (see 4.3 'Contraindications'). The use is not recommended in children below 4 years of age (see 4.4 Special warnings and precautions for use).

Well-established use	Traditional use
	Duration of use Indication 2 and 3) It is not recommended to use the medicinal product continuously for more than 2 weeks. Indication 1, 2 and 3) If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Method of administration** Indication 1) Inhalation The essential oil is added to hot water and the vapour is inhaled. Oral or oromucosal use In lozenges or oral spray. Cutaneous and transdermal use Apply a thin layer on the chest or on the back or around the nostrils. Indication 2 and 3) Cutaneous and transdermal use Apply a thin layer on the affected area.

4.3. Contraindications

Well-established use	Traditional use
Indication 1) Hypersensitivity to peppermint oil or menthol. Patients with liver disease, cholangitis, achlorhydria, gallstones and any other biliary disorders. Indication 2) Hypersensitivity to peppermint oil or menthol.	Indication 1, 2 and 3) 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**
Indication 1) The use in children under 8 years of age is not recommended due to a lack of data on safety and efficacy. The gastro-resistant solid dosage forms 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 or hiatal hernia have sometimes an exacerbation of this symptom after taking peppermint oil. Treatment should be discontinued in these patients. Indication 2) The use is not recommended in children and adolescents under 18 years of age due to lack of data on safety and efficacy. Eye contact with unwashed hands after the application of peppermint oil may potentially cause irritation. Indication 1 and 2) Other medicinal products containing peppermint oil shall be avoided during the use of this medicinal product. If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.	Indication 1) <u>Oral and oromucosal use</u> Patients who already suffer from heartburn or hiatal hernia, 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. Patients with gallstones and any other biliary disorder should be cautious using peppermint oil. <u>Inhalation, cutaneous (nasal application), oral and oromucosal use</u> The use in children between 2 and 11 years of age has not been established due to lack of adequate data. Indication 1, 2 and 3) Other medicinal products containing peppermint oil shall be avoided during the use of this medicinal product. If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. <u>Cutaneous and transdermal use</u> The use in children between 2 to 3 years of age has not been established due to lack of adequate data. 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.

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	**Traditional use**
Indication 1) Use of food or antacids administered at the same time could cause early release of the capsule content. Other medicinal products used to decrease stomach acid, such as histamine-2 blockers and proton pump inhibitors may cause premature dissolution of the enteric coating and should be avoided. Indication 2) None reported	None reported

4.6. Fertility, pregnancy and lactation

Well-established use	**Traditional use**
Indication 1) Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. It is unknown if peppermint oil constituents are excreted in human breast milk. No fertility data available. Indication 2) Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended, unless medical advice proposes that the benefit is higher than the potential risk. No fertility data available.	Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data available.

4.7. Effects on 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
Indication 1) Urine and stools with an odour of menthol were observed; dysuria and inflammation of the glans of the penis have been 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. Heartburn, perianal burning blurred vision, dry mouth, nausea and vomiting were frequent in clinical trials. Indication 2) Hypersensitivity reactions such as skin rash, contact dermatitis, and eye irritation have been reported. These reactions are usually mild and transient. The frequency is not known. Indication 1 and 2) If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	Indication 1) <u>Inhalation</u> Apnoea, broncho- and laryngo-constriction in hypersensitive patients have been reported. The frequency is not known. <u>Oral and oromucosal use</u> Allergic reactions to menthol were reported, with headache, bradycardia, muscle tremor, ataxia, anaphylactic shock, contact sensitivity on the mucosa and erythematous skin rash. The frequency is not known. Indication 1, 2 and 3) <u>Cutaneous and transdermal use</u> 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. The frequency is not known. Irritation of the skin and mucosa of the nose is possible, after local application. Indication 1, 2 and 3) If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.

4.9. Overdose

Well-established use	Traditional use
Indication 1) Overdose may cause severe gastro-intestinal symptoms, diarrhoea, rectal ulceration, epileptic convulsions, loss of consciousness, apnoea, nausea and 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.	Indication 1 <u>Inhalation</u> Inhalation of large doses of menthol may lead to dizziness, confusion, muscle weakness, nausea and double vision. <u>Oral and oromucosal use</u> Overdose may cause severe gastro-intestinal symptoms, diarrhoea, rectal ulceration, epileptic convulsions, loss of consciousness, apnoea, nausea and disturbances in cardiac rhythms, ataxia and other CNS problems, probably due to

Well-established use	Traditional use
Indication 2) No case of overdose has been reported.	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. Indication 1, 2 and 3) Cutaneous and transdermal use No case of overdose has been reported.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Indication 1) Pharmacotherapeutic group: Other drugs for functional gastrointestinal disorders. ATC code: A03AX Several studies in healthy subjects or patients indicate that peppermint oil given intraluminally (stomach or colon) or orally exert spasmolytic action on the smooth muscles of the gastrointestinal tract. Peppermint oil appears to enhance production of bile. The choleretic and antifoaming effects of peppermint oil may play an additional role to the antispasmodic action, decreasing the abdominal distension, as well as the discomfort and abdominal pain. In systematic reviews and meta-analyses, placebo-controlled studies indicate that peppermint oil shows improvement of abdominal pain and global IBS symptoms. Indication 2) Pharmacotherapeutic group: Other local anaesthetics. ATC code: N01BX Topical application of peppermint oil produces a prolonged cold sensation, by the stimulation of the cold-sensitive receptors, giving an analgesic	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC.

Well-established use	Traditional use
effect.	

5.2. Pharmacokinetic properties

Well-established use	Traditional use
Indication 1) Menthol and other terpenic 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 glucoronides. The peak menthol urinary excretion levels were lower and secretion delayed with the modified-release preparations, compared 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. Indication 2) No data available.	Not required as per Article 16c (1)(a)(iii) of Directive 2001/83/EC.

5.3. Preclinical safety data[3]

Well-established use	Traditional use
Peppermint oil was negative in two *in vitro* genotoxicity tests, the Ames test, the mouse lymphoma assay and in the *in vivo* combined micronucleus/Comet assay (liver, kidney and bladder mucosa cells) in female rats. Tests on reproductive toxicity and carcinogenicity have not been performed. Pulegone and menthofuran (1-11% of the essential oil): Pulegone and its metabolites have been demonstrated to cause carcinogenicity of the liver and the urinary tract in rats and mice. Based on results from several *in vitro* and *in vivo genotoxicity* studies, pulegone and menthofuran are considered as non-genotoxic carcinogens. The mechanism is classed as being related to sustained cytotoxicity leading to regenerative cell proliferation due to high doses (see section 6	Peppermint oil was negative in two *in vitro* genotoxicity tests, the Ames test, the mouse lymphoma assay and in the *in vivo* combined micronucleus/Comet assay (liver, kidney and bladder mucosa cells) in female rats. Tests on reproductive toxicity and carcinogenicity have not been performed. Pulegone and menthofuran (1-11% of the essential oil): Pulegone and its metabolites have been demonstrated to cause carcinogenicity of the liver and the urinary tract in rats and mice. Based on results from several *in vitro* and *in vivo genotoxicity* studies, pulegone and menthofuran are considered as non-genotoxic carcinogens. The mechanism is classed as being related to sustained cytotoxicity leading to regenerative cell proliferation due to high doses (see section 6

[3] Where herbal preparations from *Mentha piperita* aetheroleum are used, the total exposure to pulegone and menthofuran must be considered from a safety standpoint.

Well-established use	Traditional use
'Pharmaceutical particulars' for more details).	'Pharmaceutical particulars' for more details).

6. Pharmaceutical particulars

Well-established use	Traditional use
The amount of pulegone and menthofuran has to be specified in the given product. The daily exposure has to be below 37.5 mg per person per day pulegone and menthofuran. For children, the daily exposure has to be below 075 mg/kg bw per day pulegone and menthofuran. For further details see the "Public statement on the use of herbal medicinal products containing pulegone and menthofuran)" (EMA/HMPC/138386/2005 Rev1).	The amount of pulegone and menthofuran has to be specified in the given product. The daily exposure has to be below 37.5 mg per person per day pulegone and menthofuran. For children, the daily exposure has to be below 0.75 mg/kg bw per day pulegone and menthofuran. For further details see the "Public statement on the use of herbal medicinal products containing pulegone and menthofuran)" (EMA/HMPC/138386/2005 Rev1).

7. Date of compilation/last revision

15 January 2020