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SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

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

Draft – Revision 1

<b>Initial assessment</b>	
Discussion in Working Party on European Union monographs and European Union list (MLWP)	January 2007 March 2007 May 2007
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	8 May 2007
End of consultation (deadline for comments)	15 August 2007
Re-discussion in MLWP	October 2007
Adoption by HMPC Monograph (EMA/HMPC/349466/2006) AR (EMA/HMPC/349465/2006) List of references (EMA/HMPC/199469/2007) Overview of comments received during the public consultation (EMA/HMPC/494410/2007) HMPC Opinion (EMA/HMPC/453712/2007)	31 October 2007

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<b>First systematic review</b>	
Discussion in MLWP	September 2013 November 2013 January 2014 March 2014 January 2015 March 2015 April 2016 May/June 2016 September 2016 January 2017 March 2017 May 2017 July 2017 January 2018 March 2018 January 2019
Adopted by HMPC for release for consultation	15 May 2019
Start of public consultation	15 June 2019
End of consultation (deadline for comments). Comments should be provided using this <a href="#">template</a> to <a href="mailto:hmpc.secretariat@ema.europa.eu">hmpc.secretariat@ema.europa.eu</a>	15 September 2019

Keywords	Herbal medicinal products; HMPC; European Union herbal monographs; well-established medicinal use; traditional use; <i>Mentha x piperita</i> L., aetheroleum; <i>Menthae piperitae</i> aetheroleum; peppermint oil
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<p>BG (bългарски): Лютива мента, масло  CS (čeština): silice máty peprné  DA (dansk): Pebermynteolie  DE (Deutsch): Pfefferminzöl  EL (elliniká): έλαιο μίνθης-αιθέριο έλαιο μίνθης  EN (English): peppermint oil  ES (español): 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</p>	<p>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): peppermynnteolje</p>
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# 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<sup>1, 2</sup>

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC <i>Mentha x piperita</i> 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 <i>Mentha x piperita</i> 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.

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

<sup>2</sup> The material complies with the Ph. Eur. monograph (ref.: 0405)

## 4. Clinical particulars

### 4.1. Therapeutic indications

Well-established use	Traditional use
<p><b>Indication 1)</b></p> <p>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.</p> <p><b>Indication 2)</b></p> <p>Herbal medicinal product for the symptomatic relief of mild tension type headache.</p>	<p><b>Indication 1)</b></p> <p>Traditional herbal medicinal product used for the relief of symptoms in coughs and colds.</p> <p><b>Indication 2)</b></p> <p>Traditional herbal medicinal product used for the symptomatic relief of localised muscle pain.</p> <p><b>Indication 3)</b></p> <p>Traditional herbal medicinal product used for the symptomatic relief of localised pruritic conditions in intact skin.</p> <p>The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.</p>

### 4.2. Posology and method of administration

Well-established use	Traditional use
<p><b>Posology</b></p> <p><b>Indication 1)</b></p> <p><i>Adolescents, adults and elderly</i></p> <p>0.2–0.4 ml in solid gastro-resistant dosage forms.</p> <p>Daily dose 0.6–1.2 ml divided in two or three times daily.</p> <p><i>Children between 8 to 11 years of age</i></p> <p>0.2 ml solid gastro-resistant dosage forms three times daily. Daily dose 0.6 ml.</p> <p>The use is not recommended in children under 8 years of age (see section 4.4 'Special warnings and precautions for use').</p> <p>See section 6 for content of pulegone and menthofuran</p> <p><b>Indication 2)</b></p> <p><i>Adults and elderly</i></p> <p>In liquid or semi-solid preparations 10% in</p>	<p><b>Posology</b></p> <p><b>Indication 1)</b></p> <p><u>Inhalation</u></p> <p><i>Adolescents, adults and elderly</i></p> <p>0.08-0.16 ml of essential oil up to three times daily. Daily dose 0.08–0.48 ml.</p> <p>The use in children under 2 years of age is contraindicated (see section 4.3 'Contraindications').</p> <p>The use is not recommended in children between 2 years to 11 years of age (see 4.4 'Special warnings and precautions for use').</p> <p><u>Oral or oromucosal use</u></p> <p><i>Adolescents, adults and elderly</i></p> <p>0.08-0.12 ml essential oil, 3-4 times per day. Daily dose 0.24-0.48 ml.</p> <p>The use in children under 2 years of age is contraindicated (see section 4.3</p>

Well-established use	Traditional use
<p>ethanol.</p> <p>The treatment consists of one application, which can be repeated two times at 15 minutes intervals. One treatment daily.</p> <p>The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').</p> <p><b>Duration of use</b></p> <p><b>Indication 1)</b></p> <p>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.</p> <p><b>Indication 2)</b></p> <p>If the symptoms persist or worsen during the use of the medicinal product, a doctor should be consulted.</p> <p><b>Method of administration</b></p> <p><b>Indication 1)</b></p> <p><u>Oral use</u></p> <p>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').</p> <p><b>Indication 2)</b></p> <p><u>Cutaneous use</u></p> <p>The preparation should be rubbed on the skin of the forehead and temples.</p>	<p>'Contraindications').</p> <p>The use is not recommended in children between 2 to 11 years of age (see 4.4 Special warnings and precautions for use).</p> <p><u>Cutaneous use</u></p> <p><i>Adolescents, adults and elderly</i></p> <p>Nasal ointments 1-5%.</p> <p>Up to three times daily</p> <p>The use is not recommended in children between 2 to 11 years of age (see 4.4 Special warnings and precautions for use).</p> <p><b>Indication 1, 2 and 3)</b></p> <p><u>Cutaneous and transdermal use</u></p> <p><i>Adults and elderly</i></p> <p>Semi-solid and oily preparations 5-20%</p> <p>Hydroethanolic preparations 5-10%</p> <p>Up to three times daily</p> <p><i>Adolescents</i></p> <p>Semi-solid preparations 5-15%</p> <p>Hydroethanolic preparations 3-6%</p> <p>Up to three times daily</p> <p><i>Children 4 to 11 years of age</i></p> <p>Semi-solid preparations 2-10%</p> <p>Hydroethanolic preparations 2-4%</p> <p>Up to three times daily</p> <p>See section 6 for content of pulegone and menthofuran</p> <p>The use in children under 2 years of age is contraindicated (see 4.3 'Contraindications').</p> <p>The use is not recommended in children below 4 years of age (see 4.4 Special warnings and precautions for use).</p> <p><b>Duration of use</b></p> <p><b>Indication 2 and 3)</b></p>

Well-established use	Traditional use
	<p>It is not recommended to use the medicinal product continuously for more than 2 weeks.</p> <p><b>Indication 1, 2 and 3)</b></p> <p>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.</p> <p><b>Method of administration</b></p> <p><b>Indication 1)</b></p> <p><u>Inhalation</u></p> <p>The essential oil is added to hot water and the vapour is inhaled.</p> <p><u>Oral or oromucosal use</u></p> <p>In lozenges or oral spray.</p> <p><u>Cutaneous and transdermal use</u></p> <p>Apply a thin layer on the chest or on the back or around the nostrils.</p> <p><b>Indication 2 and 3)</b></p> <p><u>Cutaneous and transdermal use</u></p> <p>Apply a thin layer on the affected area.</p>

### 4.3. Contraindications

Well-established use	Traditional use
<p><b>Indication 1)</b></p> <p>Hypersensitivity to peppermint oil or menthol.</p> <p>Patients with liver disease, cholangitis, achlorhydria, gallstones and any other biliary disorders.</p> <p><b>Indication 2)</b></p> <p>Hypersensitivity to peppermint oil or menthol.</p>	<p><b>Indication 1, 2 and 3)</b></p> <p>Children under 2 years of age, because menthol can induce reflex apnoea and laryngospasm.</p> <p>Children with history of seizures (febrile or not).</p> <p>Hypersensitivity to peppermint oil or menthol.</p>

### 4.4. Special warnings and precautions for use

Well-established use	Traditional use
<p><b>Indication 1)</b></p> <p>The use in children under 8 years of age is not</p>	<p><b>Indication 1)</b></p>

Well-established use	Traditional use
<p>recommended due to a lack of data on safety and efficacy.</p> <p>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.</p> <p>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.</p> <p><b>Indication 2)</b></p> <p>The use is not recommended in children and adolescents under 18 years of age due to lack of data on safety and efficacy.</p> <p>Eye contact with unwashed hands after the application of peppermint oil may potentially cause irritation.</p> <p><b>Indication 1 and 2)</b></p> <p>Other medicinal products containing peppermint oil shall be avoided during the use of this medicinal product.</p> <p>If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.</p>	<p><u>Oral and oromucosal use</u></p> <p>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.</p> <p>Peppermint oil should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract.</p> <p>Patients with gallstones and any other biliary disorder should be cautious using peppermint oil.</p> <p>The use in children between 2 and 11 years of age has not been established due to lack of adequate data.</p> <p><b>Indication 1, 2 and 3)</b></p> <p>Other medicinal products containing peppermint oil shall be avoided during the use of this medicinal product.</p> <p>If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.</p> <p><u>Cutaneous and transdermal use</u></p> <p>The use in children between 2 to 3 years of age has not been established due to lack of adequate data.</p> <p>Eye contact with unwashed hands after the application of peppermint oil may potentially cause irritation.</p> <p>Peppermint oil should not be applied on broken or irritated skin.</p>

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

Well-established use	Traditional use
<p><b>Indication 1)</b></p> <p>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</p>	<p>None reported</p>

Well-established use	Traditional use
<p>premature dissolution of the enteric coating and should be avoided.</p> <p>Indication 2)</p> <p>None reported</p>	

#### 4.6. Fertility, pregnancy and lactation

Well-established use	Traditional use
<p>Indication 1)</p> <p>Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.</p> <p>It is unknown if peppermint oil constituents are excreted in human breast milk.</p> <p>No fertility data available.</p> <p>Indication 2)</p> <p>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.</p> <p>No fertility data available.</p>	<p>Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.</p> <p>No fertility data available.</p>

#### 4.7. Effects on ability to drive and use machines

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

#### 4.8. Undesirable effects

Well-established use	Traditional use
<p>Indication 1)</p> <p>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.</p> <p>Allergic reactions to menthol were reported, with</p>	<p>Indication 1)</p> <p><u>Inhalation</u></p> <p>Apnoea, broncho- and laryngoconstruction in hypersensitive patients have been reported. The frequency is not known.</p>



Well-established use	Traditional use
<p>headache, bradycardia, muscle tremor, ataxia, anaphylactic shock and erythematous skin rash. The frequency is not known.</p> <p>Heartburn, perianal burning blurred vision, dry mouth, nausea and vomiting were frequent in clinical trials.</p> <p><b>Indication 2)</b></p> <p>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.</p> <p><b>Indication 1 and 2)</b></p> <p>If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.</p>	<p><u>Oral and oromucosal use</u></p> <p>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.</p> <p><b>Indication 1, 2 and 3)</b></p> <p><u>Cutaneous and transdermal use</u></p> <p>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.</p> <p>Irritation of the skin and mucosa of the nose is possible, after local application.</p> <p><b>Indication 1, 2 and 3)</b></p> <p>If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.</p>

#### 4.9. Overdose

Well-established use	Traditional use
<p><b>Indication 1)</b></p> <p>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.</p> <p>In the event of overdose, the stomach should be emptied by gastric lavage. Observation should be carried out with symptomatic treatment if necessary.</p> <p><b>Indication 2)</b></p> <p>No case of overdose has been reported.</p>	<p><b>Indication 1</b></p> <p><u>Inhalation</u></p> <p>Inhalation of large doses of menthol may lead to dizziness, confusion, muscle weakness, nausea and double vision.</p> <p><u>Oral and oromucosal use</u></p> <p>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.</p> <p>In the event of overdose, the stomach should be emptied by gastric lavage. Observation should be carried out with symptomatic treatment if necessary.</p> <p><b>Indication 1, 2 and 3)</b></p>

Well-established use	Traditional use
	<p><u>Cutaneous and transdermal use</u></p> <p>No case of overdose has been reported.</p>

## 5. Pharmacological properties

### 5.1. Pharmacodynamic properties

Well-established use	Traditional use
<p><b>Indication 1)</b></p> <p>Pharmacotherapeutic group: Other drugs for functional gastrointestinal disorders.</p> <p>ATC code: A03AX</p> <p>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.</p> <p>Peppermint oil appears to enhance production of bile. The choloretic 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.</p> <p>In systematic reviews and meta-analyses, placebo-controlled studies indicate that peppermint oil shows improvement of abdominal pain and global IBS symptoms.</p> <p><b>Indication 2)</b></p> <p>Pharmacotherapeutic group: Other local anaesthetics.</p> <p>ATC code: N01BX</p> <p>Topical application of peppermint oil produces a prolonged cold sensation, by the stimulation of the cold-sensitive receptors, giving an analgesic effect.</p>	<p>Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC.</p>

### 5.2. Pharmacokinetic properties

Well-established use	Traditional use
<b>Indication 1)</b>	Not required as per Article 16c (1)(a)(iii) of

Well-established use	Traditional use
<p>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 glucuronides. The peak menthol urinary excretion levels were lower and secretion delayed with the modified-release preparations, compared with the immediate release preparations.</p> <p>In one clinical study with peppermint oil and one clinical study with menthol, some inhibition of CYP3A4 activity has been described.</p> <p><b>Indication 2)</b></p> <p>No data available.</p>	<p>Directive 2001/83/EC.</p>

### 5.3. Preclinical safety data<sup>3</sup>

Well-established use	Traditional use
<p>Peppermint oil was negative in two <i>in vitro</i> genotoxicity tests, the Ames test, the mouse lymphoma assay and in the <i>in vivo</i> combined micronucleus/Comet assay (liver, kidney and bladder mucosa cells) in female rats.</p> <p>Tests on reproductive toxicity and carcinogenicity have not been performed.</p> <p>Pulegone and menthofuran (1-11% of the essential oil):</p> <p>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 <i>in vitro</i> and <i>in vivo</i> 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 'Pharmaceutical particulars' for more details).</p>	<p>Peppermint oil was negative in two <i>in vitro</i> genotoxicity tests, the Ames test, the mouse lymphoma assay and in the <i>in vivo</i> combined micronucleus/Comet assay (liver, kidney and bladder mucosa cells) in female rats.</p> <p>Tests on reproductive toxicity and carcinogenicity have not been performed.</p> <p>Pulegone and menthofuran (1-11% of the essential oil):</p> <p>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 <i>in vitro</i> and <i>in vivo</i> 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 'Pharmaceutical particulars' for more details).</p>

<sup>3</sup> Where herbal preparations from *Mentha piperita* aetheroleum are used, the total exposure to pulegone and menthofurane must be considered from a safety standpoint.

## 6. Pharmaceutical particulars

Well-established use	Traditional use
<p>The amount of pulegone and menthofuran has to be specified in the given product.</p> <p>The daily exposure has to be below 37.5 mg per person per day pulegone and menthofuran.</p> <p>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).</p>	<p>The amount of pulegone and menthofuran has to be specified in the given product.</p> <p>The daily exposure has to be below 37.5 m per person per day pulegone and menthofuran.</p> <p>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).</p>

## 7. Date of compilation/last revision

15 May 2019