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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Mentha x piperita* L., folium and aetheroleum

Final – Revision 1

Based on Article 10a of Directive 2001/83/EC (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Mentha x piperita</i> L. Whole or cut dried leaf of <i>Mentha x piperita</i> L.
Herbal preparation(s)	<u><i>Mentha x piperita</i>, folium</u> (TU) a) Comminuted herbal substance b) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V) c) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% (V/V) <u><i>Mentha x piperita</i>, aetheroleum</u> (TU and WEU) Essential oil (obtained by steam distillation from the fresh aerial parts of the flowering plant).
Pharmaceutical form(s)	<u><i>Mentha x piperita</i>, folium</u> (TU) Herbal substance or comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid dosage forms for oral use. <u><i>Mentha x piperita</i>, aetheroleum</u> (TU) Herbal preparations in liquid or solid dosage forms for oral and oromucosal use.



	<p>Herbal preparations in liquid dosage forms for inhalation.</p> <p>Herbal preparations in liquid or semi-solid dosage forms for cutaneous or transdermal use.</p> <p><u><i>Mentha x piperita</i>, aetheroleum</u> (WEU)</p> <p>Herbal preparations in solid gastro-resistant dosage forms for oral use.</p> <p>Herbal preparations in liquid or semi-solid dosage forms for cutaneous use.</p>
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# 1. Introduction

## 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

The herbal substance consists of whole or cut dried leaf of *Mentha x piperita* L.

Peppermint is a perennial plant native to Europe, highly aromatic, which may grow as tall as 90 cm.

According to the European Pharmacopoeia, it contains a minimum of 12 ml/kg of essential oil for the whole drug and a minimum of 9 ml/kg of essential oil for the cut drug (Ph. Eur. Ref.: 0406).

*Mentha x piperita* L. is believed to be a hybrid of spearmint (*Mentha spicata* L) and water mint (*Mentha aquatica* L.) (Murray *et al.*, 1972), and belongs to the family Labiatae (Lamiaceae).

### Chemical constituents of peppermint leaves

The chemical components of peppermint leaves vary with plant maturity, variety, geographical region and processing conditions.

The fatty acid composition of the non-polar lipid fraction of peppermint leaves is dominated by palmitic (16:0), linoleic (18:2) and linolenic (18:3) acids (Mckay, Blumberg, 2006).

Various flavonoids are present including luteolin and its 7-glycoside, rutin, hesperidin, eriocitrin (eriodictyol 7-O-rutinoside) and highly oxygenated flavones. Other constituents include phenolic acids and small amounts of triterpenes (ESCOP 2003, Julien *et al.*, 1984, Litvinenko *et al.*, 1975, Croteau and Loomis 1973).

In a study of 40 clones of *Mentha piperita* (Guédon *et al.*, 1994), eriocitrin, with a concentration range of 6.6-15.0%, is the dominant phenolic secondary metabolite (mainly flavonoid glycosides), and is accompanied by luteolin 7-O-rutinoside, hesperidin and phenolic acid derivatives such as rosmarinic acid.

### Chemical composition of the essential oil.

Its major constituents are menthol (30-55%) and menthone (14-32%).

Other monoterpenes present are: limonene (1-3.5%), cineole (3.5-8%), menthofuran (1-8%), isomenthone (1.5-10%), menthyl acetate (2.8-10%), pulegone (maximum 3%), carvone (maximum 1%). The ratio of 1,8-cineole content to limonene content is at minimum 2 (Ph. Eur. Ref.: 0405).

- Herbal preparation(s)

a) Comminuted herbal substance

About 75% of the polyphenolic compounds present in the leaves are extracted in an infusion (Mckay, Blumberg 2006).

An infusion of dried leaves is reported to contain 21% of the original essential oil (25 mg/l) (Duband *et al.*, 1992), while in another study by Niesel (1992) peppermint leaves shown that 20-25% of the essential oil could be found in the preparation after 10 minutes (tea preparation with boiling water).

In a publication of Wiśniewski (1962), the content of essential oil determined in *Menthae folium* (the herbal substance) was 1.5%. In decoctions, using the modified method described in the Suppl II of the Farmakopea Polska (1959) the content of the oil was 26.6%. The authors observed that in a case of

*Menthae folium* the extraction of essential oil by decoction was not influenced by an addition of emulgators; however, the prolonged heating caused a loss of the oil.

Volatiles from aqueous extract of peppermint commercial sachets were investigated through gas chromatography/flame ionization detection (GC/FID) and GC/mass spectrometry (MS). Samples were prepared under similar conditions as in homemade teas. Volatiles were isolated using solid phase extraction method (SPE) with Porapak Q trap followed by desorption with acetone. The major volatiles were terpenes (275-382 µg/kg) that reached 89% of the total composition. A total of 16 compounds, among them dodecane, acetoin, acetol, citral, geraniol and octanoic acid have been described for the first time in peppermint tea. These findings could be attributed to the different analytical approach employed, mainly the use of different extraction/pre-concentration techniques. Given the apparently lower proportion of terpenes in the aqueous extract it may be that the chemical properties of the peppermint essential oil are not entirely reproduced with homemade tea (Riachi *et al.*, 2012).

- b) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V)
- c) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% (V/V)

The European Pharmacopoeia describes the dry extract produced from Peppermint leaf (0406). It contains a minimum 0.5 per cent of rosmarinic acid (C<sub>18</sub>H<sub>16</sub>O<sub>8</sub>; M<sub>r</sub> 360.33) (dry extract), produced from the herbal drug by a suitable procedure using ethanol (30-50 per cent V/V) or water of minimum 60°C (Ph. Eur. ref.: 2382).

- d) *Menthae piperita aetheroleum*

Peppermint oil is obtained by steam distillation from the fresh aerial parts of the flowering plant of *Mentha x piperita* L.

It is a colourless, pale yellow or pale greenish-yellow liquid with a characteristic odour and taste followed by a cold sensation.

### Major chemical constituents

To comply with the European Pharmacopoeia, the major constituents exactly as described previously are:

Menthol (30-55%) and menthone (14-32%). Other monoterpenes present are: limonene (1-3.5%), cineole (3.5-8%), menthofuran (1-8%), isomenthone (1.5-10%), menthyl acetate (2.8-10%), pulegone (maximum 3%), carvone (maximum 1%) and isopulegol (maximum 0.2%). The ratio of 1,8-cineole content to limonene content is at minimum 2 (Ph. Eur. Ref.: 0405).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable

## 1.2. Search and assessment methodology

The current report updates the information available for *Mentha x piperita* L. and folium, and makes the revision of previous information according to scientific publications.

Online bibliographic databases (Medline, PubMed, Cochrane Database of Systematic Reviews, EMBASE, BioMed, topline) were searched for the terms; *Mentha piperita*, peppermint oil, *mentha piperita* leaves, folium, IBS, tension headache, toxicology, adverse effect, functional abdominal pain, children.

Also the literature available by the interested parties was considered. The full texts and abstracts more relevant for the revision were considered, especially the articles published after the publication of the monograph, 2008.

## 2. Data on medicinal use

### 2.1. Information about products on the market

#### 2.1.1. Information about products on the market in the EU/EEA Member States

##### Information on medicinal products marketed in the EU/EEA

**Table 1a:** Overview of data obtained from marketed medicinal products - peppermint leaf

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Tincture 1:20 <i>Mentha x piperita</i> L. folium, extraction solvent ethanol 90% V/V containing 65 mg/g peppermint oil	Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence	20 oral drops 3 times per day	Lithuania, since 1968 (Monograph Nr.689 Ph-USSR)
Peppermint leaf for herbal tea	Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence	Adults: 4.5–9 g; children over 4 years: 3-6 g	TU, Lithuania, since 1995
Tincture 1:20 <i>Mentha x piperita</i> L. folium, extraction solvent ethanol 90% V/V, also contain <i>Mentha piperitae aetheroleum</i> 59 mg/g	Symptomatic relief in case of gastro-intestinal disorders (dyspepsia and flatulence).	Adults and adolescents from 12 years, 10-15 drops maximum 3 times per day.  Children 8-12 years 8-10 drops maximum 3 times per day.	WEU, Latvia, since 1970
Peppermint leaf for	Traditional herbal medicinal product for	A) 2 g in 100 ml of boiling water as a	Poland, before 1980

<b>Active substance</b>	<b>Indication</b>	<b>Pharmaceutical form Posology Duration of use</b>	<b>Regulatory Status</b>
herbal tea (infusion)	the symptomatic relief of digestive disorders such as dyspepsia and flatulence	herbal infusion  Children aged 4 to 12 years: 100 ml of herbal infusion 1-2 times daily; Children aged 12 to 16 years: 100 ml of herbal infusion 2-3 times daily; Adults: 100 ml of herbal infusion 3 times daily  B) 2 g in 200 ml of boiling water as a herbal infusion  Children aged 4 to 10 years: 100 ml of herbal infusion 2-3 times daily; Children aged 10 to 16 years: 200 ml of herbal infusion 2-3 times daily; Adults: 200 ml of herbal infusion 2-3 times daily	
Comminuted herbal substance for infusion	Spastic complaints of the gastrointestinal tract as well as gallbladder and bile ducts.	1.5 g herbal substance 2-4 times daily	Standardzulassung, Germany, since 1982

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

**Table 1b:** Overview of data obtained from marketed medicinal products - peppermint oil

<b>Active substance</b>	<b>Indication</b>	<b>Pharmaceutical form Posology Duration of use</b>	<b>Regulatory Status</b>
Peppermint oil	<i>Internal use:</i>  Treatment of gastrointestinal disorders like flatulence, mild spasm of the gastrointestinal and bile tract, irritable	<i>Elderly, adults and adolescents:</i>  <i>Oral use:</i>  Average daily dose: 6-12 drops (2-3 times daily 3-4 drops).	TU, Hungary, since 14.06.1991 as a healing product  Since 26.05.2005 as TU.

<b>Active substance</b>	<b>Indication</b>	<b>Pharmaceutical form Posology Duration of use</b>	<b>Regulatory Status</b>
	bowel syndrome  <i>Intake or inhalation:</i>  Treatment of cough and cold symptoms of the upper respiratory tract  <i>External use:</i>  Rheumatic symptoms and myalgia; treatment of the symptoms of itching and urticaria in case of sensitive skin.	<i>Inhalation:</i> 2-3 times 3-4 drops daily into 300 ml hot water.  <i>Cutaneous use:</i>  Several drops should be applied directly to the affected skin parts	
Peppermint oil	For relief of symptoms in coughs and colds	Liquid preparation for inhalation  2-3 drops up to three times daily	TU, Spain, since 2001
Peppermint oil	Herbal medicinal product to balance mild, temporary and functional disorders in digestive tract and to treat symptoms of cold	Oral drops, solution adults (0.08-0.12 ml) 3-4 times per day (0.2-0.5 ml)	TU, Finland, since 2003
Peppermint oil	Herbal medicinal product to treat symptoms of cold	for inhalation  adults 2-3 drops spread evenly on a stick of a pocket inhalator and to inhale with deep breath not more than three times daily through mouth and/or nose	
Peppermint oil	Herbal medicinal product for temporary headache	for external use  For adults 1-2 drops not more than five times a day to rub oil into the skin area in question.	
Peppermint oil	For the relief of symptoms in coughs and colds	Solution for Nasal or oromucosal spray  Nasal or oromucosal	TU, France, since 2005  THMP since 2012

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		spray 4 times daily a spray=0.125 mg of essential oil	
Peppermint oil	Symptomatic treatment of minor spasm of the gastrointestinal tract, flatulence and abdominal pain.	Gastro-resistant capsule, soft (0.2 ml per Capsule peppermint oil)  Child >12 years, adult, elderly:  Oral use, 1 capsule, 1-3 times per day, if necessary maximum 2 capsules, 3 times per day  Children 8-12 years:  1 capsule, maximum 3 times per day	WEU, Belgium, since August 2013
Peppermint oil	Conditions of cold symptoms  Conditions of cold symptoms  Sore muscles and minor pain of the muscles	Inhalation:  3-4 drops in a glass of hot water or 2-3 drops in the inhalation straw  Oral use:  3-4 drops in a glass of temperate water 2-3 times daily  Cutaneous solution  Few drops applied locally around aching muscles.	WEU/MA, Denmark since 1999
Peppermint oil	Oral use:  a) Symptomatic relief of minor spasms of the gastrointestinal and biliary tract.  b) For the relief of symptoms of coughs and colds.  Inhalation: Relief of	a) Oral use (100% essential oil):  a+b) 3-4 drops 2-3 times per day  Inhalation (100% essential oil): 3-4 drops in 300 ml hot water, 2-3 times per day	WEU/MA, Germany, since 1978

<b>Active substance</b>	<b>Indication</b>	<b>Pharmaceutical form Posology Duration of use</b>	<b>Regulatory Status</b>
	<p>symptoms in coughs and colds.</p> <p>Cutaneous use: Symptomatic treatment of neuralgic pain and muscle pain.</p>	<p>Cutaneous use (100% essential oil): Some drops locally</p>	
Peppermint oil	<p>Oral use:</p> <p>a) Symptomatic relief of minor spasms of the gastrointestinal and biliary tract.</p> <p>b) For the relief of symptoms of coughs and colds.</p> <p>c) Inflammation of the oral mucosa</p> <p>Inhalation: Relief of symptoms in coughs and colds.</p> <p>Cutaneous use:</p> <p>a) Symptomatic treatment of neuralgic pain and muscle pain. Coughs and colds.</p>	<p>a, b, c) 3-4 drops of essential oil (100%) in a glass of warm water or on a sugar cube 2-3 times per day</p> <p>Inhalation: 3-4 drops of essential oil (100%) in hot water</p> <p>Cutaneous use: Some drops to be applied locally.</p>	Standardzulassung, Germany, since 1982
Peppermint oil	Symptomatic relief of minor spasms of upper intestine	<p>Coated tablet</p> <p>adults adolescents: 1-2 tablets (37.5-75 mg) 3 times per day</p>	WEU, Germany 1978-2008
Peppermint oil	Symptomatic treatment neuralgic pain, in mild to moderate tension headache	<p>Cutaneous liquid: local application of the forehead with an applicator every 15 minutes up to 3 times</p>	WEU/MA, Germany since 1996

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		per day	
Peppermint oil	Relief of symptoms in coughs and colds.  Symptomatic relief of minor spasms of the gastrointestinal tract.	Soft capsule  adults and adolescents: 1 capsule (100 mg essential oil) 2 times per day	WEU, Germany  1978-2011
Peppermint oil	Symptoms of IBS like abdominal pain, flatulence, repletion, obstipation and diarrhoea.	Gastro-resistant capsule, soft  adults and adolescents: 1 capsule (182 mg essential oil) 3 times per day	WEU/MA, Germany, since 1983
Peppermint oil	Symptomatic relief of minor spasms of the gastrointestinal and biliary tract.	gastro-resistant capsule, soft  adults and adolescents: 1 capsule (182 mg essential oil) 3 times per day	WEU/MA, Germany, since 1991
Peppermint oil	Symptomatic treatment of neuralgic pain, for example in mild to moderate tension headache	Cutaneous liquid  adults, adolescents and children over 6 years of age: local application of the forehead with an applicator every 15 minutes until 2 hours or 3 times per day	WEU/MA, Germany, since 1978
Peppermint oil	For the treatment of symptoms of discomfort and of abdominal colic and distension experienced by patients with irritable bowel syndrome.	(0.2 ml per capsule) Gastro-resistant capsules  Adults: one capsule three times daily, taken 30-60 minutes before food. The dose may be increased up to 2 capsules 3 times daily when discomfort is severe. Duration of use 1-2 weeks.  Not to be used longer	WEU/MA, Ireland, since 1985  WEU/MA, Czech Republic, since 1997

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		than 2-3 months per course.	
Peppermint oil	Herbal medicinal product for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain	<p>Gastro-resistant soft capsule Gastro-resistant soft capsule (0.2 ml per capsule peppermint oil)</p> <p>For oral use</p> <p>Adolescents over 12 years of age, adults and elderly</p> <p>The starting dose is 1 capsule 1-3 times daily. The dosage may be increased as necessary up to a maximum dose of 2 capsules 3 times daily.</p> <p>Children between 8 to 12 years of age</p> <p>1 capsule (0.2 ml in gastro-resistant</p> <p>Duration of use:</p> <p>2-4 weeks. Not be used longer than 3 months per course.</p>	WEU/MA, Netherlands, since 2012
Peppermint oil	Symptomatic treatment of spasmodic gastrointestinal complaints, flatulence and abdominal pain, especially in patients with irritable colon disease.	<p>Gastro-resistant capsule, soft (0.2 ml per capsule peppermint oil)</p> <p>Oral use; Children aged 8 to 12 years: 1 capsule (182 mg <i>Menthae piperitea aetheroleum</i>) up to 3 times daily, before meals.</p> <p>Adolescents, adults and elderly:</p>	WEU/MA, Poland, before 2000

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		<p>1 to 2 capsules up to 3 times daily before meals.</p> <p>Duration of use: until symptoms stop, usually 1 to 2 weeks. If symptoms are more persistent, continued use up to 3 months per 1 treatment cycle is recommended.</p>	
Peppermint oil	The product is indicated for the treatment of discomfort, abdominal pain and distension in patients with irritable bowel syndrome	<p>Gastroresistant capsules (187 mg peppermint oil)</p> <p>Oral use; adults and adolescents 1 capsule 3 times daily to be used 30 to 60 minutes before meal;</p> <p>Up to 2 capsules 3 times daily. Not to be taken longer than 2 to 3 months</p>	WEU/MA, Austria, since 1986
Peppermint oil	Symptomatic relief of minor spasms of the GI tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome	<p>1 capsule contains 200 µl=187 mg <i>Menthae pip. aetheroleum</i></p> <p>Oral use:</p> <p>adults, adolescents:</p> <p>3 times daily 1-2 capsules;</p> <p>children 8-12 years:</p> <p>up to 3 times 1 capsule daily</p>	WEU, Austria, since 2005

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

#### Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable

## Information on other products marketed in the EU/EEA (where relevant)

Not applicable

### 2.1.2. Information on products on the market outside the EU/EEA

Health Canada, 2008:

- Dose information for peppermint leaf presented as dose per day.

Subpopulation		Peppermint leaf (g/day)	
		Minimum	Maximum
Children <sup>1</sup>	2-4 y	0.2	2
Children and adolescents <sup>1</sup>	5-9 y	0.3	3
Adolescents <sup>1</sup>	10-14 y	0.6	6
Adolescents and adults <sup>1,2</sup>	≥ 14 y	1.2	12

<sup>1</sup>Children and adolescent doses were calculated as a fraction of the adult dose (JC 2008). The use of peppermint leaf in children and adolescents is supported by the following references: McIntyre 2005; Bove 1996.

<sup>2</sup>Adult dose supported by the following references: Mills and Bone 2005; ESCOP 2003; Blumenthal et al. 2000; Bradley 1992

Dried leaf:

- ▶ 6-12 g, per day (Mills and Bone 2005)
- ▶ 3-6 g, per day (Blumenthal et al. 2000)
- ▶ 2-3 g, 3 times per day (Bradley 1992)

Infusion:

- ▶ 6-12 g dried leaf, per day (Mills and Bone 2005)
- ▶ 1.5-3 g dried leaf, 3 times per day (ESCOP 2003)
- ▶ 2 g dried leaf, 2 to 3 times per day (Blumenthal et al. 2000)
- ▶ 2-3 g dried leaf, 3 times per day (Bradley 1992)

#### Directions for use:

- ▶ Pour 250 ml of boiling water over dried leaf and infuse in a covered container for 10 minutes. This may be drunk as often as desired (Hoffmann 2003).
- ▶ Take on an empty stomach (Boon and Smith 2004).

Fluidextract:

2 g dried equivalent, 2 to 3 times per day  
(1:1, 2 ml) (Blumenthal et al. 2000)

Tincture:

- ▶ 2 g dried equivalent, 2 to 3 times per day  
(1:5, 10 ml) (Blumenthal et al. 2000)
- ▶ 0.4-0.6 g dried equivalent, 3 times per day  
(1:5, in 45% ethanol, 2-3 ml) (Bradley 1992)

**Directions for use:** Take on an empty stomach (Boon and Smith 2004)

Solid extract:

1.54-2.57 g dried equivalent, 2 to 3 times per day  
(3.5-4.5:1, 0.44-0.57 g) (Blumenthal et al. 2000)

## 2.2. Information on documented medicinal use and historical data from literature

Peppermint is widely known to relieve digestive ailments, being a popular remedy for at least the last two centuries. It is available in most parts of the world for flavouring, cosmetic and medicinal uses.

In Antiquity the Egyptians, Greeks and Romans knew it as flavouring for food as well as for its medical purposes. It was first cultivated in England commercially around 1750. For medicinal effects, the aerial portion of the plant is the most widely used (Murray *et al.*, 1972).

At the herbarium of the English botanist John Ray (1628-1705) one of the oldest specimens of hybrid of peppermint (between spearmint (*Mentha spicata* L) and water mint (*Mentha aquatica* L.) can be found.

The English Dictionary of Medicinal and Surgical Knowledge, in 1800, already considered peppermint oil as "an aromatic stimulant to allay nausea, relieve spasmodic pain to the stomach and the bowels, expel flatus or cover the taste or the quality of gripping effects of other medicine" (Jones, 1981 cited by Kline *et al.*, 2001)

**Table 2a:** Overview of historical data - peppermint leaves

<b>Herbal preparation</b>	<b>Documented use / Traditional use</b>	<b>Pharmaceutical form Strength, Posology Duration of use</b>	<b>Reference</b>
Infusion of dried peppermint leaves  Tincture (1:5, 45% ethanol)	Dyspepsia, flatulence, intestinal colic, biliary disorders	Oral use  Usually prepared with one or two teaspoons (1.5 to 3.0 g) of the dried leaves per 8 ounces of water, 3 times daily  2 to 3 ml, three times daily	Bradley 1992 British Herbal Compendium
Infusion of dried peppermint leaves  Tincture (1:5, 45% ethanol)	Used in the symptomatic treatment of digestive disorders such as dyspepsia, flatulence and gastritis	Oral use  Adult  As an infusion, 1.5–3 g of the drug to 150 ml of water, three times daily  Children from 4 years of age, daily dose as infusions only:  4-10 years, 3-5 g  10-16 years, 3-6 g  Tincture-2-3 ml, three times daily	ESCOMP, 2nd edition, 2003, Wichtl (2002) and Bradley 1992 (adults)  Dorsch <i>et al.</i> , 2002 (children)
Tincture (1:5, 70% ethanol)  Herbal tea	Spastic complaints of the gastrointestinal tract as well as gallbladder and bile ducts.	Oral use  5–15 g tincture daily  3-6 g of comminuted herbal substance per	Germany (Blumenthal published 30.11.85, amended 13.3.90 and 1.9.90)

Herbal preparation	Documented use / Traditional use	Pharmaceutical form Strength, Posology Duration of use	Reference
		day	
Infusion Tincture (1:5, 45% ethanol)	Symptomatic treatment of dyspepsia, flatulence and intestinal colic.	1.5-3 g (one tablespoon) dried leaves in 150 ml water, 3 times daily before meals  2-3 ml three times daily	WHO monographs on <i>Menthae piperitae</i> folium 2002

**Duration of use:**

No restriction. If symptoms persist or worsen after 2 weeks, a doctor or a qualified health practitioner should be consulted.

**Table 2b:** Overview of historical data - peppermint oil.

Herbal preparation	Documented use/Traditional use	Pharmaceutical form Strength Posology Duration of use	Reference
Peppermint oil	Spastic discomfort of the upper gastrointestinal tract and bile ducts, irritable colon, catarrhs of the respiratory tract, inflammation of the oral mucosa.	Oral use  6-12 drops daily, that means: 3-4 drops, 2-3 times daily	Blumenthal 1998
Peppermint oil	Myalgia and neuralgia  Cough and cold	External use  Semi-solid and oily preparations 5-20%  In aqueous-ethanol preparations 5-10%  In nasal ointments, 1-5% essential oil.	
Peppermint oil	Symptomatic treatment of digestive disorders such as flatulence; irritable bowel syndrome (IBS); symptomatic treatment of coughs and colds.	<u>Oral use</u>  Digestive disorders: 0.02-0.08 ml (1-4 drops up to three times daily in dilute aqueous preparations (e.g. peppermint water or	ESCOPE monograph 2 <sup>nd</sup> edition 2003, citing Stahl-Biskup 1993, British herbal Pharmacopoeia 1983, Hansel 1999, Fintelman <i>et al.</i> , 1993

		<p>emulsion), or as drops on a lump of sugar.</p> <p>For IBS: 0.2-0.4 ml three times daily in enteric coated capsules</p> <p>Children</p> <p>Oral use: for digestive disorders, proportion of adult dose according to body weight</p>	
Peppermint oil	Aromatic carminative, relieving gastric and intestinal flatulence and colic and is employed with purgatives to prevent griping.	Peppermint spirit (B.P.C.)–Spiritus Menthae Piperitae; Peppermint oil 10 ml, alcohol (90%) to 100 ml. Dose: 0.3 to 2 ml.	Martindale, 1977
Peppermint oil	<p>Relief of coughs and colds;</p> <p>Tension-type headache;</p> <p>Symptomatic relief of rheumatic complaints;</p> <p>Pruritus, urticaria and pain in irritable skin conditions.</p>	<p><u>Inhalation</u></p> <p>3-4 drops added to hot water</p> <p>10% solution rubbed on to the skin of forehead and temples.</p> <p>In dilute liquid or semisolid preparations (equivalent to 0.1–1.0% m/m menthol) or as a counter-irritant and analgesic (equivalent to 1.25–16% m/m menthol) rubbed on the affected area.</p> <p>Children 4-10 years</p> <p>Semi-solid preparations 2 -10%; hydroethanolic preparations 2-4%</p> <p>Children 10-16 years</p> <p>Semi-solid preparations 5-15%; hydroethanolic preparations 3–6%</p>	<p>ESCOP monograph 2<sup>nd</sup> edition 2003, citing Stahl-Biskup, 1993, Hansel 1999, Gobel 1996, Dorsch <i>et al.</i>, 2002, Gilchrest 1982</p>

Peppermint oil	Powerful anodyne, anaesthetic, antiseptic and germicide used in herpes zoster, pruritus; for congestive headaches, rheumatism and neuralgia; indicated also for toothache caused by caries, and as an antiseptic for inhalation.	External use As spirit in 0.15-1.25 ml, or aqua in doses of ½-1 Libra	Indian Materia Medica by Nadkarni KM (3 <sup>rd</sup> revised edition-1976, reprinted 1999
Peppermint oil	External Symptomatic treatment of catarrh and coughs Treatment of myalgia and headache Oral use Symptomatic treatment of irritable bowel syndrome and digestive disorders such as flatulence and gastritis. Symptomatic treatment of catarrh and coughs	External use 5-20% essential oil in dilute, semisolid or oily preparations; 5-10% essential oil in aqueous-ethanol; nasal ointments containing 1-5% crude drug Oral use 0.2-0.4 ml essential oil three times daily in enteric-coated capsules 0.2-0.4 ml essential oil three times daily in dilute preparations or suspensions <u>By inhalation:</u> 3-4 drops essential oil in hot water Lozenges: 2-10 mg essential oil per lozenge	WHO monographs 2002

### **2.3. Overall conclusions on medicinal use**

#### **Peppermint leaves**

Peppermint leaves are a very well-known herbal medicinal product, widely used since a long time ago, being a popular remedy inside and outside European countries, for its antispasmodic, choleric and carminative properties.

In the literature we can find references to several preparations such as tinctures, liquid extracts and infusions, on single or combination products.

**Table 3a:** Overview of evidence on period of medicinal use of peppermint leaf -TU

<b>Herbal preparation Pharmaceutical form</b>	<b>Indication</b>	<b>Posology, Strength</b>	<b>Period of medicinal use</b>
Herbal substance or Comminuted herbal substance	Dyspepsia, flatulence, intestinal colic, biliary disorders	Usually prepared with one or two teaspoons (1.5 to 3.0 g) of the dried leaves per 8 ounces of water, 3 times daily	Bradley 1992 British Herbal Compendium
Peppermint leaf for herbal tea	Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence	<p>A) 2 g in 100 ml of boiling water as a herbal infusion</p> <p>Children aged 4 to 12 years: 100 ml of herbal infusion 1-2 times daily;</p> <p>Adolescents aged 12 to 16 years: 100 ml of herbal infusion 2-3 times daily;</p> <p>Adults: 100 ml of herbal infusion 3 times daily</p> <p>B) 2 g in 200 ml of boiling water as a herbal infusion</p> <p>Children aged 4 to 10 years: 100 ml of herbal infusion 2-3 times daily;</p> <p>Children- adolescents aged 10 to 16 years: 200 ml of herbal infusion 2-</p>	Poland, before 1980

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		3 times daily;  Adults: 200 ml of herbal infusion 2-3 times daily	
Peppermint leaf for herbal tea	Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence	Adults: 4.5–9 g; children over 4 years: 3-6 g	TU, Lithuania, registered, since 1995 but sold in pharmacies for 100 years.
Comminuted herbal substance for infusion	Spastic complaints of the gastrointestinal tract as well as gallbladder and bile ducts.	Adults: 1.5 g 2-4 times daily (3-6 g daily)	Standardzulassung, 1982  Blumenthal published 30.11.85, amended 13.3.90 and 1.9.90
Tincture (1:5, 70% ethanol)	Spastic complaints of the gastrointestinal tract as well as gallbladder and bile ducts.	5–15 g tincture daily	Blumenthal 1985, amended 1990
Tincture (1:5, 45% ethanol)	Symptomatic treatment of dyspepsia, flatulence and intestinal colic.	2-3 ml three times daily	Bradley 1992

The indication, preparations and posology already approved by HMPC on the previous version were kept without relevant changes. It was considered that there is enough literature to demonstrate traditional medicinal use of peppermint leaves, herbal substance and preparations for the following indication.

“Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence.”

### **1. Whole or cut dried leaf of *Mentha x piperita* L.**

#### **2. Herbal preparations**

- A) Comminuted herbal substance
- B) Tincture (1:5; ethanol 45% (V/V))

C) Tincture (1:5; ethanol 70% (V/V))

*Children 4-11 years of age and adolescents*

Herbal tea: 1.0-2.0 g of the herbal substance or the comminuted herbal substance in 100-150 ml of boiling water as a herbal infusion 3 times daily.

Daily dose 3-6 g

*Adults, elderly*

Herbal tea: 1.5-3.0 g of the of the herbal substance or the comminuted herbal substance in 100-150 ml of boiling water as a herbal infusion 2-3 times daily

Daily dose 3-9 g

Tincture: 6-9 ml, divided in three single doses.

### Peppermint oil

Peppermint oil has been used for a long time as a medicine, orally, topically and for inhalation.

There are sufficient data to demonstrate its traditional use for several indications, for more than 30 years across European Union.

**Table 3b:** Overview of evidence on period of medicinal use of **peppermint oil for TU**

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Peppermint oil	For the relief of symptoms of cough and cold.	Oral use: 3-4 drops (100% essential oil) in a glass of warm water 2-3 times per day	Germany, MA, since 1978
Peppermint oil	For the relief of coughs and colds	<u>Inhalation</u> 0.08-0.16 ml of essential oil up to three times daily Daily dose 0.08-0.48 ml <u>Oral and oromucosal use</u> 0.08-0.12 ml essential oil, 3-4 times per day Daily dose 0.24-0.48 ml <u>Cutaneous use</u> <u>Adults and elderly</u> 5-20% essential oil in dilute, semisolid or oily	Blumenthal <i>et al.</i> , 1998 Germany MA, 1978 Hungary, 1991 Denmark MA, 1999

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		preparations; 5–10% essential oil in aqueous-ethanol; nasal ointments containing 1–5% crude drug	
Peppermint oil	<p><i>Internal use:</i></p> <p>Treatment of gastrointestinal disorders like flatulence, mild spasm of the gastrointestinal and bile tract, irritable bowel syndrome</p> <p><i>Intake or inhalation:</i></p> <p>Treatment of cough and cold symptoms of the upper respiratory tract</p> <p><i>External use:</i></p> <p>Rheumatic symptoms and myalgia; treatment of the symptoms of itching and urticaria in case of sensitive skin.</p>	<p><i>Adolescents, adults and elderly:</i></p> <p><u>Oral use:</u></p> <p>Average daily dose: 6-12 drops (2-3 times daily 3-4 drops).</p> <p><u>Inhalation:</u> 2-3 times 3-4 drops daily into 300 ml hot water.</p> <p><u>Cutaneous use:</u></p> <p>Several drops should be applied directly to the affected skin parts</p>	<p>TU, Hungary, since 14.06.1991 as a healing product</p> <p>Since 26.05.2005 as TU.</p>
Peppermint oil	<p>Oral use:</p> <ul style="list-style-type: none"> <li>• Symptomatic relief of minor spasms of the gastrointestinal and biliary tract.</li> <li>• For the relief of symptoms of coughs and colds.</li> <li>• Inflammation of the oral mucosa</li> </ul> <p>Inhalation:</p> <p>Relief of symptoms in coughs and colds.</p> <p>Cutaneous use:</p> <ul style="list-style-type: none"> <li>• Symptomatic treatment of</li> </ul>	<p><u>Oral use</u></p> <p>a, b, c) 3-4 drops of essential oil (100%) in a glass of warm water or on a sugar cube 2-3 times per day</p> <p><u>Inhalation:</u></p> <p>3-4 drops of essential oil (100%) in hot water</p> <p><u>Cutaneous use:</u></p> <p>Some drops to be applied locally.</p>	<p>Standardzulassung, Germany, since 1982</p>

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	neuralgic pain and muscle pain. <ul style="list-style-type: none"> <li>• Coughs and colds</li> </ul>		

**Table 3c:** Overview of evidence on period of medicinal use of peppermint oil for WEU

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Peppermint oil	Symptomatic relief of minor spasms of the GI tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome	<u>Oral use:</u> 187 mg gastro-resistant capsules: 1 capsule contains 200 µl=187 mg <i>Menthae pip.</i> aetheroleum  oral; adults: 3 times daily 1 capsule	Austria, MA, 1986, 2005  Ireland, MA, 1985
		children 8-12 years: up to 3 times 1 capsule daily	Austria, WEU, 2005
		182 mg essential oil (=0.2 ml) (gastro-resistant capsule)  oral; adolescents and adults: 3 times daily 1 capsule	Germany, MA, 1983
Peppermint oil	Symptomatic treatment neuralgic pain, in mild to moderate tension headache	<u>Cutaneous use</u> Peppermint oil in ethanol solution in an applicator, treatment of the forehead every 15 minutes, up to 3 times	WEU, Germany, since 1996

Peppermint oil must have a controlled posology, due to the potential toxicity. In this sense, the indications and respective methods of administration that are not able to provide a safe posology will not be considered.

The preparations and the posology included in the previous version of the monograph for traditional use (EMA/HMPC/193909/2007) were kept, as they were considered to have a safe profile and are in accordance with the traditional use, based on the literature and market overview:

### **Traditional Use**

a) For the relief of symptoms of cough and cold

#### Inhalation

*Adolescents, adults and elderly*

0.08-0.16 ml of essential oil up to three times daily

Daily dose 0.08–0.48 ml

#### Oral and Oromucosal use

*Adolescents, adults and elderly*

0.08-0.12 ml essential oil, 3-4 times per day

Daily dose 0.24-0.48 ml

*Adults and elderly*

#### Cutaneous use

Nasal ointments 1-5%

Up to three times daily

b) For the relief of symptoms of cough and cold, symptomatic relief of localised muscle pain and for symptomatic relief of localised pruritic conditions in intact skin

#### Cutaneous and transdermal use

*Children 4 to 11 years of age*

Semi-solid preparations 2-10%

Hydroethanolic preparations 2-4%

Up to three times daily

*Adolescents*

Semi-solid preparations 5-15%

Hydroethanolic preparations 3-6%

Up to three times daily

*Adults and elderly*

Semi-solid and oily preparations 5-20%

In hydroethanolic preparations 5 10%

Up to three times daily

### **Method of administration**

### Inhalation

The essential oil is added to hot water and the vapour is inhaled.

### Oral and 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.

Apply a thin layer on the affected area.

## **Well Established use**

The preparations and posology considered to fulfil the conditions required for the WEU are discussed in chapters 4 and 5. Nevertheless, the indications accepted by HMPC that fulfil the requirements set for WEU are kept the same as in the previous version of the monograph (EMA/HMPC/349466/2006)

Oral use

a) 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

b) Herbal medicinal product for the symptomatic relief of mild tension type headache.

## **3. Non-Clinical Data**

### ***3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof***

#### **3.1.1. Primary pharmacodynamics**

##### **Antispasmodic action and choleric activity**

###### Peppermint leaves

*In vitro*

Among other studies, alcoholic extracts of peppermint leaf have showed antispasmodic effects on the isolated guinea pig ileum. 2.5 and 10.0 ml/l of a peppermint leaf extract (1:3.5, ethanol 31% w/w) were tested using acetylcholine and histamine as spasmodic agents. Both doses produced a significant increase of the ED<sub>50</sub>, for acetylcholine and histamine-induced contractions and a significant decrease of the maximum possible contractility. The effect obtained with 10.0 ml/litre corresponded to that of 0.13 mg atropine (effective dose of atropine in the treatment of abdominal spasms: 0.5-1.0 mg) (Forster *et al.*, 1983; Forster 1980).

Flavonoids isolated from peppermint leaf and dissolved in water so that 1 ml corresponded to approximately 0.5 g of dried leaf, inhibited muscular contraction of the guinea pig ileum induced by barium chloride (Lallement-Guilbert *et al.*, 1970).

Aqueous extracts of *Mentha piperita* showed a significant, dose dependent relaxation effect on isolated rabbit duodenum. The dried leaf extract was more effective than the fresh one (Mahmood *et al.*, 2003).

The mode of action on gastric motility of the muscle strip preparations from the entire guinea pig of a combination and its individual components (hydroethanolic herbal extracts from *Iberis amara* totalis, *Menthae piperitae* folium-1:2.5-3.5, *Matricariae* flos, Liquorice root, *Angelica* radix, *Carvi* fructus, *Cardus marianus* fructus, *Melissae* folium and *Chelidonium herba*) were studied. Peppermint leaf extract did not show consistent responses in the proximal stomach, inducing relaxation and contraction (Schemann *et al.*, 2006).

In another *in vitro* study, the same product as described above (Schemann *et al.*, 2006) and some of its isolated compounds were used. The study was performed to test their activity on histamine-induced contractions and spontaneous motility, of intestinal samples from guinea pig. *Mentha piperita* leaves, as *Iberis amara*, and *Melissa* folium had significant effects on decreasing the contraction amplitude (Heinle *et al.*, 2006).

#### *In vivo*

*In vivo* experiments with cannulated dogs peppermint tea (0.4 g/kg body weight) increased the secretion of bile. Both flavonoids, as well as the essential oil, seemed to contribute to this action (Steinegger *et al.*, 1992, Pasechnik, 1966).

Mixed flavonoids from peppermint leaf (optimum dose 2 mg/kg,), showed choleric activity in dogs. Flavomentin, a flavonoid preparation from peppermint leaf, stimulated bile secretion and of bile acid synthesis in dogs at doses of 0.5-6 mg/kg (optimum 2 mg/kg) (Pasechnik, 1967).

*In vivo* experiments with cannulated rats, intravenous injection of 0.5 ml of a peppermint tea (1:5) per rat or a flavonoid preparation (dosage corresponding to 3.3 g of peppermint leaf per kg) proved effective in increasing the amount of bile acids (Lallement-Guilbert *et al.*, 1970).

In a study published by Ando *et al.*, 2003, in Holstein steers fed with peppermint, there were lower concentrations of ammonia nitrogen and reduction of the numbers of protozoa in the rumen.

The potential antiulcerogenic, antisecretory and cytoprotective activity of the combination and its individual components (hydroethanolic herbal extracts from *Iberis amara* totalis, *Menthae piperitae* folium, *Matricariae* flos, Liquorice root, *Angelica* radix, *Carvi* fructus, *Cardus marianus* fructus, *Melissae* folium and *Chelidonium herba*) were tested in male Wistar rats. A modified formulation of the combination taking out three components was also tested. Gastric ulcers were induced acutely by indometacin and cimetidine was used as a reference anti-ulcerogenic. The parameters used were the free acidity, mucin and pepsin concentrations in the gastric juice, and the prostaglandin and leukotriene levels in the gastric mucosa. The stomach was histologically examined. Both preparations and their individual components protect the stomach from the ulcerative damage caused by indometacin, inhibiting the release of aggressive factors like acid and leukotrienes, promoting the production of mucin and prostaglandins. This effect could be attributed, according to the authors, to the presence of flavonoids (Khayyal *et al.*, 2001).

### **Peppermint oil**

#### *In vitro*

In order to investigate the effects of peppermint oil and its most abundant metabolite and active constituent ((-) menthol) on 5-HT<sub>3</sub> receptors (serotonin receptor subtype) three different *in vitro* models were used : [14C]guanidinium influx into N1E-115 cells which express 5-HT<sub>3</sub> receptors, isotonic contractions of the isolated rat ileum and equilibrium competition binding studies using a

radioactively labelled 5-HT<sub>3</sub> receptor antagonist (<sup>3</sup>H)GR65630) (3-(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1-propanone). Both peppermint oil and (-)-menthol inhibited [<sup>14</sup>C] guanidinium influx through 5-HT<sub>3</sub> receptor channels as well as serotonin induced contractions of the ileum. Neither the peppermint oil nor (-)-menthol, however, was able to displace [<sup>3</sup>H] GR65630 from 5-HT<sub>3</sub> binding sites. It may be concluded that peppermint oil and (-)-menthol exert their antiemetic effect at least partly by acting on the 5-HT<sub>3</sub> receptor ion-channel complex, probably by binding to a modulatory site distinct from the serotonin binding site (Heimes *et al.*, 2011).

#### *In vivo/Ex vivo*

Peppermint oil as a 1% emulsion exhibited relaxant effects on tracheal smooth muscle of the guinea pig: the I<sub>50</sub> was 83-91 mg/l (Reiter and Brandt, 1985).

Peppermint oil emulsified with tween, 1% in aqueous solution, relaxed chemically contracted guinea pig taenia coli (I<sub>50</sub>: 22.1 µg/ml) and inhibited spontaneous activity in the guinea pig colon (I<sub>50</sub>: 25.9 µg/ml) and rabbit jejunum (I<sub>50</sub>: 15.2 µg/ml). Using whole cell clamp configuration in these jejunal muscle cells, the potential-dependent calcium currents were inhibited in a dose-dependent manner by peppermint oil. Peppermint oil reduced the peak current amplitude and increased the rate of current decay, indicating a reduction of calcium influx similar to that caused by dihydropyridine calcium antagonists. Peppermint oil demonstrated non-competitive inhibition 5-hydroxytryptamine (serotonin) and the substance P induced smooth muscle contraction (Hills *et al.*, 1991).

Both menthol and peppermint oil inhibited specific [<sup>3</sup>H] nitrendipine and [<sup>3</sup>H] PN 200-110 binding to smooth and cardiac muscle and neuronal preparations with potencies comparable to, but slightly lower than those measured in the pharmacological and <sup>45</sup>Ca<sup>2+</sup> uptake experiments. Binding of menthol and peppermint oil, studied at 78 µg/ml, was competitive against [<sup>3</sup>H] nitrendipine in both smooth muscle and synaptosome preparations. The data indicate that both menthol and peppermint oil exert Ca<sup>2+</sup> channel blocking properties which may underlie their use in irritable bowel syndrome. The authors conclude that Ca<sup>2+</sup> channel antagonism may not be the only pharmacological effect of menthol and peppermint oil contributing to intestinal smooth muscle relaxation (Hawthorn *et al.*, 1988).

Peppermint oil and menthol administered *i.v* have shown the stimulation of the choleric activity (bile flow) in rats at doses of 25–50 mg/kg (Trabace *et al.*, 1992).

In another study, the pharmacological activity of essential oils on Oddi's sphincter was studied in male guinea pigs. The authors reported that the Oddi's sphincter prolapses through *i.v.* injection of *Mentha piperita* essential oil (Anon, 1990).

Peppermint oil appears to enhance production of bile. In experiments where bile flowed out of a cannula from an anaesthetised dog, an infusion of peppermint leaves (0.4 g/kg) enhanced bile production. Menthol also produced an enhancement of bile production: 0.06 g/kg in 1 dog and 0.1-1.0 g/kg in rats. In others experimental studies in animals, menthol and peppermint oil induced a marked and dose related choleresis (Siegers *et al.*, 1991).

### **Anti-nociceptive effect**

#### Peppermint leaves

##### *In vivo*

The aqueous extract of *Mentha piperita* leaf, at the *i.p.* doses 200 and 400 mg/kg, showed significant analgesic effects against both acetic acid-induced writhing and hot plate induced thermal stimulation in

mice, with protection values of 51.79% and 20.21% respectively. Mice (n=8 each group) were placed in an observation box, and the number of writhing movements (constriction of the abdominal muscles together with stretching of the hind limbs) was counted for each mouse for a period of 20 minutes after acetic acid injection. Anti-nociceptive activity was expressed as the number of abdominal constrictions between saline treated control and animals pre-treated with *M. piperita* leaf aqueous extracts or acetyl salicylic acid. In contrast, the present study showed that the aqueous extract of *M. piperita* leaf failed to exert anti-oedematogenic effect on the increase in paw thickness induced by carrageenan injection indicating a lack of peripheral anti-phlogistic activity (Taher, 2012).

#### Peppermint oil

##### *In vivo*

A study to characterise the effects of peppermint and caraway oil individually and in combination on the visceral nociception in a rat model of post-inflammatory hyperalgesia, was performed. 28 male Lewis rats were randomised to treatment with a rectal administration of trinitrobenzene sulphonic acid (TNBS)/ethanol or physiological saline solution. After 14 days of treatment with peppermint and/or caraway oil, a reduced visceromotor response of up to 50% was found compared to placebo. Individually both oils had no significant effect on post-inflammatory visceral hyperalgesia (Adam *et al.*, 2006).

#### Menthol

In another study in identified Helix neurons, the authors indicated a modulating action of external menthol on Ca inactivation (Hawthorn *et al.*, 1988).

### **Anti-carminative activity**

#### Peppermint oil

##### *In vitro*

Peppermint oil has showed antifoaming and carminative activity *in vitro*. Reductions in gastric and intestinal foam volume were observed *in vitro* studies with peppermint oil. The carminative effect results from a combination of actions. Antifoaming activity associated with the relaxation of the oesophageal sphincter may release the gastric gas. The antimicrobial activity helps to reduce the intestinal gas (Harries *et al.*, 1978).

### **Bronchomucotropic activity**

#### Peppermint oil

In several old studies, peppermint oil was reported to depress ciliary activity, while in some other studies peppermint oil markedly stimulated it (Das *et al.*, 1970).

#### Menthol

##### *In vivo*

Menthol (1 mg of menthol/kg added to the water vaporizer, corresponding to systemic absorption of not over 20 µg/kg body weight) was given to rabbits anaesthetised with urethane. It augmented the soluble mucus content and lowered the specific gravity of respiratory tract fluid. The author concludes that the bronchomucotropic effects were due to direct local stimulation of mucus secreting cells in the respiratory tract. Inhalation of larger amounts of menthol depressed the volume output and mucus content of respiratory tract fluid (Boyd and Sheppard, 1969).

### 3.1.2. Secondary pharmacodynamics

#### Antioxidant activity

##### Peppermint leaves

The antioxidant capacity of peppermint has been determined using of different assay methods. Among some medicinal herbs, *Mentha piperita* leaves showed a high oxygen radical absorbance capacity.

Water-soluble extracts from the *Mentha* species among which *M. piperita* was screened for potential antioxidative properties. These properties included iron(III) reduction, iron(II) chelation, 1,1-diphenyl-2-picrylhydrazyl radical scavenging, and the ability to inhibit iron(III)-ascorbate-catalysed hydroxyl radical-mediated brain phospholipid peroxidation. All the extracts demonstrated varying degrees of efficacy within each antioxidant assay. The cultivar *M. x piperita* "Frantsila" appeared to be a good source of natural antioxidants, but not better than the other extracts for ferrous iron chelation. It contained the highest levels of total phenols as determined using the Folin-Ciocalteu reagent and by HPLC, due to the high levels of eriocitrin and rosmarinic acid (Dorman *et al.*, 2003).

#### Antimicrobial, antiplasmid and antiviral activity

##### Peppermint leaves

Antiviral activity was reported of aqueous extracts of peppermint leaves towards *Influenza A*, Newcastle disease virus, *Herpes simplex* virus and *Vaccinia* virus, in egg and cell culture systems (Herrmann and Kucera, 1967). The antibacterial and antifungicidal activity was reported in several studies, especially with peppermint oil.

The inhibition of the growth of *Salmonella typhimurium*, *Staphylococcus aureus* and *Vibrio parahaemolyticus* were achieved with addition of ground leaves to the agar medium at concentrations of 0.1-2.0% (w/v) (Aktug and Karapinar, 1986).

In another study, the reduction of the number of plaques of the rinderpest virus with aqueous and ethanol extracts of the leaves of *Mentha piperita*, at concentrations of 4-8 mg/ml was observed (Alwan *et al.*, 1988).

The *in vitro* susceptibility of *Helicobacter pylori* to botanical extracts used traditionally for the treatment of gastrointestinal disorders was screened. *Mentha piperita* (leaves) were among the extracts with a MIC<sub>50</sub>±100 µg/ml (Mahady *et al.*, 2005).

In a study by Blaszczyk *et al.* (2000), extracts of 56 widely used dried Chinese medical plants or their parts were screened for their antimycotic properties against pathological phyla of *Aspergillus fumigates*, *Candida albicans*, *Geotrichum candidum* and *Rhodotorula rubra*. Herba Menthae (*Mentha haplocalyx* Briq., *Mentha piperita* L.) extract has moderate antimycotic properties against all screened fungi strains.

##### Peppermint oil

The virucidal effect *in vitro* was assessed on a study, where the inhibitory activity against herpes simplex (HSV, type 1 and type 2) was tested. A plaque reduction assay was used with RC-37 cells, where the HSV-1 and 2 were grown. Peppermint oil was dissolved in ethanol (1% final concentration of ethanol) and added to the cell culture medium, at the non-toxic concentration of 0.01%. To determine the antiviral action, cells were pre-treated with peppermint oil before the infection, viruses were incubated with peppermint oil before infection and cells and viruses were incubated together during adsorption or after penetration of the virus into the host cells. All these experiments were performed in parallel with acyclovir to test the suitability of the assay and were compared to untreated controls.

Ethanol had no effect on virus titers and did not exhibit any toxic effect on the cells. At non-cytotoxic concentration of the oil, 0.01% peppermint oil, the titres of HSV-1 and 2 were reduced by 82% and 92% respectively. Higher concentrations reduced virus titers for more than 90%. The 50% inhibitory concentration (IC<sub>50</sub>) of peppermint oil was determined at 0.002% and 0.0008% for HSV-1 and 2. The peppermint oil affected the virus before adsorption exerting a direct effect on the virus, but not after penetration into the host cell (Schuhmacher *et al.*, 2003).

Peppermint oil showed antimicrobial and antiplasmodial activity, demonstrating a synergistic additive interaction with oxytetracycline (Schelz *et al.*, 2006).

In a study by Mimica-Dukic *et al.*, (2003), the antimicrobial activity and free radical scavenging capacity (RSC) of essential oils from *Mentha piperita* L. as well as *M. aquatica* L., and *M. longifolia* L. have been described. The percentage content of essential oils were 0.69% for *M. aquatica*, 3.73% for *M. piperita* and 3.21% for *M. longifolia*. The chemical profile of each essential oil was checked by TLC and determined by GC-MS. The most powerful antibacterial activity was demonstrated by *M. piperita*, in particular against multiresistant strain of *Shigella sonnei* and *Micrococcus flavus* ATCC 10240. All tested oils showed significant fungistatic and fungicidal activity, considered higher than those of Bifonazole.

### **Antiallergic action**

#### Peppermint leaves

A study was performed to clarify the effects of extracts of the leaves and stems of *Mentha piperita* L. on experimental allergic rhinitis. The extraction process includes the removal of essential oil, fat, followed by fractionation. This 50% ethanol extract had a dose-dependent effect, on the inhibition of histamine release from rat peritoneal mast cells. The compound 48/80 induced this reaction and the inhibition was observed at a concentration of 3 µg/ml. The water, 50% ethanol eluate, separated by column chromatography also shows a similar effect at a dose of 1 µg/ml. The oral administration of 50% EtOH inhibited sneezing and nasal rubbing induced by antigen-antibody reaction. The repeated administration was more effective than a single administration (Innoue *et al.*, 2001).

Following these results, the same authors further studied the antiallergic effect of the flavonoid glycosides obtained from *Mentha piperita* L. Among the flavonoids isolated from the aerial part of *M. piperita* L., luteolin-7-O-rutinoside showed a dose-related inhibitory effect of an antigen induced nasal response at doses of 100 and 300 mg/kg.

### **CNS action**

#### Peppermint leaves

An aqueous extract of peppermint leaf (50 g of dried leaf infused for 10 minutes in 500 ml hot water, then spray-dried) administered orally in 2 single doses of 300 mg/kg and 1000 mg/kg in 16 mice showed a weak sedative action in several tests: hexobarbital-induced sleep, exploratory behaviour, spontaneous motility and motor coordination (Della Loggia *et al.*, 1990).

The peppermint extract at a dose of 1000 mg/kg causes a biphasic effect with initial stimulation followed by depression, in the behavioural tests in rats. It seems that the effect observed is due to the oil contained in the extract. At a lower dose, 300 mg/kg, the excitatory response is too weak and transient, and only the depressive effect is recorded (Della Loggia *et al.*, 1990).

### **Anticonvulsivant effect**

#### Peppermint oil

The effect of pre-treatment with essential oils administered 60 minutes prior to intraperitoneal injection of a lethal dose of pentylenetetrazol-(PTZ) on the seizure latency and severity, to eight groups of Balb-c mice was assessed. Control group received only one i.p. PTZ injection. *M. piperita* essential oil (EO) was the most effective from all with no seizures observed after the administration of PTZ. The survival of animals after the treatment was 100%, showing that it is extremely tolerable by the animals and has the best anticonvulsant results (Koutroumanidou *et al.*, 2013).

### **Diuretic effect**

#### Peppermint leaves

The effect of peppermint on diuresis is weak. The effective dose is about 30 times higher than that of aminophylline. At 1000 mg/kg oliguria was observed (Della Loggia *et al.*, 1990).

### **Chemopreventive effects**

#### Peppermint leaves

In studies where some agents induced carcinogenicity, peppermint showed a preventive and reduction effect. A study was performed comparing a powdered tobacco mixture (15 g) with and without 15 g of peppermint leaves, on the induction of morphological changes and tumors. These mixtures were painted onto the cheek pouches of Syrian golden hamsters 3 times per week for 20 weeks. The non-mint tobacco mixture increased mucosal thickening (n=20/22 in non-peppermint groups vs 9/15 in peppermint containing group), leukoplasia (20/22 vs 3/15) and frank tumors (19/22 vs 0/15) in the oral cavity. 86.3% of the animals in the group without peppermint present tumor bearing at week 30, while the group with peppermint had 0% of tumors (Samman *et al.*, 1998).

The results of the study performed by Sameena and Ashok (2001), on the papillomagenesis of the skin induced by 7,12-dimethylbenz (a) anthracene (DMBA) in mice, suggest that there is a chemopreventive effect of peppermint on the development of skin papillomas, being most effective during the promotional stage of carcinogenesis.

An aqueous extract of *Mentha piperitae* leaves was evaluated using 9-week medium term model of benzo[a]pyrene (BP)-induced lung tumors in newborn Swiss albino mice. The number of lung tumors was reduced after oral administration of *Mentha* extract, in an inhibition rate of 61.26% in the *Mentha* treated group with respect to the reference group. *Mentha* extract reduced the frequency of BP induced chromosomal aberrations and micronuclei in bone marrow cells and decreased the levels of lipoperoxides and increased sulfhydryl groups in liver and lung (Samarth *et al.*, 2006).

The effects of peppermint extracts against sublethal and lethal doses of gamma radiation in Swiss albino mice were tested in several studies. Pre-treatment with an aqueous extract of peppermint prior to the radiation (whole body), 1 g/kg administered 3 days before the irradiation with 8 Gy, increased the hematological parameters. The survival rate was also better on the pretreatment group compared with the irradiated control, 10 days post-irradiation (Samarth *et al.*, 2004). The serum alkaline phosphatase was increased and the acid phosphatase decreased, using the same protocol, compared with the control, after irradiation, returning to normal after 5 days (Samarth *et al.*, 2002).

The intestinal mucosa of mice suffered increased villus height, total number of mitotic cells, and decreased the number of goblet and dead cells after taking 1 g/Kg peppermint extract, within 20 days post-irradiation at 8 Gy (Mckay and Blumberg, 2006).

A study was held to investigate the protective and anticancer effect of *Mentha* leaves aqueous extract on oral epithelium of mice tongues. A total of 80 Egyptian albino mice were divided into three groups. Group I served as control (not subjected to any kind of treatment), and groups II and III were subjected to two-stage chemical carcinogenesis through topical application of

dimethylbenz[*a*]anthracene (DMBA) followed by formaldehyde on dorsal and ventral surfaces of tongues for 9 weeks. Peppermint leaves extract was administered to group III at the time of cancer induction. Histological changes were assessed in H&E sections at 3-week intervals. The anticarcinogenic effect of *M. piperita* was tested using immunostain with anticaspase antibody. The authors report that oral administration of peppermint leaves extract reduced the appearance of dysplastic cellular changes with 61% and inhibited tumor incidence with 100%. Group I showed moderate-to-strong cytoplasmic caspase expression. At 6-week interval, group II showed weak-to-moderate caspase expression, while sections from group III showed moderate-to-strong caspase expression. The authors also report highly significant statistical difference in the total score of caspase 3 expression between specimens obtained from animals sacrificed at 6 weeks in groups I, II, and III ( $p=0.001^{**}$ ) and conclude that *Mentha piperita* has inhibited the initiation and promotion of oral dysplastic lesions (Kasem *et al.*, 2014).

The possible molecular mechanisms underlying the cytotoxicity and anticarcinogenic potential of *Mentha* leaf extracts (petroleum ether, benzene, chloroform, ethyl acetate, methanol, and water extracts) on 6 human cancer (HeLa, MCF-7, Jurkat, T24, HT-29, MIAPaCa-2) and normal (IMR-90, HEK-293) cell lines were studied. Of all the extracts tested, chloroform and ethyl acetate extracts of *M. piperita* showed significant dose- and time-dependent anticarcinogenic activity leading to G1 cell cycle arrest and mitochondrial-mediated apoptosis, perturbation of oxidative balance, upregulation of Bax gene, elevated expression of p53 and p21 in the treated cells, acquisition of senescence phenotype, while inducing pro-inflammatory cytokines response. The authors stated that the exhibited results provide the first evidence of direct anticarcinogenic activity of Mint's leaf extracts (Jain *et al.*, 2011).

A chemopreventive action and an antigenotoxic effect were observed in an evaluation of aqueous extracts of *Mentha piperita* leaves, administered after an initial dose of benzo[*a*]pyrene (0.5 mg) in newborn Swiss albino mice (Akdogan *et al.* 2004a, Samarth *et al.*, 2006).

Six herbal infusions (*Matricaria chamomilla*, *Tilia cordata*, *Mentha piperita*, *Mentha pulegium*, *Uncaria tomentosa* and *Valeriana officinalis*) were tested for antigenotoxicity, using the SMART test in *Drasophila melanogaster*. Hydrogen peroxidase was used as an oxidative genotoxicant. The infusion of *M. pulegium* is desmutagenic in the SMART when assayed with hydrogen peroxide in combined treatments. Both *M. piperita* and *M. pulegium* infusions showed similar levels of anti-genotoxicity (141 and 134%, respectively). The authors conclude that the results of inhibition obtained for *M. chamomilla*, *T. cordata*, *M. piperita*, *M. pulegium* and *V. officinalis* surpassing 100% (ranging from 125 to 141%), can only be explained by a synergism between their phenolic contents and the hydrogen peroxide, due to the known ability of phenols to scavenge reactive oxygen species such as those generated by hydrogen peroxide (Romero-Jimenez *et al.*, 2005).

### Menthol

After 20 weeks of oral dosing with 1% (-) menthol, a significant inhibition of induced mammary gland carcinogenesis ( $p<0.001$ ) was reported (Russin *et al.*, 1989).

## **Renoprotective effects**

### Peppermint leaves

A study was carried out to evaluate the renoprotective effect of *Mentha piperita* against gentamicin induced nephrotoxicity. Fresh plant leaves of *M. piperita* were collected from Pakistan. Extraction was done with ethanol after drying the leaves under shade. A total of 24 male rabbits were divided into four groups of 6 each and each group was treated independently, group C with 0.9% saline only 2 ml/kg (i.m) for 21 days, group G with gentamicin 80 mg/kg (i.m) for 21 days, group GM-pi with gentamicin 80 mg/kg (i.m)+*M. piperita* 200 mg/kg (p.o) for 21 days and the group M-pi with *M. piperita* 200

mg/kg (p.o) for 21 days. Three rabbits in each group were sacrificed on day 21 of study period for examination of the kidneys. Histological examination of the kidneys of Group G showed proximal tubular necrosis with loss of cellular pattern. Glomerular atrophy and ruptured tubules with hydropic changes were also observed while in case of Group C animals' normal tubules with no evidence of necrosis and normal glomeruli or hydropic changes were observed. Groups GM-pi and M-pi also showed normal histology with no common abnormality or significant toxicity. Significant rise in the serum creatinine, blood urea nitrogen and serum uric acid with fall in creatinine clearance were observed in Group G animals when compared with control, which was reversed to almost control values in the extract treated animals. The authors report that it showed the protective role of *M. piperita* against toxic effects of gentamicin on kidney. They concluded that concurrent administration *M. piperita* successfully prevented renal damage associated with gentamicin, explored by various biochemical and histological examinations. Furthermore, the study also shows that concomitant use of *M. piperita* does not decline the efficacy of gentamicin with respect to its antibacterial activities (Naveed *et al.*, 2014).

### **Hepatoprotective effect**

#### Peppermint leaves

A study to evaluate the protective activity of leaves of *Mentha piperita* L (*Mentha* leaves water extract) in adult Swiss mice against arsenic-induced hepatopathy was performed by Sharma *et al.*, (2007). Pre and post treatment of *Mentha* with arsenic alters the biochemical parameters in the liver, reducing ACP, ALP, SGOT, SGTP and LPO content. A significant increase in body and liver weight, GSH content and LDH activity in liver was estimated. The authors concluded that the results indicate that *Mentha* extract may be useful in reducing the side effects of arsenic-induced hepatopathy (Sharma *et al.*, 2007).

### **3.1.3. Safety pharmacology**

These data are included in other chapters.

### **3.1.4. Pharmacodynamic interactions**

#### Peppermint oil

Peppermint oil has been reported to demonstrated competitive antagonism on calcium channels in animals (*in vivo*) and *in vitro*. From a theoretical point of view, the calcium channels blockers effectiveness may be modified (Hawthorn, 1988).

In a study using excised rat skin (Abdullah *et al.*, 1996), peppermint oil demonstrated a 46-fold increase in the penetration of 5-fluorouracil.

In another study, the influence of acute and chronic intake of peppermint oil (Peppermint oil –*Mentha piperita* L., Lamiaceae; prepared as emulsion for oral use) on pentobarbitone-induced sleeping time, analgesic effect of codeine and impairment of motor coordination caused by midazolam in mice were observed. Applied doses of peppermint oil were 0.1 and 0.2 ml/kg. The authors report that chronic peppermint oil intake (in both doses) led to significant decrease of analgesic effect of codeine, while acute intake of peppermint oil did not change this effect. Acute peppermint oil pretreatment in higher dose caused significant prolongation of pentobarbitone-induced sleeping time, while it was significantly shortened by chronic peppermint oil pretreatment at the same dose. Midazolam effect was enhanced and prolonged significantly by chronic peppermint oil intake at higher dose, while acute intake of peppermint oil did not change this effect. Gut motility was increased only by acute intake of higher peppermint oil dose. Regarding the fact that peppermint oil produces changes in tested drug effects,

the authors concluded that the interaction between drugs and phytopreparations containing peppermint oil should be additionally followed/confirmed in humans (Samojlik *et al.*, 2012).

### **3.1.5. Conclusions**

#### Peppermint leaves

The antispasmodic effects on gastrointestinal tissue and the antinociceptive effect on animal models were reported in the non-clinical studies. They are specially attributed to the content in essential oil.

Stimulation of bile secretion in dogs has been reported. Nevertheless, the flavonoids's content of peppermint leaves have also been reported to inhibit contraction of guinea pig ileum and to stimulate bile secretion *in vivo* in dogs.

The non-clinical data support the traditional use of peppermint leaf preparations, for the symptomatic relief of digestive disorders such as dyspepsia and flatulence.

#### Peppermint oil

In non-clinical *in vitro* and *in vivo* studies, antispasmodic activity on the gastrointestinal smooth muscle has been reported. The mechanism seems to be related to the reduction of the calcium influx and the block of non-competitive contraction induced by 5-hydroxytryptamine.

Cholagogic activity *in vivo* has also been reported and could possible contribute to the carminative activity.

The antimicrobial activity combined with reduction in gastric and intestinal foam volume, as well the relaxation of the oesophageal sphincter could potentially contribute to the carminative activity.

The competitive antagonism at calcium channels in animals and *in vitro* raises the possibility of interaction with other calcium blockers.

The bronchomucotropic effects were contradictory, with depressing and stimulatory action of mucus secreting cells in the respiratory tract.

### ***3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof***

#### Peppermint leaves

Maliakal and Wanwimolruk, (2001) reported modulatory effects of peppermint tea on selected hepatic phase I metabolising enzymes in a study on female Wistar rats. According to the authors, after pre-treatment with a 2% solution for 4 weeks ( $n=5$ ), the activities of cytochrome P450 isoforms CYP1A2 (24%) and CYP2E (48%) were significantly reduced, compared with a control group.

#### Peppermint oil

##### **Dermal absorption**

The absorption rate for peppermint oil was measured after the application of eserine in a peppermint oil vehicle, to a 2.2 cm<sup>2</sup> 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 (Nair, 2001).

##### **Inhalation**

#### Menthol

Pulmonary absorption depends on various factors, like the kind of compound and the breathing mechanics of the subjects. In one study, it was demonstrated that the release of compounds from water into the headspace depended on water temperature. Elimination half-lives for inhaled menthol and camphor were 35.5 and 39.9 minutes respectively. This indicates that there should be no accumulation during long-term application (Kohlert *et al.*, 2000).

### **Oral absorption and metabolism**

The major biliary metabolite is menthol glucuronide, which undergoes enterohepatic circulation.

Metabolism of l-menthol in rats was investigated both *in vivo* and *in vitro*. The following were metabolites isolated and characterised from the urine of rats after oral administration (800 mg/kg of body weight per day) of l-menthol: p-menthane-3, 8-diol (II), p-menthane-3, 9-diol (III), 3, 8-oxy-p-menthane-7-carboxylic acid (IV), and 3, 8-dihydroxy-p-menthane-7-carboxylic acid (V). Compounds II and V were the major urinary metabolites *in vivo*. Repeated oral administration (800 mg/kg of body weight/day) of l-menthol to rats for 3 days resulted in the increase of both liver microsomal cytochrome P-450 content and NADPH-cytochrome c reductase activity by nearly 80%. Further treatment (for 7 days total) considerably reduced their levels, although the levels were still higher than the control values. Both cytochrome b5 and NADH-cytochrome c reductase levels were not changed during the 7 days of treatment. Rat liver microsomes readily converted l-menthol to p-menthane-3, 8-diol (II) in the presence of NADPH and O<sub>2</sub>. This activity was significantly higher in microsomes obtained from phenobarbital (PB)-induced rats than from control microsomal preparations, whereas 3-methylcholanthrene (3-MC)-induced microsomes failed to convert l-menthol to compound II in the presence of NADPH and O<sub>2</sub>. L-Menthol elicited a type I spectrum with control (K<sub>s</sub>=60.6 microM) and PB-induced (K<sub>s</sub>=32.3 microM) microsomes whereas it produced a reverse type I spectrum with 3MC-induced microsomes (Madyastha and Srivatsan, 1988).

One randomised 4-way crossover study was designed to determine the effect of peppermint oil and ascorbylpalmitate on cytochrome P4503A4 (CYP3A4) activity *in vitro* and oral bioavailability of felodipine in humans. The method was the study of the reversible mechanism-based inhibitions of nifedipine oxidation in human liver microsomes. Oral administration of 10-mg extended-release tablet of felodipine with grapefruit juice (300 ml), peppermint oil (600 mg), ascorbyl palmitate (500 mg), or water, were given to 12 healthy volunteers, and the pharmacokinetics of felodipine and dehydrofelodipine were determined. The authors concluded that peppermint oil, menthol, menthyl acetate, and ascorbyl palmitate were moderately potent reversible inhibitors of *in vitro* CYP3A4 activity. Nevertheless further investigation should be done (Dresser *et al.*, 2002).

A study compared the effects of peppermint oil with ketoconazole and D-alpha-tocopheryl poly (ethylene glycol 1000) succinate (TPGS), on the inhibition of cyclosporine oral bioavailability in rats. Peppermint oil (100 mg/kg) tripled the mean cyclosporine maximum concentration. The author suggests that inhibition of cytochrome P450 3A is not the only mean by which peppermint oil enhances cyclosporine bioavailability (Wacher *et al.*, 2002).

### **Excretion**

The urinary metabolites result from hydroxylation at the C-7 methyl group at C-8 and C-9 of the isopropyl moiety, forming a series of mono- and dihydroxymenthols and carboxylic acids, some of which are excreted in part as glucuronic acid conjugates. Studies with tritiated l-menthol in rats indicated about equal excretion in faeces and urine. The main metabolite identified was menthol-glucuronide. Additional metabolites are mono- or di-hydroxylated menthol derivatives (Grigoleit and Grigoleit, 2005a).

### Pulegone and menthofurane

Pharmacokinetic data related to pulegone and menthofuran are summarised in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1).

### **Assessor's overall conclusions on pharmacokinetics**

The studies on the pharmacokinetics and bioavailability are few and contradictory.

According to existing studies, in animals, peppermint is rapidly absorbed. The major biliary metabolite is menthol glucuronide, which undergoes enterohepatic circulation. After inhalation, pulmonary absorption depends on various factors and the rapid elimination indicates that there should be no accumulation during long-term application.

The urinary metabolites are excreted in part as glucuronic acid conjugates. Studies in rats indicated equal excretion of essential oil compounds in faeces and urine. The main metabolite identified was menthol-glucuronide.

Pharmacokinetic data related to pulegone and menthofuran are summarised in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1).

### **3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof**

#### **3.3.1. Single dose toxicity**

##### Peppermint leaf extract

A dry peppermint leaf water extract, was given to 12 mice as a single dose at 4000 mg/kg body weight. None of the animals died or showed macroscopic signs of toxicity over a 7-day period (Della Logia *et al.*, 1990).

##### Peppermint oil

The oral LD<sub>50</sub> of peppermint oil U.S.P. in fasted Wistar male rats was found to be 4441±653 mg/kg after 24 hours and 2426 mg/kg after 48 hours (Nair, 2001).

#### **3.3.2. Repeat dose toxicity**

##### Peppermint leaves

20 g/l of *M. piperita* tea was given to 48 rats during 30 days; serum iron and ferritin levels were reduced ( $p < 0.05$ ), and increased unsaturated iron-binding capacity ( $p < 0.01$ ) were observed in a study of Akdogan *et al.*, (2004a).

In another study, the biochemical and histopathological effects of *Mentha piperitae* L. and *Mentha spicata* L on liver tissue of rats were investigated. AST and ALT activities were increased, but not statistically significantly in the group with 20 g/l of *M. piperita* tea, daily, during 30 days, and minimal hepatocyte degeneration was found in the histopathological evaluation. The damage seems to be dose dependent, according to the author (Akdogan *et al.*, 2004b).

A similar study on the kidney of Wistar albino rats found no evidence of nephrotoxicity on the group drinking 20 g/l of *M. piperita* tea, daily, during 30 days. Slight histopathological changes were observed, in the group of *M. piperita* compared with the group of *M. spicata*. They consist of hydropic

degeneration of tubular epithelial cells, epithelial cells with picnotic nuclei and eosinophilic cytoplasm, enlargement of bowman capsules (Akdogan *et al.*, 2003).

#### Pulegone/menthofuran

Repeat-dose toxicity studies of pulegone and menthofuran are summarised in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1).

#### Menthone

In a 28 days study rats were orally dosed with 0, 200, 400 and 800 mg menthone/kg bw per day, respectively. The decrease in plasma creatinine and the increase in phosphatase alkaline and bilirubin were dose dependent. Relative weights of liver and spleen were increased. Cyst-like spaces were histopathologically seen in the white matter of the cerebellum of the two highest dose groups. The non-observed effect level (NOEL) was lower than 200 mg/kg bw per day (HED=<32 mg/kg) (Madsen *et al.*, 1986).

### **3.3.3. Genotoxicity**

#### Peppermint oil

*Salmonella* strains TA1537, TA98, TA1535 and TA100 were used to test peppermint oil at concentrations of 800, 160, 32 and 6.4 µg per plate. No mutagenic properties were observed until 160 µg per plate. 800 µg peppermint oil/plate displayed cytotoxicity. Menthol and pulegone were also negative at the same concentrations. Peppermint oil was negative at a dose of 150 µg/ml, in a mouse lymphoma L5178Y TK±cell mutagenesis assay and at a concentration of 155 µg/ml, in an unscheduled DNA synthesis assay, on rat hepatocytes (Nair, 2001).

The genotoxic activity of dill, peppermint and pine essential oils were studied using chromosome aberration (CA) and sister chromatid exchange (SCE) tests in human lymphocytes *in vitro* and *Drosophila melanogaster* somatic mutation and recombination test (SMART) *in vivo*. The essential oil of *M. piperita* was shown to weakly induce SCE in a dose independent manner and to be genotoxic in the wing somatic mutation and recombination tests (SMART). Peppermint oil was the most cytotoxic and inhibited mitotic activity of human lymphocytes (Lazukta *et al.*, 2001).

Peppermint oil was negative in the *in vivo* combined micronucleus/Comet assay (liver, kidney and bladder mucosa cells) in female rats (up to 750 mg/kg). Further evaluation of the genotoxicity of peppermint oil, related to pulegone and menthofuran, are summarised in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2015 Rev. 1).

#### Menthol

The mutagenic potential of natural Brazilian menthol was tested in the cytogenetic assay (rats), the host-mediated assay (mice), and the dominant lethal assay (rats). The assays were done with menthol doses of 1.45, 14.5, and 145.0 mg/kg and in some instances, subacute and acute studies were done with doses of 500, 1150, and 3000, or 5000 mg/kg. In the host-mediated assay, a weakly positive but significant response was noted with the acute high dose against *Salmonella typhimurium* TA1530, and elevated recombinant frequencies were noted with the subacute doses against *Saccharomyces* D3. All other assays were negative (Nair, 2001 citing Litton Bionetics, Inc. 1975).

#### Menthone

Menthone exhibited mutagenic responses in several *Salmonella* tester strains, although responses were rather inconsistent in terms of concentration and requirement of S9. It was also positive in the wing somatic mutation and recombination tests (SMART) and genotoxic in *D. melanogaster* (Lazukta *et al.*, 2001). It was weakly positive in the host-mediated assay (mice), but not in cytogenetic or dominant lethal assays (rats) (Nair, 2001).

#### Pulegone and Menthofuran

The genotoxicity of pulegone and menthofuran are evaluated in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1).

### **3.3.4. Carcinogenicity**

#### Peppermint oil

The Final report on the Safety Assessment of *Mentha piperita* (2001) presents a carcinogenicity study of toothpaste and its components, where groups of 52 male pathogen-free CFLP (ICI-rede. ned) mice were dosed by gavage with 4 or 16 mg peppermint oil/kg per day, 6 days a week for 80 weeks. A 16- to 24-week observation period followed treatment. An untreated group of 52 male mice and a vehicle group of 260 male mice that received the toothpaste base (which did not contain chloroform, eucalyptol, or peppermint oil) were maintained as controls. Body weight gain was initially reduced in animals of the 16-mg/kg per day group. At least one neoplasm at any site was observed in 73%, 69%, 65%, and 71% of mice of the low dose, high-dose, untreated-control, and vehicle-control groups, respectively. Malignant neoplasms were noted in 39%, 35%, 23%, and 31% of mice of the low-dose, high-dose, untreated control, and vehicle-control groups, respectively. The incidence of neoplasms of the lungs and kidneys were comparable among mice of the treated and non-treated groups.

This report mentioned also the study by Roe *et al.*, (1979), where hepatic cell tumor incidence for peppermint oil-dosed mice (25%) was comparable to the incidence for mice of the vehicle-control group (27%); the incidence for the untreated group was 19%. Malignant lymphoma was found in 25%, 21%, 10%, and 14% of mice of the low-dose, high-dose, untreated, and vehicle-control groups, respectively. The researchers did not discuss if the difference in the incidence rate was significant. (Nair, 2001)

A review of the study by the British Industrial Biological Research Association (1992) noted that it was not designed to examine the carcinogenic potential of peppermint oil and thus "would have had only a very limited sensitivity to this particular component" (Nair, 2001).

#### Menthol

The National Cancer Institute found no evidence of carcinogenicity after dosing Fisher 344 rats with 3750 or 7500 ppm oral dose, or B6C3F<sub>1</sub> mice with 2000 or 4000 ppm *d, l*-menthol, in a two year study, in 1979. In female mice, dose related increased deaths were noted (US National Cancer Institute, 1979).

#### Pulegone/Menthofuran

The carcinogenicity of pulegone and menthofuran are evaluated in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1).

### **3.3.5. Reproductive and developmental toxicity**

#### Peppermint leaves

The effects of *Mentha piperita* and *Mentha spicata* herbal teas on plasma total testosterone, luteinizing hormone and follicle-stimulating hormone levels and testicular histologic features were evaluated. The rats (200-250 g) were randomised in four groups of 12 each. The experimental group was given 20 g/l *M. piperita* tea, or 20 g/l *M. spicata* tea or 40g/l *M. spicata* tea. The control group control had commercial drinking water. The follicle-stimulating hormone and luteinizing hormone had increased and total testosterone had decreased levels, compared with the control group, being statistically significant. The Johnsen testicular biopsy scores were different but not statistically significantly (Akdogan *et al.*, 2004c).

#### Menthol

No clear discernible effect on nidation (or on maternal or fetal survival) was observed after oral administration of up to 185 mg/kg (body weight) of Brazilian menthol to pregnant mice for 10 consecutive days. The number of abnormalities seen in the test group didn't differ from the sham-treated controls. No teratogenic effects were noted after oral intubations of Brazilian menthol on pregnant mice, rats, hamsters and rabbits (Food and Drug Research Labs, 1973).

For maximum oral doses of 190, 220, 400, and 430 mg/kg per day, respectively, teratogenic effects in mice, rats and hamsters were not observed (FAO/WHO expert on Food Additives, 2000).

### **3.3.6. Local tolerance**

Peppermint oil is recognised to produce immediate contact reactions (urticaria) (Nair, 2001, citing DeGroot, 1994).

5% and 10% menthol produced a strong burning sensation but 0.2% and 2% of menthol is reported to have a coolant action (Nair, 2001, citing Eccles, 1994).

The local tolerance depends on the concentration of peppermint oil as well on the excipients used in the final product.

### **3.3.7. Other special studies**

#### Immunotoxicity

At very high dose levels (1250 mg/kg per day), peppermint did increase mortality and reduce survival time in the host resistance assay, in the rapid screening protocol, to evaluate humoral and cell-mediated immune responses (Gaworsky *et al.*, 1994).

#### Phototoxicity

No effects were produced after the application of 100% peppermint oil on the back of hairless mice, irradiated with light from a fluorescent black light at an integrated UVA. The same result was obtained on a second experiment using the same protocol with two miniature swine (Nair, 2001, citing Research Institute for Fragrance Materials, 1996).

### **3.3.8. Conclusions**

Toxicological studies on peppermint leaves and peppermint oil are scarce.

The oral LD<sub>50</sub> of peppermint oil U.S.P. in fasted Wistar male rats after 24 hours was found to be 4441±653 mg/kg and after 48 hours 2426 mg/kg.

Peppermint oil was negative in the Ames test (up to 160 µg per plate), the mouse lymphoma assay (up to 150 µg/ml), and in the *in vivo* combined micronucleus/Comet assay (liver, kidney and bladder

mucosa cells) in female rats (up to 750 mg/kg). Weak and inconsistent genotoxic responses in other non-validated tests are probably toxicologically inconsequential. There is more evidence for genotoxicity potential of menthol or menthone 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.

Tests on reproductive toxicity and carcinogenicity do not exist for peppermint oil or for preparations from peppermint leaves. No photosensitivity of peppermint oil was found.

#### Pulegone/Menthofuran

The toxicity of pulegone and menthofuran have been evaluated by HMPC and presented in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1). In brief, based on a 3-month repeat-dose toxicity study in rats, the NOAEL was taken as 37.5 mg/kg bw, due to liver and kidney toxicity. A plausible mechanism for toxicity is the formation of reactive metabolites when cellular levels of glutathione are depleted. Based on the results from this study, and considering an uncertainty factor of 50, an intake of pulegone+menthofuran up to 37.5 mg/person per day, for an adult of 50 kg body weight, can be accepted for herbal medicinal products as a lifetime intake. For children, the daily amount of pulegone + menthofuran has to be adjusted to the body weight of the age group: e.g. body weight of 20 kg would lead to an acceptable daily intake of 15 mg per day. Furthermore, on the basis of results from several *in-vitro* and *in-vivo* genotoxicity studies, pulegone and menthofuran are considered non-genotoxic. In a 2 year study with orally administered pulegone there was no evidence of carcinogenicity in male rats up to 75 mg/kg (HED=12 mg/kg). In female rats there was clear evidence of carcinogenicity at the dosage of 37.5 mg/kg (HED=6 mg/kg), as well as in male and female mice, at the lowest dosage of 37.5 mg /kg per day (HED=3 mg/kg). The mechanism is considered to be related to the formation of reactive metabolites and sustained cytotoxicity. These findings require a long-term exposure to pulegone and/or menthofuran at doses, which are not relevant in the human situation.

#### Menthol

No evidence of carcinogenicity was found for d,l-menthol in a carcinogenicity study in rats with 3750 or 7500 ppm oral dose, or B6C3F<sub>1</sub> mice with 2000 or 4000 ppm. No teratogenic effects were noted in the studies performed on oral doses of 190, 220, 400, and 430 mg/kg per day.

#### Menthone

The oral toxicity of menthone was evaluated in an animal model. The decrease in plasma creatinine and the increase in phosphatase alkaline and bilirubin were dose dependent, after levels of 0, 200, 400 and 800 mg/kg bw per day. The non-observable- effect-level (NOEL) for menthone in this study was lower than 200 mg/kg bw per day. A NOEL of 400 mg/kg bw per day was reported in a 28 day toxicity study in rats.

### **3.4. Overall conclusions on non-clinical data**

#### Peppermint leaves

The antispasmodic effects on gastrointestinal tissue and the antinociceptive effect on animal models were reported in the non-clinical studies. They are specially attributed to their essential oil content.

Stimulation of bile secretion in dogs have been reported. Nevertheless, the flavonoids present in the leaves have also been reported to inhibit contraction of guinea pig ileum and to stimulate bile secretion *in vivo* in dogs.

These pharmacological actions support the traditional use in digestive disorders and the therapeutic indication proposed in this assessment report for the monograph–symptomatic relief of digestive disorders such as dyspepsia and flatulence.

Specific data on pharmacokinetics is not available.

Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

As there is no adequate information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

#### Peppermint oil

In non-clinical studies, antispasmodic activity on the gastrointestinal smooth muscle has been reported. The mechanism seems to be related to the reduction of the calcium influx and the block of non-competitive contraction induced by 5-hydroxytryptamine.

Cholagogic activity *in vivo* has also been reported and could possibly contribute to the carminative activity.

Peppermint oil was negative in two *in vitro* genotoxicity tests, 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/Menthofuran

Among the components of peppermint oil, pulegone and menthofuran raise concerns from a toxicological point of view. The toxicity of pulegone and menthofuran have been evaluated by HMPC and presented in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1).

The highest daily dosage of peppermint oil is 1.2 ml i.e. 1080-1099 mg (based on relative density 0.9-0.916 g/cm<sup>3</sup> according Ph. Eur. 8.1 (2014)), which contains maximum 32.4-32.97 mg pulegone and 86.4-87.92 mg menthofuran (according to Ph. Eur. 8.1 limits for pulegone and menthofuran in peppermint oil). For a 50 kg person this would correspond to a daily intake of 0.540-0.549 mg/kg bw of pulegone and 1.44-1.46 mg/kg bw of menthofuran, all together 99-100.45mg per day.

Based on the results from toxicity studies summarised in this public statement, the HMPC concludes that an intake of pulegone+menthofuran up to 37.5 mg per person per day, for an adult of 50 kg body weight, can be accepted for herbal medicinal products as a lifetime intake. For children, the daily amount of pulegone+menthofuran has to be adjusted to the body weight of the age group: e.g. body weight of 20 kg would lead to an acceptable daily intake of 15 mg/day, (life-long exposure) or 30 mg per day for a short-term exposure (less than 1 year).

For treatment durations of less than 1 year an intake (pulegone+menthofuran) of 75.0 mg per day for an adult of 50 Kg body weight (e.g. for children with a body weight of 20 kg 30mg per day) can be accepted. In the case of intermittent dosing, the acceptable daily intake should be based on the total number of dosing days instead of the time interval over which the doses are administered. For example, a drug administered once per week for 5 years (i.e., 260 dosing days) would have an acceptable intake per dose of 75.0 mg.

No quantitative data concerning absorption of pulegone and menthofuran through the skin exist although it is known that pulegone has been used as a "penetration enhancer". It is to ensure that the sum of pulegone and menthofuran within the daily dose is <37.5 mg for adults. The short-term use (maximum 14 days) is restricted to intact skin (EMA/HMPC/138386/2005 Rev. 1).

Higher contents within the products would be possible if low absorption rates for the relevant product can be shown (implying the relevant matrix, because absorption might be greatly influenced by the excipients, for instance essential oils as enhancers), not exceeding the daily intake of 37.5 mg for adults (EMA/HMPC/138386/2005 Rev. 1).

To reach the limits, peppermint oil with adequate quality (specification of adequate limits of pulegone and menthofuran) are required.

## 4. Clinical Data

### 4.1. Clinical pharmacology

#### 4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

##### Peppermint leaves

No data available.

##### Peppermint oil

Peppermint oil relaxes the oesophageal sphincter when administered orally (15 drops of oil suspended in 30 ml of water), eliminating the pressure differential between the stomach and oesophagus and allowing reflux to occur (Sigmund and McNally, 1969).

Another study documents the relaxation of the muscles around the border from oesophagus to the stomach through peppermint oil (Anon, 1990).

In other study peppermint oil reduced colonic spasms during endoscopy in 20 patients. Peppermint oil was injected along the biopsy channel of the colonoscope. Colonic spasm was relieved within 30 s (Sigmund and McNally, 1969).

An aqueous suspension of peppermint oil injected along the biopsy tract in 20 patients prevented the colonic spasms that would otherwise occur in endoscopic examinations (Leicester, 1982).

A randomised double-blind, double dummy, controlled trial was conducted in 100 patients to compare the antispasmodic effects of hyoscine-N-butylbromide i.m. and a placebo solution intraluminally administered by the endoscope. Also, the effects of a placebo solution i.m. were compared with those of a peppermint oil solution intraluminally administered. The percent change in diameter of the pyloric ring before and after the administrations was defined as the opening ratio, and the percent change in diameter between the maximally and minimally opened pyloric ring states was defined as the contraction ratio. Time until disappearance of the contraction ring(s) in the gastric antrum and side effects of the drugs were also determined. The opening ratio was significantly higher in the peppermint oil administration group than in the hyoscine-N-butylbromide injection group. The contraction ratio was lower in the peppermint group. The time required for the disappearance of the antral contraction was shorter in the peppermint oil group ( $97.1 \pm 11.4$ ) than in the hyoscine-N-butylbromide group ( $185.9 \pm 10.1$  s;  $p < 0.0001$ ). No significant side effects were associated with peppermint oil, whereas such as hyoscine-N-butylbromide injection produced side effects such as dry mouth, blurred vision and urinary retention (Hiki *et al.*, 2003).

In nine (9) studies, 269 healthy subjects or patients were exposed to peppermint oil by either topical intraluminal (stomach or colon) or oral administration of single doses or 2 weeks treatment (n=19). Methods used to detect effects were oro-cecal transit time by hydrogen expiration, total gastrointestinal transit time by carmine red method, gastric emptying time by radiolabelled test meal

or sonography, direct observation of colonic motility or indirect recording through pressure changes or relieve of colonic spasms during barium enema examination. The dose range covered in single dose studies is 0.1-0.24 ml of peppermint oil per subject. With one exception, which show an unexplained potentiation of neostigmine stimulated colon activity; all other studies result in effects, indicating a substantial spasmolytic effect of peppermint oil of the smooth muscles of the gastrointestinal tract. This effect commences as early as 0.5 minutes after topical (intestinal tract) application and may last up to 23 minutes.

This is evidently a very short time period to treat e.g. IBS. To expose the target organ, i.e. the large bowel to a constant concentration of peppermint oil to maintain the short-lasting effect a sustained release formulation is needed to secure constant exposure of the organ to constant concentrations of peppermint oil (Grigoleit and Grigoleit, 2005a)

Heartburn, one of the major adverse events of oral peppermint oil may be caused to a large extent by inappropriate release of the oil in the upper GI tract (Grigoleitb, 2005 citing Sigmund and McNally, 1969) resulting in relaxation of the lower esophageal sphincter thus facilitating reflux. To minimize these adverse events an appropriate delayed release formulation may be useful (Grigoleit and Grigoleit, 2005a).

The effectiveness of peppermint oil added to barium sulphate suspension in relieving colonic muscle spasm during contrast barium enema examination was assessed in a double blind study with 141 patients. No residual spasm was evident in a significant proportion of patients in the treated group (60%) compared with the control group (35%). There were no adverse effects. (Sparks *et al.*, 1995).

Another comparative study, with 383 patients on DCBE (double-contrast barium contrast), with positive results from occult blood tests were performed. The patients were divided into 4 groups, peppermint in barium, peppermint in tube, Buscopan or no treatment. In the group using peppermint oil or buscopan, the rate of patients with non spasm examination was higher than that in no-treatment group ( $p < 0.0005$ ). Peppermint oil had the same spasmolytic effect as the systemic administration of Buscopan (n-butylscopolamine.) in the transverse and descending colon (Asao *et al.*, 2003).

A pharmacodynamic study on the effect of peppermint oil (90 mg) and caraway oil on gastrointestinal motility in healthy volunteers was performed, using simultaneous determination of gastric and gall-bladder emptying and orocecal time, in comparison with placebo, cisapride and n-butylscopolamine. Peppermint oil shows a relaxing effect on the gallbladder ( $p = 0.04$ ) and slows the small intestinal transit ( $p = 0.004$ ) (Goerg and Spilker, 2003).

160 patients scheduled for outpatient colonoscopy were randomised in a double blind design. The objective was to determine the efficacy of peppermint oil versus placebo instillation over the ileocecal valve in the cecum, on the success rate and the duration of time required for terminal ileum intubation. The time required for TI intubation was shorter in peppermint oil group (102 seconds) than the control group (137 seconds)–  $p = 0.045$  (Sanaka Madhusudhan *et al.*, 2004).

The effect of acute peppermint oil administration on intragastric pressure (IGP) profiles and gastric sensorimotor functions was investigated. Healthy volunteers underwent IGP measurement before and during continuous intragastric infusion of a nutrient drink (n=13), and gastric barostat studies (n=13). A single capsule of peppermint oil (182 mg) or placebo was administered during the studies in a randomised controlled crossover design. Throughout the studies, healthy volunteers scored 11 epigastric symptoms on a visual analogue scale (VAS); satiation was scored on a 6-point Likert scale during intragastric infusion. During fasting, IGP and motility index (MI) of the proximal stomach significantly decreased after peppermint oil administration compared with placebo ( $p < 0.0001$  and  $< 0.05$ , respectively). In contrast, during intragastric infusion of the nutrient drink, no significant differences were detected between peppermint oil and placebo in IGP profiles, MI, satiation scores, and

epigastric symptoms. The maximum infused volume, gastric compliance or sensitivity to balloon distension did not differ between both treatment arms. However, reduced appetite scores were seen during fasting after peppermint oil treatment, as compared with placebo ( $p=0.01$ ). Postprandial VAS scores were similar between peppermint oil and placebo. Peppermint oil reduces IGP, proximal phasic contractility, and appetite, with negligible effects on gastric sensitivity, tone, accommodation, and nutrient tolerance in health (Papathanasopoulos *et al.*, 2013).

### **Respiratory action**

The inhalation of the peppermint essential oil for treating congestion due to common cold is believed to ease congestion, aiding respiration, by stimulating cold receptors in the respiratory tract (Eccles, 2003).

A secretolytic action in the bronchi (ESCOMP monographs, 2003, citing Hansel R *et al.*, 1984, 1999, Haen 1989, Schilcher H 1986) and decongestant in the nose (ESCOMP monographs, 2003 citing Reiter *et al.*, 1985) were reported in several publications.

#### **Menthol**

The effects of inhalation of L-menthol, D-isomenthol and D-neomenthol, upon nasal resistance and sensation to airflow were investigated in 40 subjects. L-menthol caused a highly significant enhancement of nasal sensation of airflow but despite their great similarity in structure and a similar peppermint smell the isomers D-isomenthol and D-neomenthol had no effect on nasal sensation of airflow. These findings show that L-menthol has a specific pharmacological action on nasal sensory nerve endings which is not related to its peppermint smell. It seems that menthol acts upon trigeminal sensory nerve endings within the nose (Eccles *et al.*, 1988).

Lindemann *et al.*, showed that menthol inhalation does not have an effect on nasal mucosal temperature and nasal patency with anterior rhinomanometry. They reported that menthol leads to a direct stimulation of cold receptors modulating the cool sensation, entailing the subjective feeling of a clear and wide nose in healthy subjects (Lindeman 2008 cited by Demirbas *et al.*, 2011).

On other study by Pereira *et al.*, (2013) the effects of menthol (L-menthol) inhalation were evaluated on upper airway resistance (UAR) in healthy human participants, without nasal congestion, while awake during quiet breathing. Menthol inhalation was not associated with any change in ventilation and UAR, suggesting that cold receptor stimulation does not modulate UAR in awake human subjects.

#### Exercise performance

An experiment with 12 healthy male students, consuming 500 ml bottle of mineral water containing 0.05 ml of peppermint oil for ten days effected changes in physiological parameters (spirometry and gas analysis) and functional indicators of exercise performance. There was improvement in the spirometric measurements [forced vital capacity (FCV), peak expiratory flow (PEF), peak inspiratory flow (PIF)] and ventilation during treadmill exercise, as well as an increase in the maximum chest circumferences. Also significant changes in the gas analysis after 10 days of the experiment were observed (Meamarbashi and Rajabi, 2013).

### **Sleep/alertness action**

Twenty-one (21) healthy sleepers (11 women and 10 men) completed three consecutive laboratory sessions, to study the peppermint oil odour effect on polysomnographic sleep, alertness and mood, when presented before bedtime. Polysomnographic recordings, mood questionnaires like the Stanford Sleepiness Scale and the Profile of Mood States Questionnaire, and also Liker scales for stimulus perception, were performed. Peppermint reduced fatigue and improved mood. The subjects who rated peppermint as very intense had more total sleep than those rating it as moderately intense, showing

more slow-wave sleep than in the control session. It increased NREM sleep in women, but this was not true in men, where alertness was more evident than in women. So, there are individual factors influencing the results on the physiological sleep, self-rated mood and alertness (Adam *et al.*, 2006). Another study examined the influence of essential oils and components (peppermint, jasmine, ylang-ylang, 1, 8-cineole and menthol) on core attention function. Six experimental groups were compared with corresponding control groups receiving water (n=20–4 groups; n=30–2 groups). The results did not reach statistical significance. The authors indicate complex correlations between subjective evaluations of substances and objective performance, concluding that the effects are mainly psychological (Ilmberger *et al.*, 2001).

#### External use effects

The topical application of peppermint oil produces a prolonged cold sensation at the site of application, by the stimulation of the cold-sensitive receptors, via a reversible, steric change, thus blocking voltage dependent type L (long lasting) calcium channels. This is going to depolarize the cold –sensitive receptors, transmitting more electrical charge possibly responsible for the analgesic effect. Cold stimuli may exert a segmental inhibition of pain stimuli along the conduction pathways, and if the pain originates in the scalp or in the face it can be inhibited in the brain stem (Fachinfo Euminz, 1997).

The application of peppermint oil plus ethanol (10% peppermint oil in ethanol 90%) to the forehead showed a significant reduction of the M temporalis wave and a pronounced increase in blood flow through the capillaries of the skin, as compared to the ethanol solution in the study on the EMG activity by Gobel *et al.*, (1995) in 32 healthy subjects. Also the significant reduction of 7% ( $p < 0.5$ ) in the duration of late exteroceptive suppression (ES2) was achieved. Pain sensitivity to experimental ischaemia of the pericranial musculature was significantly reduced by 27% ( $p < 0.1$ ) by the combination of peppermint oil plus ethanol (10% peppermint oil in ethanol 90%).

Peppermint oil may act locally at the origin of the pain by modifying pain receptor sensitivity, giving an analgesic activity.

#### Assessor's comment:

##### Digestive action

*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.*

*An appropriate delayed release formulation may be important to expose the colon to a constant concentration of peppermint oil to get a prolonged effect and avoid the inappropriate release of the oil in the upper GI tract, causing adverse effects like heartburn.*

*The choleric, cholagogic and antifoaming effects of peppermint oil may potentially play an additional role in its medicinal use.*

##### Respiratory action

*Various studies did not demonstrate a change on inspiratory or expiratory nasal airway resistance, but there was an enhancing of the sensation of nasal airway produced by the inhalation of menthol.*

##### External use effects

*The topical application of peppermint oil stimulates the cold sensitive receptors, exerting a local and a probably segmental inhibition of pain, producing an analgesic effect. The experimental laboratory findings point to the possible mechanism of action in tension headache.*

#### 4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

##### Peppermint leaves

Hurrell *et al.*, (1999), observed that different polyphenol containing beverages reduce the bioavailability of non-heme iron. Herb teas from *Matricaria recutita* L., *Verbena officinalis* L., *Tilia cordata* Mill., *Mentha pulegium* L. and *Mentha piperita* L. or complex polyphenol polymerization products (black tea and cocoa) were potent dose dependent inhibitors of Fe absorption and reduced absorption of a bread meal, depending on the content of total polyphenols. Eight separate Fe absorption studies were performed in a total of seventy seven healthy volunteer subjects, measuring the incorporation of radiolabeled Fe (<sup>55</sup>Fe or <sup>59</sup>Fe) into erythrocytes. Compared with a water control meal, inhibition by black tea was 79-94%, peppermint tea 84%, pennyroyal 73%, cocoa 71%, vervain 59%, lime flower 52% and chamomile 47%. At higher polyphenol concentrations (about 200mg per serving), black tea and peppermint tea were equally inhibitory, higher than the other beverages.

##### Peppermint oil

###### **Oral administration**

Peppermint oil is relatively rapidly absorbed after oral administration and eliminated mainly via the bile (Grigoleit and Grigoleit, 2005a).

##### Menthol

To determine the disposition kinetics and to examine subjective and cardiovascular effects of menthol, a crossover placebo-controlled study that compared pure menthol versus placebo, along with an uncontrolled exposure to menthol in food or beverage was conducted. Twelve subjects were studied; each received a 100 mg l-menthol capsule, a placebo capsule, and 10 mg menthol in mint candy or mint tea on three different occasions. Plasma and urine levels of menthol and conjugated menthol (glucuronide), cardiovascular measurements, and subjective effects were measured at frequent intervals. Menthol was rapidly metabolised, and only menthol glucuronide could be measured in plasma or urine. The plasma half-life of menthol glucuronide averaged 56.2 minutes (95% confidence interval [CI], 51.0 to 61.5) and 42.6 minutes (95% CI, 32.5 to 52.7) in menthol capsule and mint candy/mint tea conditions, respectively ( $p < 0.05$ ). The plasma area under the plasma concentration-time curve ratios for menthol capsule to mint candy/mint tea treatment averaged 9.2 (95% CI, 8.2 to 10.1) (Hadley and Gaarder, 2005).

In a randomised placebo-controlled study performed, 24 healthy male Japanese volunteers were randomly assigned an L-menthol preparation (NPO-11) directly sprayed onto gastric mucosa which was assessed for tolerability and pharmacokinetics during gastrointestinal endoscopy. It was rapidly absorbed, with peak concentrations within 1 hour after administration. Single doses of NPO-11 up to 320 mg were well tolerated. 70% of the metabolites were excreted in the urine, the principal as menthol glucuronide and the others as mono or hydroxylated menthol derivatives. The treatment tended to decrease the occurrence of gastric peristalsis in relation with the period before (Hiki *et al.*, 2011).

In one randomised, double blind, two-way crossover study with eleven (11) subjects, comparing the kinetics and effects of a single oral dose of felodipine ER tablet (Plendil 10 mg), with menthol (test) or placebo (reference), the effect of menthol on the pharmacokinetics and pharmacodynamics of felodipine was studied in healthy subjects. The results concluded that the pharmacokinetics parameters of felodipine and dehydrofelodipine were not markedly different during the measurements (Gelal, 2004).

After ingestion of enteric coated peppermint oil a patient suffering from achlorhydria described by Rhodes (1976), (cited by Grigoleit and Grigoleit, 2005a) complained of heartburn and eructation; investigations demonstrated that the capsule disintegrated in the stomach due to the high pH.

### **Dermal**

Using sensitive and selective gas-chromatographic methods the systemic absorption was examined after skin application of camphor, menthol and methyl salicylate. Concentration time profiles were erratic and variable and the half-lives relatively shorts (Martin *et al.*, 2004).

### **Excretion**

In a cross over study, excretion of menthol (as glucuronide derivative) from orally ingested peppermint oil contained in enteric coated capsules was compared with oil contained in two soft gelatine capsules without enteric coating, each containing a total of 0.4 ml of peppermint oil. Urine was collected in 2-hourly intervals up to 14 hours plus one 10 hours sample up to 24 hours. Total 24 hours urinary excretion of menthol was similar in the two formulations in 6 healthy volunteers, but peak menthol excretion levels were lower and excretion delayed with enteric coated capsules. Menthol excretion was reduced in 6 ileostomy patients who took enteric coated capsules and moderate amounts of unmetabolised menthol were recovered from the ileostomy effluent. This is consistent with the delayed-release form of peppermint oil. These results demonstrate that in a delayed-release form peppermint oil is released to a significant extent in the lower digestive tract and in the colon, where the antispasmodic effects are expected. The gelatine capsule release pattern does not meet the therapeutic requirements. (Somerville, 1984).

Pharmacokinetic studies reveal that fractionated urinary recovery of menthol is dependent on the kind of formulation used for the application of peppermint oil. Optimal pH triggered enteric coated formulations start releasing peppermint oil in the small intestine extending release over 10-12 hours thus providing peppermint oil to the target organ in irritable bowel syndrome, i.e. the colon. The hypothesis is supported by anecdotal observations in patients with achlorhydria or ileostoma, respectively (Grigoleit and Grigoleit, 2005a)

It is unknown if peppermint oil constituents are excreted in human breast milk.

## **4.2. Clinical efficacy**

### **4.2.1. Dose response studies**

There are no dose-finding studies available.

The recommended dosage of 0.2 ml–0.4ml of peppermint oil for adolescents, adults, elderly (2–3 times daily) and 0.2 ml of peppermint oil for children over 8 years (3 times daily) are supported by clinical investigations as cited below, for the treatment of irritable bowel syndrome (IBS).

### **4.2.2. Clinical studies (case studies and clinical trials)**

#### **Peppermint oil**

- Oral administration

#### **A - Irritable bowel syndrome (IBS)**

##### Controlled studies

Multiple controlled clinical studies were performed using several diagnostic criteria, some predating the Rome process and including small groups, not adequate to demonstrate statistical significance versus

placebo, as it is expressed in table 4. The studies cited in text below have the most significant number of patients and are more eligible for conclusions.

Liu *et al.*, (1997) conducted a prospective, randomised, double-blind, placebo-controlled clinical study in one hundred ten (110) outpatients (66 men/44 women; 18-70 years of age) with symptoms of IBS. Fifty-two patients on peppermint oil (one capsule containing 187 mg of peppermint oil) and 49 on placebo completed the study three to four times daily, 15-30 minutes before meals, for one month. Forty-one patients on peppermint oil (79%) experienced an alleviation of the severity of abdominal pain (29 were pain-free); 43 (83%) had less abdominal distension, 43 (83%) had reduced stool frequency, 38 (73%) had fewer borborygmi, and 41 (79%) less flatulence. Corresponding figures for the placebo group were: 21 patients (43%) with reduced pain (4 were pain-free), 14 (29%) with reduced distension, 16 (32%) with reduced stool frequency, 15 (31%) with fewer borborygmi, and 11 (22%) with less flatulence. Symptom improvements after peppermint oil were significantly better than after placebo ( $p < 0.05$ ; Mann-Whitney U-test). One patient on peppermint oil experienced heartburn (because of chewing the capsules) and one developed a mild transient skin rash. There were no significant changes in liver function test results. 3 patients on peppermint oil and 6 on placebo dropped-out. The random sequence generation on this study was not described. The expected outcomes were reported.

Capanni *et al.*, (2005) included one hundred seventy eight (178) consecutive patients with IBS in a randomised, double blind controlled trial, using the Rome II diagnostic criteria, to evaluate the efficacy of peppermint oil formulation. The randomisation was by computer generated lists. The outcome was measured by a validated questionnaire every 3 weeks. The test group (91 patients (22 M, 69 F), mean age 41 years old; range 18-72 years old) received enteric coated capsules of 225 mg 2 capsules, 3 times a day, before meals for 3 months and the placebo group (87 patients (23 M, 64 F; mean age 44 years old; range 21-74 years old) received 225 mg of maltodextrin with mint flavour. 3 dropouts due to other diseases and 2 due to pyrosis. Peppermint oil, improved IBS overall symptoms [73/91 (80%) vs 31/87 (36%) patients ( $p < 0.02$ )] and gastroenteric symptoms [88/91 (97%) vs 29/87 (33%) patients ( $p < 0.01$ ), psychological discomfort, in 34/91 (37%) vs 16/87 (18%) patients ( $p < 0.05$ ), and socio-familial impact, in 69/91 (76%) vs 37/87 (43%) patients. ( $p < 0.04$ ). The authors found a statistically significant benefit for peppermint oil relative to placebo for global improvement in IBS symptoms. All expected outcomes were described and the methods used for randomization were reported.

Cappello *et al.*, (2007) performed a study with 57 patients with IBS, without small intestinal bacterial overgrowth, lactose intolerance and celiac disease (randomisation computer generated) according to Rome II criteria using two enteric-coated capsules (225 mg each capsule) twice per day or placebo 1 hour before meals for 4 weeks in a double blind study. The patients of age under 18 and over 80 years, previous surgery on the abdomen except appendectomy, inflammatory bowel disease, colonic diverticular disease, intestinal neoplasia, systemic disease, thyroid disease and chronic assumption of medication that could interfere with intestinal motility, secretion and sensation were excluded. The symptoms were assessed before therapy (T(0)), after the first 4 weeks of therapy (T(4)) and 4 weeks after the end of therapy (T(8)). The symptoms evaluated were: abdominal bloating, abdominal pain or discomfort, diarrhoea, constipation, feeling of incomplete evacuation, pain at defecation, passage of gas or mucus and urgency at defecation. A score from 0 to 4 was used for each symptom intensity and frequency. The total irritable bowel syndrome symptoms score was also calculated as the mean value of the sum of the average of the intensity and frequency scores of each symptom. The data from fifty patients, were available for comparison. 7 dropouts, 1 due to pyrosis occurred. Twenty-four (24) patients were in the peppermint oil group (18 women, 6 men; mean age 42, range 22-58) and 26 patients (20 women and 6 men; mean age 40, range 20-60) in the placebo group. At T(4), 75% of the patients in the peppermint oil group showed a >50% reduction of basal (T(0)) total irritable bowel syndrome symptoms score compared with 38% in the placebo group ( $p < 0.009$ ). A statistically

significant reduction of the total irritable bowel syndrome symptoms score was found with peppermint oil at T(4) and at T(8) compared with T(0) (T(0): 2.19±0.13, T(4): 1.07±0.10\*, T(8): 1.60±0.10\*, \*p<0.01 compared with T(0), mean±S.E.M.), while no change was found with the placebo. (\*  $\chi^2$ -test). The authors concluded that there is a statistically significant benefit for peppermint oil relative to placebo for global improvement in IBS symptoms. The methods of randomization were described and all expected outcomes were reported.

Merat *et al.*, (2010) conducted a randomised double-blind placebo-controlled study on ninety (90) outpatients with IBS (Rome II criteria). The symptoms and quality of life was evaluated after the first, fourth, and eighth weeks.

Patients were randomised into study or placebo groups using a computer-generated randomization table. Patients in the study group took one capsule containing 187 mg or 0.2 ml of peppermint oil, three times daily 30 minutes before each meal for 8 weeks. The placebo group received an identical looking placebo. Ninety patients were included, 45 in each group. Sixty patients completed the study.

The most common presenting complaint was abdominal pain in 53 (88.3%) followed by distension in 52 (86.7%) and flatulence in 50 (83.3%).

The number of subjects free from abdominal pain or discomfort changed from 0 at week 0 to 14 at week 8 in the peppermint oil group and from 0 to 6 in controls (p<0.001). The severity of abdominal pain was also reduced significantly in the peppermint oil group as compared to controls. Quality of life in the two groups did not differ significantly at the beginning of the trial but after eight weeks, the patients on peppermint oil showed statistically significant improvement in the SF-36 domains of bodily pain, general health, social functioning, and role limitations due to emotional problems as compared to controls. The summary scores, however, were not significantly different. The authors point some limitations to the study. The major is the number of participants who were lost to follow-up (30%) and another limitation was related with the fact that the researcher and patient questionnaires were not validated.

Alam *et al.*, (2013, abstract), observed the efficacy of peppermint oil for relieving the symptoms and changes of QoL in diarrhoea predominant IBS, through a prospective double blind randomised placebo-controlled study from July 2008 to September 2009. Patients who fulfilled ROME II were initially selected with exclusion of those presenting signs or any organic disease. Seventy four (74) patients were enrolled in the study and randomly allocated to receive either peppermint oil (unspecified) or placebo three times daily for six weeks. The symptoms were assessed on a three week interval during treatment and two weeks after the end of treatment. Sixty five (65) patients completed the trial. It was observed that, at six weeks of therapy abdominal pain is markedly improved (mean±SD) 4.94±1.30 in peppermint oil group compared with 6.15±1.24 in placebo group and the difference was highly statistically significant (p>0.001). But two weeks after end of trials pain score again increased (6.09±1.93). Other symptoms and quality of life did not improve significantly. The authors conclude that the study demonstrate that peppermint oil is effective in transiently relieving only abdominal pain in diarrhoea predominant IBS. As there is no adequate information about the dose, no conclusion can be reached for this monograph.

Cash *et al.*, (2016) evaluated the efficacy and tolerability of a novel formulation of peppermint oil designed for sustained release in the small intestine in patients with IBS-M and IBS-D. They performed a 4-week, randomised, double-blind, placebo-controlled clinical trial of peppermint oil (180mg per capsule) or identical placebo 3 times daily in patients fulfilling Rome III criteria for IBSM (mixed type) or IBS-D (diarrhoea). The primary endpoint was the change from baseline in the Total IBS Symptom Score (TISS) after 4 weeks of treatment.

Seventy two (72) patients, peppermint oil (n=35) or placebo (n=37) were selected and had to meet Rome III criteria for IBS-M or IBS-D with an average daily IBS related abdominal pain rating of  $\geq 4$  on a 0–10 scale and a Total IBS Symptom Score (TISS) of  $\geq 2$  on a 0–4 scale.

Subjects had to be between 18 and 60 years of age, and had to confirm that they were not planning to change their usual diet and lifestyle during the study.

Exclusion criteria included a diagnosis of IBS-C (constipation predominant) or IBSU (unclassified) as defined by the Rome III criteria or a history of inflammatory or immune-mediated gastrointestinal disorders, including celiac disease. Also excluded were subjects with a history of organic gastrointestinal disorders including intestinal obstruction, stricture, toxic megacolon, perforation, faecal impaction, adhesions, ischemic colitis or impaired intestinal circulation, cholecystitis, or major gastrointestinal surgery, including cholecystectomy. Additional exclusion criteria included a history of cardiovascular events, uncontrolled hypertension, unstable renal, hepatic, metabolic, or hematologic conditions, human immunodeficiency virus (HIV) infection, or a history of alcohol abuse or binge drinking. Subjects who refused to discontinue one or more prohibited medications for at least 7 days before beginning the baseline diary and throughout the remainder of the study were excluded. The protocol did not allow concomitant or rescue medications during the trial. The randomization scheme was computer generated, using the PLAN procedure with SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) and concealed allocation of assignment was utilised via a central randomisation centre.

The primary endpoint was change in the TISS from baseline 28 days after the start of therapy.

The trial was conducted at four geographically diverse study sites in the USA, in accordance with good clinical practice (GCP). Secondary outcomes included the TISS score at 24 hours after start of therapy, reduction from baseline in the frequency and intensity of the 8 individual symptoms included in the TISS (abdominal pain or discomfort, bloating or distension, pain at evacuation, urgency of BM, constipation, diarrhoea, passage of mucus or gas, and sense of incomplete evacuation), reduction in severe or unbearable symptom intensity and frequency, and treatment emergent adverse events (TEAEs). The delivery system for peppermint oil used in this study consists of a triple-coated microsphere formulation with sustained release of peppermint oil in the small intestine, to improve the tolerability.

At 4 weeks, peppermint oil was associated with a 40% reduction in the TISS from baseline (mean change -1.16, SD  $\pm$  0.807), superior to the 24.3% decrease (mean change -0.70, SD  $\pm$  0.737) observed with placebo ( $p=0.0246$ ). The decrease in the TISS of 19.6% (mean change -0.55, SD  $\pm$  0.613) in the peppermint oil group at 24 hours was also significantly larger than placebo (-10.3%, mean change -0.27, SD  $\pm$  0.342) ( $p=0.0092$ ). At trial completion, patients in the peppermint oil group experienced greater improvement in multiple individual gastrointestinal symptoms as well as in severe or unbearable symptoms, compared to placebo. Peppermint oil was well tolerated with few adverse events. Withdrawals were rare, with more than 94% of randomised subjects completing the trial. The 4 individual IBS symptoms that were more responsive to peppermint oil (abdominal pain or discomfort, abdominal bloating or distension, pain at evacuation, and urgency of BM) were clustered around viscerosensory perception, compared to motility related symptoms such as constipation, diarrhoea, or passage of gas or mucus.

This TISS scale has never been used to measure 24 hours efficacy and has not been previously validated.

The authors explained that this scale was chosen based on its previous use in a trial of peppermint oil in patients (Cappello, 2007) with IBS as well as the fact that there is no specific regulatory guidance

regarding endpoints for a randomised controlled trial including patients with more than one IBS subtype.

Reviews/Meta-analysis

In the review of Grigoleit and Grigoleit (2005b), 16 clinical trials in the literature search using 180-200 mg enteric-coated peppermint oil in IBS or recurrent abdominal pain in children (1 study) with 651 patients enrolled were identified. There was a prevalence of women.

Some of the studies were performed before the Rome II criteria, but according to the authors of this review, the inclusion criteria appear to be adequate. The treatment duration was from 2 to 11 weeks and in one open study was 6 months.

Nine out of 16 studies were randomised double blind cross over trials with (n=5) or without (n=4) run in and/or wash out periods, five had a randomised double-blind parallel group design and two were open label studies. Placebo served in 12 and anticholinergics in three studies as comparator.

In 11 of the studies there was a daily patient rating of selected symptoms such as abdominal pain, distension, flatulence, stool frequency, urgency, bloating, stool quality, frequency of attacks, severity of attacks, or the overall assessment. In two studies, the rating by patients was at intervals of two weeks. In two studies the interval was not given. In one open trial the physician rating was at the end of the week. To make this data comparable, the variable "overall success" was used (% of responders) (Grigoleit and Grigoleit, 2005b). Eight out of 12 placebo-controlled studies show statistically significant effects in favour of PO. Average response rates in terms of "overall success" are 58% (range 39-79%) for peppermint oil and 29% (range 10-52%) for placebo. The three studies versus smooth muscle relaxants did not show differences between treatments hinting for equivalence of treatments. A total of 71 patients dropped out most of them for reasons unrelated with the study. Other reasons were (n=6 worsening of symptoms, peppermint oil or placebo; n=2 nausea and vomiting by peppermint oil; n=3 perianal burning by peppermint oil; n=2 peppermint taste and pyrosis).

Adverse events reported were generally mild and transient, but very specific. Peppermint oil caused the typical GI effects like heartburn and anal/perianal burning or discomfort sensations, whereas the anticholinergics caused dry mouth and blurred vision. Anticholinergics and 5HT3/4-antagonists do not offer superior improvement rates; placebo responses cover the range as in peppermint oil trials, conclude the authors (Grigoleit and Grigoleit 2005b).

The authors concluded that the clinical data in IBS reveals that peppermint oil in an enteric coated form is safe and efficacious in a sufficient number of studies, as a symptomatic remedy in a short term treatment (Grigoleit and Grigoleit 2005b).

Characteristics of the studies reviewed by Grigoleit and Grigoleit 2005b:

Study no./Ref.	Design	Study drug(s)	Comparator(s)	Treatment weeks	Patients enrolled
1 Rees (1979)	db,co,wash out period	One to two capsules t.i.d.b	Placebo 1-2 capsules t.i.d.	3/treatment	18
2 Evans <i>et al.</i> , (1982)	db,co,randomised,wash out?	One to two capsules t.i.d.d	Placebo	2/treatment	20
3 Dew <i>et al.</i> , (1984)	db,co,wash out period	One to two capsules t.i.d.b	Placebo 1-2 capsules t.i.d.	2/treatment	29
4 Nash <i>et al.</i> , (1986)	db,co,no wash out, randomised	Two capsules t.i.d.a	Placebo 2 capsules t.i.d.	2/treatment	41

5 Munst <i>et al.</i> , (1987)	db,co,wash out, double dummy, randomised	One capsule t.i.d.a	Matching mebeverine 135 mg 1 tablet t.i.d.	3/treatment	16
6 Weiss and Kolbl (1988)	db,pg,randomised	One capsule t.i.d.a	Placebo,1 capsule t.i.d.	3	60
7 Lawson <i>et al.</i> , (1988)	db,co,no wash out	One capsule t.i.d.b	Placebo,1 capsule t.i.d.	4	25
8 Lech <i>et al.</i> , (1988)	db,pg,randomised	One capsule t.i.d.d	Placebo,1 capsule t.i.d.	4	47
9 Wildgrube (1988)	Matched pairs, db pg, randomised	Capsules	Matching placebo capsules	2	40
10 Carling <i>et al.</i> (1989)	db,3 way co, wash out	One to two capsules t.i.d.a and matching placebo	Hyoscyamine 0.2 mg and matching placebo,1–2 tablets t.i.d.	2/treatment	40
11 Schneider and Otten (1990)	db,co,wash out, randomised	One capsule t.i.d.a	Placebo 1 capsule t.i.d.	6/treatment	60
12 Fernandez (1990)	Open	One capsule t.i.d.b		4	50
13 Ambross (1990)	db,co,randomised	Not specified	Alverine citrate	11/treatment	18
14 Shaw <i>et al.</i> , (1991)	Open, pg, randomised	One capsule t.i.d.a	Stress management program, median 6 psychotherapy sessions of each 40 min/patient	24	35
15 Liu <i>et al.</i> , (1997)	db,pg,randomised	One capsule t.i.d. or q.i.d.a	Placebo 1 capsule t.i.d. or q.i.d.	4	110
16 Kline and Barbero (1997)	db,pg,randomised	One to two capsules t.i.d.a	Placebo 1–2 capsules t.i.d.	2	42

db = double blind, co =cross over, pg = parallelgroups.

A Colpermin

B Enteric-coated peppermint oil capsule.

C Mentacur

D Unspecified peppermint oil formulation.

(Grigoleit and Grigoleit, 2005b).

#### Summary of “overall success” data for peppermint oil in IBS in the studies by Grigoleit and Grigoleit 2005b:

Study no.	Overall success (%) peppermint oil	Comparator	Overall success comparator (%)	Comments
1	50	Placebo	13	p<0:01
2	No numerical data	Placebo	No numerical data	Overall success in favor of peppermint oil (p<0:025)
3	41	Placebo	10	p<0:001
4	39	Placebo	52	n.s.
5	No numerical data	Mebeverine	No numerical data	Except for “fullness” no difference between treatments
6	74	Placebo	17	p<0:001

7		Placebo		Increase in stool frequency (p<0:05),formulation problem
8	68	Placebo	26	p<0:02
9	No numerical data	Placebo	No numerical data	All symptoms improved in favour of peppermint oil (p<0:05)
10	57	Placebo	37	Symptom score before/after peppermint oil p<0:01; placebo and hyoscyamine p>0:05
		Hyoscyamine	38	
11 /12	57/ 93	Placebo	39	Difference n.s. p<0:08 Open study
13	No numerical data	Alverine	No numerical data	No difference between treatments
14	18	Stress management program	72	Strongly in favour of psychotherapy after 6 months
15	79	Placebo	32	Overall success calculated from mean improvement values of single symptoms p<0.05
16	70	Placebo	43	Children/recurrent abdominal pain, p<0:002

Pittler and Ernst (1998) performed a statistical meta-analysis of eight (8) studies showing that the treatment of irritable bowel syndrome with peppermint oil was more effective than treatment with a placebo. It should be noted that some of the older studies had serious methodological problems including vague inclusion criteria for patients and treatment periods that were too short. Five double blind, placebo-controlled RCTs were entered in a metaanalysis and scored at least 3 of 5 points on the scoring system to measure the likelihood of bias (Carling *et al.*, 1989, Dew *et al.*, 1984, Lech *et al.*, 1988, Nash *et al.*, 1986, Rees *et al.*,1979). Three (3) studies had to be excluded from the meta-analyses. Two studies (Lawson *et al.*, 1988, Schneider *et al.*, 1990) presented data in insufficient detail and one study (Shaw *et al.*, 1991) was not double-blind and placebo controlled. In five trials the treatment period ranged from two to four (2-4) weeks and the doses were 0.2 to 0.4 ml three times daily. In the descriptive review, one small controlled trial suggested that stress treatment had better results than peppermint oil on a period of six months. The other two trials, placebo controlled, had or no significant improvement on pain relief or no difference from placebo.

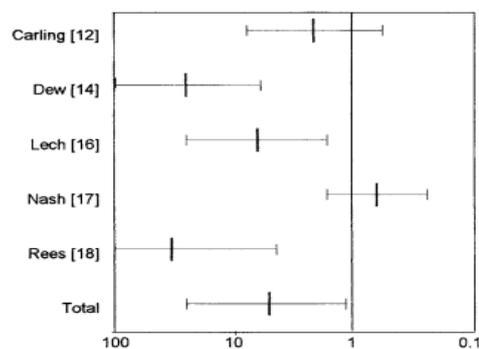
Peppermint for IBS (Pittler and Ernst 1998):

Randomized Clinical Trials of Peppermint Oil for IBS

First Author [Reference]	Quality Score (maximum 5)	Design	Patients Entered	Drop-outs	Medication [dose]/control	Treatment Period (wk)	Compliance Monitored	Outcome: Global Improvement (verum vs control) Main Result
Meta-analysis Carling <i>et al.</i> [12]	3	3-armed, double-blind cross-over	40	2	Colpermin® [3 × 0,2-0,4 ml]/ placebo	2	Y	17/30 vs 5/13
Dew <i>et al.</i> [14]	3	double-blind cross-over	29	n.r.	enteric coated Elanco LOK® caps [3 × 0,2-0,4 ml]/ placebo	2	N	24/29 vs 5/29
Lech <i>et al.</i> [16]	3	double-blind 2 parallel groups	47	5	enteric-coated capsules [3 × 0,2 ml]/ placebo	4	N	13/19 vs 6/23
Nash <i>et al.</i> [17]	4	double-blind cross-over	41	8	Colpermin® [3 × 0,4 ml]/ placebo	2	N	13/33 vs 17/33
Rees <i>et al.</i> [18]	3	double-blind cross-over	18	2	enteric coated Elanco LOK® caps [3 × 0,2-0,4 ml]/ placebo	3	N	13/16 vs 2/16
Review Lawson <i>et al.</i> [15]	4	double-blind cross-over	25	none	enteric-coated capsules [3 × 0,2-0,4 ml]/ placebo	4	Y	no significant difference between verum and placebo in symptom score and global assessment of symptoms
Schneider <i>et al.</i> [19]	3	double-blind cross-over	60	13	Colpermin® [dose n.r.]/ placebo	6	N	significant improvement in pain relief ( $p = 0.03$ ) and general assessment of pain ( $p = 0.002$ ) in verum compared to placebo
Shaw <i>et al.</i> [6]	2	open, 2 parallel groups	35	none	Colpermin® [3 × daily]/ stress management programme	6 months	Y	3/17 on peppermint oil and 13/18 in the stress management group reported overall benefit

n.r., not reported; Y, yes; N, no.

The next table shows the metaanalysis of the five (5) trials using the global improvement of symptoms as an endpoint. Two (2) trials (Carling *et al.*, 1989, Nash *et al.*, 1986) could not demonstrate a significant difference between peppermint oil and placebo. Three studies (Dew *et al.*, 1984, Lech *et al.*, 1988 Rees *et al.*, 1979) significantly favour treatment with peppermint oil over placebo. Overall, this metaanalysis suggests a significant ( $p < 0.001$ ) positive effect of peppermint oil compared with placebo in the symptomatic treatment of IBS.



Three of eight trials (Dew *et al.*, 1984, Nash *et al.*, 1986, Schneider and Otten 1990) failed to define any inclusion criteria for patients with IBS. Thus, a definitive classification of 44% of the patients studied is impossible. The authors concluded that the role of peppermint oil in the symptomatic treatment of IBS is far from established. Well designed and carefully executed studies are needed to clarify the role of peppermint oil in IBS. (Pittler and Ernst 1998).

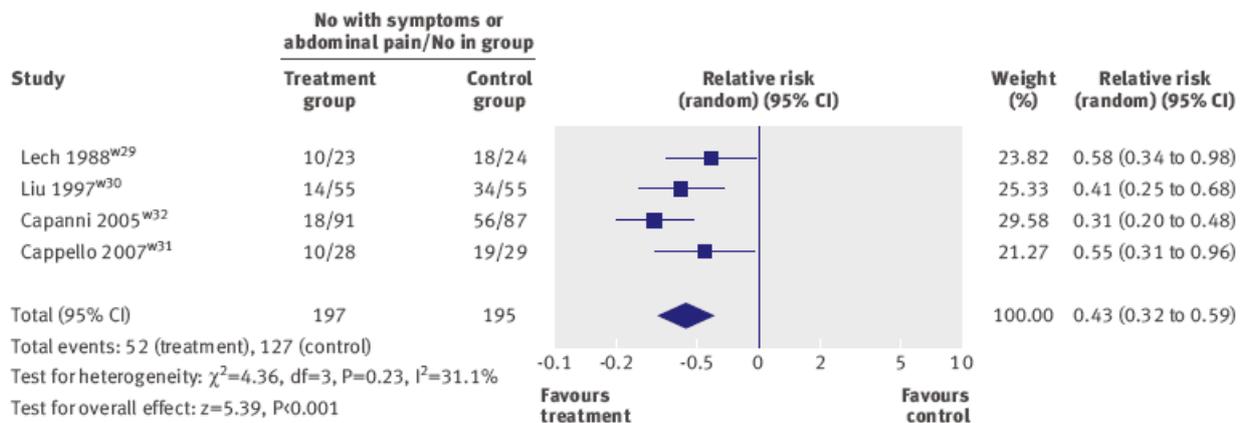
A systematic review and meta-analysis of randomised controlled trials using databases such as Medline, Embase, Cochrane controlled trials register up to April 2008 to determine the effect of fibers, antispasmodics and peppermint oil in the treatment of IBS was performed by Ford (2008). The comparison used was the placebo or no treatment and the minimum duration of therapy considered

was one week. The studies had to report either a global assessment of cure of or improvement in symptoms, or cure of or improvement in abdominal pain (primary outcomes).

In this report, just the results involving peppermint oil are mentioned.

Four studies compared peppermint oil with placebo in 392 patients - Lech *et al.*, 1988, Liu *et al.*, 1997, Capanni 2005 and Cappello 2007. The proportion of women in each trial ranged from 40% to 76%. Only one study reported on disease subtype according to stool pattern and recruited 25% of patients with predominant constipation and 75% with predominant diarrhoea.

Fifty two (52) out of 197 (26%) patients randomised to peppermint oil had persistent symptoms compared with 127 of 195 (65%) receiving placebo (relative risk 0.43, 0.32 to 0.59), with statistically significant heterogeneity detected between studies ( $I^2=31.1\%$ ,  $p=0.23$ ). The number needed to treat with peppermint oil to prevent one patient having persistent symptoms was 2.5 (2.0 to 3.0). When only the three studies that scored 4 or more on the Jadad scale were considered in the analysis, the relative risk of persistent symptoms was of a similar magnitude (0.40, 0.29 to 0.55), with no statistically significant heterogeneity detected between studies ( $I^2=22.0\%$ ,  $p=0.28$ ).



Peppermint oil was superior to placebo, besides the statistically significant heterogeneity detected between the results. Three of the four studies scored more than 4 on the Jadad scale, but the treatment effect was similar when only these studies were included in the meta-analysis, and the heterogeneity observed was no longer detected.

According to the authors, this systematic review and meta-analysis shows that ispaghula husk, antispasmodics (particularly hyoscine), and peppermint oil are all effective treatments for IBS. More trials including more patients, defined according to the Rome criteria and using validated outcome measures are warranted (Ford *et al.*, 2008).

In a systematic review from Cochrane (Ruepert *et al.*, 2011) to evaluate the efficacy of bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome, a total of 56 studies (3725 patients) were included. These included 12 studies of bulking agents (621 patients), 29 of antispasmodics (2333 patients) and 15 of antidepressants (922 patients). The risk of bias was low for most items.

Primary outcome measures included:

- Improvement of symptoms of abdominal pain;
- Improvement of patients overall global assessment and
- Improvement of IBS-symptom score.

Subgroup analyses included:

- Soluble and insoluble bulking agents;
- Individual antispasmodics;
- Selective serotonin releasing inhibitors (SSRIs) and tricyclic antidepressants (TCAs).

A sensitivity analysis excluded studies with poor methodological quality.

5 studies of peppermint oil were included.

A statistically significant effect for improvement of global assessment was found for peppermint oil (RR 2.25; 95% CI 1.70 to 2.98; 225 patients) (cited Capanni *et al.*, 2005; Lech *et al.*, 1988). A statistically significant effect for improvement of IBS symptom score was found for peppermint oil (RR 1.94; 95% CI 1.09 to 3.46; 269 patients) (cited Capanni *et al.*, 2005; Cappello *et al.*, 2007; Czalbert *et al.*, 1990).

None of the studies involving peppermint-oil had adequate allocation concealment. When the authors analysed the studies with adequate allocation concealment separately, the results get weaker and only improvement of abdominal pain still has a statistically significant benefit. According to them, spasmolytics are extensively studied for their use in the treatment of IBS, however due to the diversity of types of spasmolytic agents, the number of studies for each compound are limited. Therefore most subgroups could not be pooled, and a type II error could have occurred.

The authors concluded that the subgroup analyses for different types of antispasmodics found statistically significant benefits for cimetopium/ dicyclomine, peppermint oil, pinaverium and trimebutine. (Ruepert *et al.*, 2011).

Another systematic review and meta-analysis (Khanna *et al.*, 2014) assessed the efficacy and safety of enteric-coated peppermint oil capsules compared with placebo for the treatment of active irritable syndrome (IBS). The authors made a literature search on MEDLINE (Ovid), EMBASE (Ovid), PubMed, and the Cochrane Library up to February 2013 and considered randomised placebo-controlled trials with minimum treatment duration of 2 weeks and Crossover studies that provided outcome data before the first cross-over. Patients of any age with active IBS as defined by the Manning, Rome I, or Rome II criteria or clinical symptoms with the exclusion of organic disease were considered for inclusion. An additional 8 studies were identified by searching conference proceedings and the references of review articles.

Outcomes included global improvement of IBS symptoms, improvement in abdominal pain, and adverse events. Outcomes were analysed using an intention-to-treat approach. Study quality was evaluated using the Cochrane risk of bias tool.

Nine (9) studies that evaluated 726 patients were identified. Data were analysed using the Cochrane Collaboration software Review Manager (RevMan 5).

The risk of bias was low for most of the factors assessed.

The preparations used were caps (0.1 or 0.2 ml peppermint oil (5 studies), mint oil (225g peppermint oil) (3 studies) and one unspecified, against placebo.

Six (6) of the eight (8) trials included in the Pittler and Ernst review had treatment periods of  $\leq 1$  month. Two of the studies included in the present meta-analysis had treatment periods of 8 and 12 weeks and found a statistically significant benefit for peppermint oil relative to placebo for improvement in abdominal pain and global IBS symptoms.

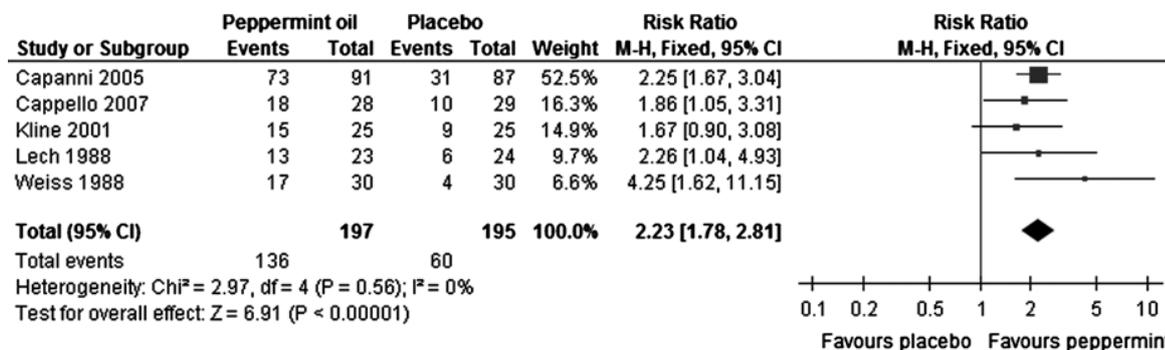
The authors conclude that peppermint oil is a safe and effective short-term treatment for IBS.

Characteristics of included studies (Khanna *et al.*, 2014):

References	No. Patients	Country No. Centers	Interventions	Duration of Therapy (wk)	Methods
Alam <i>et al</i> <sup>9</sup>	74	1 country 1 center	Peppermint oil (unspecified) or placebo	6	Double-blind
Capanni <i>et al</i> <sup>33</sup>	178	1 country 1 center	Peppermint oil (Mintoil) 2 capsules tid or placebo	12	Double-blind
Cappello <i>et al</i> <sup>34</sup>	57	1 country 1 center	Peppermint oil (Mintoil) 225 mg peppermint oil) 2 capsules bid or placebo	4	Double-blind
Kline <i>et al</i> <sup>37</sup>	50 children	1 country 3 centers	Peppermint oil (Colpermin) (0.2 mL or 0.1 mL/capsule) 2 capsules tid (patients weighing >45 kg) or 1 capsule tid (weight 30-45 kg) or placebo	2	Double-blind
Lech <i>et al</i> <sup>35</sup>	47	1 country 1 center	Peppermint oil (Mintoil) 50 mg capsules 4 capsules tid or placebo	4	Double-blind
Liu <i>et al</i> <sup>36</sup>	110	1 country 1 center	Peppermint oil (Colpermin) 187 mg peppermint oil 1 capsule tid or qid or placebo	4	Double-blind
Merat <i>et al</i> <sup>8</sup>	90	1 country 1 center	Peppermint oil (Colpermin) capsules 0.2 mL/capsule 1 capsule tid or placebo	8	Double-blind
Schneider and Otten <sup>7</sup>	60	1 country 1 center	Peppermint oil (Colpermin) capsules 0.2 mL/capsule (tid) or placebo	6	Double-blind Cross-over
Weiss and Koelb <sup>6</sup>	60	1 country 1 center	Peppermint oil (Colpermin) 1 capsule tid or placebo	3	Double-blind

bid indicates twice daily; qid, 4 times daily; tid, 3 times daily.

Peppermint oil versus placebo: global improvement. CI indicates confidence interval:



Peppermint oil versus placebo: improvement in abdominal pain. CI indicates confidence interval:

Study or Subgroup	Peppermint oil		Placebo		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Kline 2001	16	25	4	25	8.4%	4.00 [1.55, 10.29]	
Lech 1988	12	23	6	24	12.3%	2.09 [0.94, 4.63]	
Liu 1997	41	55	21	55	43.9%	1.95 [1.35, 2.83]	
Merat 2010	14	45	6	45	12.5%	2.33 [0.98, 5.53]	
Schneider 1990	19	30	11	30	23.0%	1.73 [1.00, 2.97]	
<b>Total (95% CI)</b>		<b>178</b>		<b>179</b>	<b>100.0%</b>	<b>2.14 [1.64, 2.79]</b>	
Total events	102		48				
Heterogeneity: Chi <sup>2</sup> = 2.55, df = 4 (P = 0.64); I <sup>2</sup> = 0%							
Test for overall effect: Z = 5.60 (P < 0.00001)							

Summary of Findings Table:

Peppermint Oil vs. Placebo for Treatment of IBS						
Patient or Population: Patients With Active IBS						
Settings: Outpatients						
Intervention: Enteric-coated Peppermint oil Capsules vs. Placebo						
Illustrative Comparative Risks* (95% CI)						
Outcomes	Assumed Risk		Relative Effect (95% CI)	No. Participants (Studies)	Quality of the Evidence (GRADE)	
	Control	Corresponding Risk				
Global improvement in IBS symptoms	308 per 1000†	687 per 1000 (548 to 866)	RR 2.23 (1.78-2.81)	392 (5 studies)	⊕⊕⊕⊖ moderate‡	
Improvement in abdominal pain	268 per 1000†	574 per 1000 (440 to 748)	RR 2.14 (1.64-2.79)	357 (5 studies)	⊕⊕⊕⊖ moderate§	
Adverse events	126 per 1000†	218 per 1000 (160 to 297)	RR 1.73 (1.27-2.36)	474 (7 studies)	⊕⊕⊕⊖ moderate	

GRADE Working Group grades of evidence. *High quality*: further research is very unlikely to change our confidence in the estimate of effect. *Moderate quality*: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. *Low quality*: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. *Very low quality*: we are very uncertain about the estimate.

\*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†Control group risk estimates come from control arm of meta-analysis, based on included trials.

‡Sparse data (224 events).

§Sparse data (150 events).

||Sparse data (83 events).

A review from Wall *et al.*, 2014, summarizes the recent evidence-based treatment of IBS including older, "classic" treatments as well as newer agents and "alternative" therapies in IBS. This review reports the results for peppermint oil of Ford *et al.*, review (2008). The authors conclude that, despite advances in the understanding of the pathophysiology of this disorder, targeted treatments do not exist yet. Based on the literature reviewed in this review, the authors have constructed an algorithm to guide practicing clinicians to treat this disorder, including peppermint oil capsules in the first line, as well dicyclomine, pinavarium and trimebutine for "Abdominal pain with mixed bowel symptoms (IBS-M)", for 4-6 weeks.

The American College of Gastroenterology published a Monograph on the Management of Irritable Bowel Syndrome (IBS) and Idiopathic Constipation (Ford *et al.*, 2014), considering the evidence grade of the treatments available. It included manuscripts that studied adults (aged > 16 years) using any

definition of IBS or CIC. For IBS, this included a clinician defined diagnosis, the Manning criteria the Kruis score or Rome I, II or III criteria. For CIC, this included symptoms diagnosed by any of the Rome criteria as well as a clinician-defined diagnosis. They included only parallel-group randomised controlled trials (RCTs) comparing active intervention with either placebo or no therapy. Crossover trials were eligible for inclusion, provided extractable data were provided at the end of the first treatment period, before crossover. For IBS, the following treatments were considered:

1. Diet and dietary manipulation
2. Fiber
3. Interventions that modify the microbiota: probiotics, prebiotics, antibiotics
4. Antispasmodics
5. Peppermint oil
6. Loperamide
7. Antidepressants
8. Psychological therapies, including hypnotherapy
9. Serotonergic agents
10. Prosecretory agents
11. Polyethylene glycol

#### Summary of results of monograph on interventions for IBS (Ford 2014):

Statement	No. of trials	No. of patients	RR symptoms (95% CI)	NNT (95% CI)	Recommendation	Quality of evidence
Specialized diets may improve symptoms in individual IBS patients.	3	230	NA	NA	Weak	Very low
Fiber provides overall symptom relief in IBS.	14	906	0.86 (0.80–0.94)	10 (6–33)	Weak	Moderate
Psyllium, but not bran, provides overall symptom relief in IBS (data presented for psyllium).	7	499	0.83 (0.73–0.94)	7 (4–25)	Weak	Moderate
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	2	198	NA	NA	Weak	Very low
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.	23	2,575	0.79 (0.70–0.89)	7 (4–12.5)	Weak	Low
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	5	1,805	0.84 (0.78–0.90)	9 (6–12.5)	Weak	Moderate
Certain antispasmodics provide symptomatic short-term relief in IBS.	23	2,154	0.69 (0.59–0.81)	5 (4–9)	Weak	Low
Peppermint oil is superior to placebo in improving IBS symptoms.	5	482	0.51 (0.33–0.79)	3 (2–4)	Weak	Moderate
There is insufficient evidence to recommend loperamide for use in IBS.	2	42	0.44 (0.14–1.42)	NA	Strong	Very low
As a class, antidepressants are effective in symptom relief in IBS.	17	1,084	0.67 (0.58–0.77)	4 (3–6)	Weak	High
A variety of psychological interventions are effective in improving IBS symptoms.	32	2,189	0.68 (0.61–0.76)	4 (3–5)	Weak	Very low
Allosteron is effective in females with IBS-D.	8	4,987	0.79 (0.69–0.90)	8 (5–17)	Weak	Moderate
Mixed 5-HT <sub>4</sub> agonists/5-HT <sub>3</sub> antagonists are not more effective than placebo at improving symptoms of IBS-C.	9	2,905	0.96 (0.83–1.11)	NA	Strong	Low
Linaclootide is superior to placebo for the treatment of IBS-C.	3	2,028	0.80 (0.75–0.85)	6 (5–8)	Strong	High
Lubiprostone is superior to placebo for the treatment of IBS-C.	3	1,366	0.91 (0.87–0.95)	12.5 (8–25)	Strong	Moderate
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	2	166	NA	NA	Weak	Very low

CI, confidence interval; 5-HT<sub>3</sub>, serotonin subtype 3; 5-HT<sub>4</sub>, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; NA, not available; NNT, number needed to treat; RR, relative risk.

5 RCTs for peppermint oil were included (Cappani *et al.*, 2005, Cappello *et al.*, 2007, Lech *et al.*, 1988, Liu *et al.*, 1997, Merat *et al.*, 2010) involving 492 patients, using an enteric-coated preparation of

peppermint oil employed in doses ranging from 187 to 225 mg per single dose, 2-6 single doses per day, divided in two to four times daily.

The authors mention that the most of the trials did not differentiate between the types of IBS patients recruited, with only one study, from Capanni providing data on this, considering only one RCT (Merat) at low risk of bias, with the remainder being unclear. The authors conclude that there was a statistically significant effect in favour of peppermint oil compared with placebo with the NNT of 3 (95% CI 2-4). Adverse events were not higher on peppermint oil groups compared to placebo (RR of experiencing any adverse event=1.26, 95% CI 0.75-2.12).

The conclusion by the authors was:

Peppermint oil is superior to placebo in improving IBS symptoms. The risk of adverse events is no greater with peppermint oil than with placebo.

Recommendation: weak. Quality of evidence: moderate.

In specific formulations, which may not be universally available, peppermint oil is effective in IBS.

## **B -Dyspepsia**

### *Controlled studies*

A placebo controlled double-blind study has been studied in sixty nine (69) women in the treatment of abdominal distension and dyspepsia following routine gynaecological surgery, using Peppermint oil in enteric coated capsules, 187 mg/caps., 2 capsules, 3 times per day, during 5 days. No differences were found in abdominal distension, flatulence or abdominal pain between the two groups. Peppermint oil was not effective, but safe (Barnick and Cardozo, 1990).

In a double blind, randomised, placebo controlled, multicentre, 4-week trial, thirty nine (39) patients with dyspepsia (non ulcerative), and moderate to severe pain were given a combination (of peppermint (90mg) and caraway oil (50mg)). Decrease in pain intensity was significantly greater in the treatment group (15 days - 84.2%, p=0.002; 29 days - 89.9%, p=0.015) than in the placebo group (15 days - 50%; 29 days - 45%) (Barnick and Cardozo, 1990).

## **C – Chemotherapy-induced nausea and vomiting**

### *Controlled study*

A randomised, double-blind clinical trial study was performed to assess the efficacy of *Mentha spicata* (*M. spicata*) and *Mentha × piperita* (*M. × piperita*) in preventing chemotherapy-induced nausea and vomiting. Prior to the study, patients were randomly assigned into four groups to receive *M. spicata* or *M. × piperita*.

The inclusion criteria were patients with any cancer diagnosis (colon adeno-carcinoma, breast cancer, colorectal cancer, oesophageal cancer, liver cancer, lung cancer, Hodgkins lymphoma, non-Hodgkins lymphoma, melanoma, nasopharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, sarcoma, stomach cancer, testicular cancer, and vaginal cancer), who were about to receive chemotherapy on an outpatient basis, and who were chemotherapy naïve. Patients who were experiencing nausea and vomiting from causes other than chemotherapy reasons (i.e. intestinal obstruction, stomach cancer, pre-menstrual syndrome, motion sickness), or were deemed physically incapable of participating by the investigators, were excluded from the study.

The treatment and placebo groups applied essential oils of *M. spicata*, *M. × piperita*, via the oral route or a placebo, while the control group continued with their previous antiemetic regimen. Patients or

guardians recorded the number of emetic events, the intensity of nausea over 20 h of chemotherapy, as well as any possible adverse effects that occurred during this time.

During each cycle, patients received their normal antiemetic regimen (granisetron, dexamethason or metocloprimide) plus spearmint and peppermint capsules (containing two drops of each essential oil every four hours, filled with sugar, and administered 30 minutes before they received their chemotherapy treatment, again four hours after first capsule and finally four hours later at home) for all patients, independent of their age or weight. No significant side effects were found when increasing the dose.

Fifty (50) patients were analysed for each group. Patients treated with *M. spicata* and peppermint oil were found to have a statistically significant reduction of the median emetic events during 24 h of treatment (acute phase) in which patients treated with placebo presented up to 1.8 emetic events versus 0.6 and 0.7 in the *M. spicata* and *M. × piperita*, respectively ( $p < 0.05$ ).

The intensity of nausea was also significantly reduced in the *M. spicata* and *M. × piperita* groups during 24 h of treatment compared with placebo ( $p < 0.05$ ).

There was no statistical difference between spearmint and peppermint in controlling emetic events and intensity of nausea ( $p > 0.05$ ).

The authors concluded that the essential oils of spearmint and peppermint are less expensive, and a safe and effective therapeutic option for the treatment of chemotherapy-induced nausea and emesis in patients. (Tayarani-Najaran *et al.*, 2013).

### **Post-operative Nausea**

A study was performed with eighteen (18) patients in a three condition experimental design, to investigate the efficacy of peppermint oil on the relief of postoperative nausea in gynaecological surgical patients - (control group - no treatment; placebo - peppermint essence; experimental - peppermint oil), isolated from each other's due to the volatile nature of the compound. The experimental group had an increased number of intra-abdominal procedures, received more opioid analgesia postoperatively and required less traditional antiemetics (Tate, 1997).

- **External application**

### **Tension headache**

#### *Controlled studies*

The analgesic effect of peppermint oil (10% in ethanol) was investigated in thirty two (32) healthy subjects in a double blind placebo-controlled, randomised, four-fold crossover study. Neurophysiological, psychological and experimental algometric parameters were investigated. Four different test preparations were applied to large areas of the forehead and temples using a small sponge. Preparations containing peppermint with or without *Eucalyptus* were superior in pain reduction and had a muscle relaxing and mentally relaxing effect. (Göbel *et al.*, 1994, 1995).

Compared to the application of placebo, 10% peppermint oil in ethanol solution significantly reduced the clinical headache intensity already after 15 minutes ( $p < 0.01$ ). This clinically significant reduction in pain intensity was sustained over the one-hour observation period (Göbel *et al.*, 1994, 1995).

The effect of a locally applied peppermint oil preparation on tension-type headache was examined in the design of a randomised, placebo-controlled double-blind crossover study. The preparation was tested against both the reference substance acetaminophen and the corresponding placebo. The liquid test preparation contained 10 g of peppermint oil and ethanol (90%) ad 100 (test preparation LI 170, Lichtwer Pharma, Berlin); the placebo was a 90% ethanol solution to which traces of peppermint oil

were added for blinding purposes. The reference preparation contained 500 mg acetaminophen; the placebo tablet was identical to the verum in size and appearance. The study included the analysis of 164 headache attacks of forty one (41) patients of both sexes ranging between 18 and 65 years of age, suffering from tension-type headache in accordance with the IHS classification, for 14, 12 years on 4. 99 days per month. No other medication with possible effect on the symptoms was allowed. The patients were accepted in the order of appearance in the out-patient clinic and went through examination phases 1, 2, 3 and 4 in a balance sequence according to the randomization schedule (Latin squares). A minimum interval of 24h between two subsequent episodes had to be observed. Cutaneous application consisted of spreading the oil largely across forehead and temples and repeated twice (after 15 and 30 minutes). The patients rated their pain intensities according to a standardised categorical rating scale - 0 (no pain) to 4 (severe). The 10% peppermint oil in ethanol solution significantly reduced the clinical headache intensity already after 15 minutes ( $p < 0.01$ ), compared to placebo. This clinically significant reduction in pain intensity was sustained over the one-hour observation period. Acetaminophen, too, proved to be efficient compared to placebo ( $p < 0.01$ ). There was no statistically significant difference between the efficacy of 1000 mg of acetaminophen and 10% peppermint oil in ethanol solution (Göbel *et al.*, 1996).

The topical application of peppermint oil produces a prolonged cold sensation at the site of application, by the stimulation of the cold-sensitive receptors, generating an analgesic effect.

Safety data were available for one hundred fifty (150) Patients without AE's.

### **Analgesic effect**

#### *Case study*

Report of a post-herpetic neuralgia study, on a 76 years woman, with relief of the pain during 4-6 hours after the local application of peppermint oil (containing 10% menthol). During two months of treatment she continued to feel the same effect (Davies *et al.*, 2002)

### **Table 4A:** Clinical studies

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score e.g. Jadad score	Comments on clinical relevance of results
Review of clinical studies for <b>IBS</b>							
Rees <i>et al.</i> , 1979	Double-blind placebo cross-over study, wash out period of 3 weeks	Peppermint oil 0.2 ml in enteric-coated capsules, 1-2/day	18 patients. 2 dropouts	Patients with IBS	IBS symptoms using scores assessed by the patients  Peppermint oil group overall assessment significantly better - $p < 0.001$  Peppermint oil group better for abdominal pain $p < 0.05$  The differences of the analysis of the symptom grade with the placebo were not statistically significant	Paired T test	Small group, insufficient to assess the clinical relevance.

Dew 1984	Double-blind, multicentre placebo cross-over study 2 weeks	Peppermint oil 0.2 ml in capsules 3-6 /day	29 patients from 7 centres 21-64 years 23 females, 6 males	Patients with IBS	Overall assessment of severity of symptoms and change in symptomatology  Peppermint oil group overall assessment significantly better - $p < 0.001$  Peppermint oil group better for abdominal pain $p < 0.001$  No effect on the number of bowel movements.	Rating scale (0-4) for the severity of symptoms recorded daily by the patients and after each treatment	Better scores with peppermint oil, but no first phase data available.
Lawson 1988	Cross-over Double blind placebo controlled study	Capsules filled with 0.2 ml Peppermint oil 1 cps 3 times per day for 4 weeks	25 patients 21 women and 4 men Age 21-70 years	Patients with IBS who took fibre supplements for 2 weeks without improvement	Improvement of IBS symptoms using scores assessed by the patients	Willcoxon matched pairs signed-ranks test was used to compare symptom scores with active drug and placebo and to compare symptom scores on placebo with those obtained at initial assessment.	No efficacy was proved
Lech <i>et al.</i> , 1988	Double blind, randomised placebo controlled study	Peppermint oil 50 mg, 4 capsules (200mg) tid or placebo 4 weeks	47 patients selected. Mean age 42 years 7% female  42 completed the study.	IBS Flatulence, abdominal pain, intestinal disturbances with alternance)	Improvement of symptoms using scores of 5 points after 4 weeks. $p = 0.02$ , considered significant.  68% overall success for peppermint oil / 26% for placebo	Fisher test	Clinically relevant  .
Carling 1989	Double blind-cross over study 3 groups	Peppermint oil 1-2 capsules 0.2 ml 3 times per day hyoscyamine 0.2 mg placebo 2 weeks	40 patients 14 males 26 females mean age 44 years 10 drops out	Symptoms score	Success treatment score (both from patients and doctors)	ITT	Better scores with peppermint oil, but small groups  Questionable clinical relevance

Fernandez 1990	Observational study	"Mentha piperita " capsules 3 times per day not further specified	50 patients 18-69 years 31 females 29 males 4 drop out		Success treatment score from doctors	Descriptive part and McNemar and Student tests.	Improvement. But not randomised not placebo-controlled, no info on herbal product
Liu <i>et al.</i> , 1997	Double blind study, randomised, parallel group	1 capsule 187 mg (0.2 ml) 3 or 4 times per day 4 weeks	110 patients 40% female; 18-70 years of age  52 patients on peppermint oil and 49 on placebo completed the study  9 drop-outs – 3 on peppermint oil and 6 on placebo.	IBS symptoms	Mean improvement values of symptoms  Symptom improvements after peppermint oil were significantly better than after placebo.  p<0.05	Mann-Whitney U-test	Clinically relevant
Freise,1999	Prospective randomised, reference- and double-blind controlled multicentre	Test formulation: Combination of 90 mg peppermint oil and 50 mg caraway oil in an enteric coated capsule  Reference formulation: 36 mg peppermint oil and 20 mg caraway oil in an enteric soluble formulation	223 patients  Drop out:30  108 patients on the test preparation  105 patients on the reference preparation	Non-ulcer dyspepsia (dysmotility type dyspepsia or essential/idiopathic dyspepsia, also in combination with irritable bowel syndrome)	Difference in pain intensity between the beginning and the end of therapy  Equivalent efficacy of both preparations was demonstrated	Two-sided one-sample t-test	The objects of the study are combinations of peppermint oil and caraway oil.  Results are not relevant to conclude about the effects of peppermint oil used as single ingredient
Capanni, 2005	Randomised, controlled, double-blind	Test Product: Capsules: 225 mg of	178 patients	IBS diagnosis, according to	Global IBS symptoms assessed by a validated	Chi-square test	Results are considered clinically relevant

		<p>peppermint oil and 45 mg of excipient;</p> <p>Placebo: 225 mg of maltodextrin with mint flavour</p> <p>2 capsules, 3 times a day, before meals for 3 months</p>	<p>Drop out:5</p> <p>Test group: 91 patients (22 M, 69 F); mean age 41 years old; range 18-72 years old)</p> <p>Placebo group: 87 patients (23 M, 64 F; mean age 44 years old; range 21-74 years old).</p>	<p>the Rome II criteria</p>	<p>questionnaire.</p> <p>Peppermint oil, improved IBS overall symptoms [73/91 (80%) vs 31/87 (36%) patients (p&lt;0.02)]</p> <p>and gastroenteric symptoms [88/91 (97%) vs 29/87 (33%) patients (p&lt;0.01), psychological discomfort, in 34/91 (37%) vs 16/87 (18%) patients (p&lt;0.05), and socio-familiar impact, in 69/91 (76%) vs 37/87 (43%) patients (p&lt;0.04)].</p>	<p>concerning the efficacy and safety of peppermint oil in patients with IBS.</p>
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Cappello 2007	Randomised double-blind placebo-controlled,	Two enteric-coated capsules (225mg) twice per day or placebo) for 4 weeks	<p>57 patients 76% female Mean age 42 years</p> <p>28 taking peppermint oil and 29 taking a placebo.</p> <p>7 dropouts (3 on each group, excluded from the study)</p> <p>One patient in the peppermint group withdrew due to intense heartburn after taking the medication</p>	IBS Rome II criteria	<p>Assessment T0, T4 and T8 of symptoms:</p> <p>Abdominal pain, continuous;</p> <p>IBS-symptom score, continuous and dichotomous;</p> <p>symptom intensity and frequency from 0 to 4 were scored</p> <p>A p-value <math>\leq 0.05</math> was considered statistically significant.</p> <p>75% of the patients in the peppermint oil group showed a &gt;50% reduction of basal (T0) total irritable bowel syndrome symptoms score compared with 38% in the placebo group (p&lt;0.009)</p>	<p>chi-square test</p> <p>Student's t-test for paired data</p> <p>Mann-Whitney U test (two-tailed)</p>	Statically significant benefit for peppermint oil and clinically relevant for IBS symptoms.
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Merat <i>et al.</i> , (2010)	Randomised double-blind placebo-controlled	<ul style="list-style-type: none"> <li>- 187 mg or 0.2 ml peppermint oil;</li> <li>- three times daily, 30 minutes before each meal;</li> <li>- oral use (capsules)</li> <li>- 8 weeks</li> </ul>	<p>90 patients, 45 in test group, 45 in placebo group.</p> <p>Drop-out:30</p> <p>Finished study: 33 in placebo; 27 in test group;</p> <p>15 male, 45 female</p>	<p>Patients diagnosed according the Rome II criteria.</p> <p>Major complains: abdominal pain, distension and flatulence.</p>	<p>Week 1, 4, 8</p> <p>Primary outcome: absence of abdominal pain or discomfort at week 8</p> <p>Secondary outcomes</p> <p>Score with the SF-36 form for assessment of QOL</p> <p>Score with a non-validated patient questionnaire</p> <p>Score with a non-validated researcher questionnaire</p> <p>The number of subjects free from abdominal pain or discomfort changed from 0 at week 0 to 14 at week in the peppermint oil group and from 0 to 6 in controls (p/0.001).</p> <p>The severity of abdominal pain was also reduced significantly in the peppermint oil group compared to controls</p>	<p>ITT analysis - No p-values of 0.05 were considered significant.</p>	<p>The study evidences improvement of abdominal pain and discomfort.</p> <p>However, almost 30% of subjects did not complete the study (no ITT analysis).</p> <p>Low number of subjects.</p> <p>Questionnaires were not validated</p> <p>The clinical relevance of the results is questionable</p>
Alam <i>et al.</i> , 2013 The abstract is available, only	Double blind placebo controlled study	<p>Peppermint oil (unspecified)</p> <p>3 times per day for 6 weeks</p>	<p>74</p> <p>9 drop out</p>	<p>Patients with IBS (who fulfilled the ROME II criteria)</p>	<p>Efficacy in relieving the symptoms, changes of quality of life (QOL) in diarrhoea predominant IBS</p>	<p>Paired and unpaired T-Test</p> <p>P&lt;0.01 for abdominal pain at 6 weeks</p> <p>Other symptoms and QoL did not improve significantly.</p>	<p>Improvement after six weeks, but worsening after 8</p>

Cash, 2016	Randomised, double-blind, placebo-controlled clinical trial	Peppermint oil (180mg), tricoated capsules 3 times per day, for 4 weeks	72 Patients, mean age 40.7 years, 75% female, 77.8% white	Rome III criteria for IBS-M or IBS-D with an average daily IBS related abdominal pain rating of C4 on a 0-10 scale and a Total IBS Symptom Score (TISS) of C2 on a 0-4 scale	Primary endpoint was change from baseline in the TISS 28 days after the start of therapy  Secondary outcomes included the TISS score at 24 h  Symptomatic improvement in patients with non-constipated IBS based on significant reductions in a global IBS symptom score (40% reduction in the peppermint oil group versus 24.3% reduction in the placebo group after 4 weeks, $p=0.0246$ ) and reduced frequency and/or intensity of individual IBS symptoms	Wilcoxon rank-sum test was used to compare results from the peppermint oil and placebo groups.  Paired t tests were used to compare follow-up score to baseline within each treatment group.	Results are considered to be significant and clinically relevant concerning the efficacy and safety of peppermint oil in patients with IBS-M and D.
Review of Clinical Studies for <b>Endoscopy-induced spasm</b>							
Asao, <i>et al.</i> , 2001	Prospective. placebo controlled.  Only a preliminary study (N=71) was randomised.	Eight ml of peppermint oil and 0.2 ml of Tween 80 mixed in 1 L of water  30 ml injected intraluminally	N=445 patients  Treated group: N=409; Male/Female 309/100 Age (yr) $56.8 \pm 11.3$ /	Inclusion criteria for colonoscopy: positive test for occult blood in feces, an abnormal barium enema, or surveillance after	Colonic spasm was estimated by using a 4-grade score:  Efficacy was calculated as the percentage of patients with either a +0 or a +1 score.	The chi-square test or Student <i>t</i> test was used for evaluation of differences.  A <i>p</i> value of less than 0.05 was considered significant.	Colonic spasm during colonoscopy was reduced by the intraluminal administration of peppermint oil.  No adverse effects were observed.

			<p>Age Range: 25-89</p> <p>Control group: N=36</p> <p>Male/Female 26/10</p> <p>Age average: 55.2 ± 11.9</p> <p>Age range: 21-76</p>	<p>previous polypectomies.</p> <p>9 Patients with a history of colectomy or severe colitis were excluded</p>			
Asao <i>et al.</i> , 2003	Prospective trial on the efficacy of peppermint oil during double-contrast barium enema (DCBE)	<p>Peppermint solution (100ml water, 8ml peppermint oil, 0.2ml Tween 80)</p> <p>Buscopan 20mg</p>	<p>383 consecutive patients</p> <p>4 groups:</p> <p>Peppermint oil in barium (91)</p> <p>Peppermint oil in tube (90)</p> <p>Buscopan (105)</p> <p>No-treatment(97)</p>	Patients undergoing DCBE who had positive results from occult blood test	<p>Evaluation of the presence of colonic spasms on a series of spot films</p> <p>Buscopan+ peppermint oil had less spasms than the no-treatment group (p&lt;0.0005)</p> <p>No significant difference between peppermint oil and Buscopan</p>	<p>Chi-square or Mann-Whitney U test.</p> <p>p&lt;0.05 was considered significant</p>	<p>Similar results for both preparations.</p> <p>Maybe useful for the barium enema.</p>
Hiki 2003	Prospective, Double-blind, double-dummy controlled trial	Peppermint oil solution administered intraluminally vs hyoshine-N-butylbromide by intramuscular injection	100 patients	Patients undergoing upper endoscopy. Exclusion criteria was used	<p>Primary outcomes – opening and contraction ratios</p> <p>Determination of gastric relaxation to a statistically significant extent with minimal side effects compared with hyoshine-N-butylbromide</p> <p>p&lt;0.001 for peppermint oil and</p>	<p>Mann-Witney U test: compare the antispasmodic effects</p> <p>Wilcoxon test: contraction ratios before and after the administration</p> <p>p&lt;0.001 for peppermint oil and p&lt;0.05 for hyoshine-N-butylbromide</p>	<p>Contraction ratio was significantly smaller after peppermint oil than after Hyoscimine injection (p&lt;0.0001)</p>

					p<0.05 for hyoshine-N-butylbromide		
Imagawa, <i>et al.</i> , 2012	non-randomised prospective study	20 ml of a 1.6% peppermint oil solution administered directly to the antrum of the stomach at the initial stage of the EGD.	8269 patients submitted to EGD mean age: 62.4 years (range 13–99 years).  Male/female ratio: 4.788/3.481  Group peppermint oil: 1893 patients  HB group: 6063 patients  GL group: 157 patients  Placebo group: 156 patients	Patients scheduled to undergo EGD (esophagogastroduodenoscopy).  Patients with clinical evidence of severe disease were excluded (ex. American Society of Anesthesiologists classification, score 4 or 5)	Primary outcome: Antispasmodic scores (1-5) for the patients younger than 70 years compared with patients 70 years or older and their dependence on antispasmodic agent.  The antispasmodic score of Group peppermint oil $4.025 \pm 0.925$ did not significantly differ from that of groups HB and GL  Placebo group score: $3.846 \pm 1.073$ , (p<0.05)	Coefficient of variation (CV) of the antispasmodic scores: CV=22.2%  Wilcoxon rank sum test: assessing the significance of differences in two independent groups;  Kruskal-Wallis test: assessing the significance of differences in more than two independent groups.  p<0.05 was considered statistically significant.	Peppermint oil is effective and useful as an antispasmodic drug for EGD, especially for elderly patients.  Irrelevant results regarding IBS
Inamori, <i>et al.</i> , 2007	randomised, two-way crossover study	0.64 ml of peppermint oil with a test meal (200 kcal per 200 ml)  Control group: meal without peppermint oil.	N=10 asymptomatic male volunteers with no history of gastrointestinal disease.	Healthy patients	Time required for gastric emptying estimated by scintigraphy  (50% of the labeled meals; <sup>13</sup> C-acetic acid breath test)  Peppermint oil enhances gastric emptying.	Wilcoxon signed-rank test.  Level of significance: p<0.05	No clinical relevance: dimension of the sample; sex distribution; healthy volunteers; no

		Second way test separated by 7 days					ITT.
Review of Clinical Studies for <b>Children</b>							
Kline, 2001	RDBCT	peppermint oil enteric-coated capsules 187 mg 1-2 cpsx3 Children and adolescents 8-17 years 2 weeks The patients weighing more than 45 kg received 2 capsules, 3 times a day. The smaller children, who weighed 30Kg to 45 kg, received 1 capsule 3 times a day.	50 children 8 - 17 years and > 30 kg 60% female 40% males 8 drop outs	IBS (Manning or Rome criteria)	Abdominal pain Urgency of stools, belching, stool pattern and consistency  75% reduction of severity of pain, but no other symptoms	SAS software for the categorical data analysis; Cochran- Armitage test for the data  ( $\chi^2[6, N=42] = 12.6; p<0.001$ )	No change in the type of symptoms but change in the severity reported by patients.  Clinically relevant especially for abdominal pain
Mint leaves							
Alves <i>et al.</i> , 2012	Cross-over double blind 2 groups: mint leaves and simethicone:  7 days in each treatment with a period of 3 days wash out.	Menta piperita (liquid drops 1 drop per kg body weight) for 7 days	30 Infants from 8 to 56 days, exclusively breastfeeding	Infants diagnosed with infantile colic	Primary: mother's opinion about responses to treatment, number of daily episodes of colic, time spent crying  Secondary: number of milk regurgitation, vomiting, diarrhoea, constipation and drowsiness.	Mann-Whitney and chi-square tests	No difference Self-limiting disease
Review of Clinical Studies for Tension Headache							
Gobel <i>et al.</i> , 1996	Randomised, double blind, placebo	Peppermint oil 10% in ethanol repeated after 15 and 30 minutes /	41pt 18-65 years old, both sexes.	Tension type headache HIS classification	Intensity of the headache. Standardised category rating scale - assessment	T test Standardised pain rating	Promising results. Clinically

	controlled, fourfold crossover study/placebo and acetaminophen	500mg acetaminophen	164 headache attacks		after 15, 30, 45 and 60 minutes by the patients Significant reduction of the intensity during 1 hour of observation similar to acetaminophen. $p < 0.01$	scale (0-4)	relevant
Gobel <i>et al.</i> , 1994, 1995	Double blind placebo controlled randomised, four-fold crossover study	Peppermint oil 10% in ethanol Four different topic preparations,	32 healthy subjects	Healthy subjects	Neurophysiologic, psychological and experimental algometric parameters  A significant analgesic effect with a reduction in sensitivity to headache was produced by the combination of peppermint oil and ethanol.	Paired t-test	Experimental design with promising results
<b>Review of Clinical Studies for Other indications</b>							
Barnick 1990	PCDB	Peppermint oil 187 mg 2 caps 3 times per day - 5 days	69 woman Age 20-66 years	Abdominal distension and dyspepsia after gynaecological surgery	Abdominal distension Dyspepsia	Mann-Whitney U test	No difference between the groups. Not relevant for the monograph
Tayarani-Najaran <i>et al.</i> , 2013	RDBCT	Peppermint oil /Spearmint/placebo Caps of 2 drops of each EO every four hours Duration?	50 pt/group 4 groups	Any cancer patient	Prevention of chemotherapy-induced nausea 1,6 emetic events in placebo group; 0.6-0.7 in <i>M. Spicata</i> and peppermint oil $p < 0.05$ Intensity of nausea was significantly reduced during 24 h $p > 0.05$		Safe and effective option. Not relevant for the monograph



**Table 4B:** Systematic Reviews and Meta-analyses

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score e.g. Jadad score	Comments on clinical relevance of results
Grigoleit and Grigoleit 2005b	Review 2-11 weeks 6 months (1 open study) 9 DBCT 5 DB parallel 2 open studies	Capsules of 180-200 mg 2-11 weeks In most studies 1 to 2 capsule t.i.d. were administered	651 patients 71 drop outs  Prevalence of women	IBS (older studies were before Rome II) Recurrent abdominal pain in children (1 study).	Abdominal pain, distension, flatulence	"Overall success" (overall benefit, global improvement, overall assessment) was used (% of responders). Placebo response is in the range from 10% to 52% (mean 29%) for all studies. DBCT- peppermint oil efficacy in the range from 39% to 79% (mean 58%).	Peppermint oil is efficacious in a sufficient number of studies as a symptomatic short term treatment

Pittler, Ernst 1998	Meta-analysis of five placebo-controlled, double blind trials of 8 studies enrolled.	0.2-0.4ml 3 times daily 2-6 weeks. 1 open study – 26 W	295 pt 18 dropouts	IBS The older studies have vague inclusion criteria		Jadad score was used. Chi-squared test used. 3 studies-p<0.001  1 small trial – stress> peppermint oil in 6 months  2 trials – peppermint oil similar to placebo on pain relief	Overall significant Benefit on three of the five DBPCT. Methodological flaws in some of the studies.
Ford <i>et al.</i> , 2008	Meta-analysis 4 studies- PO/placebo	Peppermint oil, fibers, antispasmodic 4 weeks-3 months 187 to 225 mg per single dose, 2-6 single doses per day, divided in two to four times daily.	392 pt Women from 40-76% in each trial	IBS	Abdominal pain 1 study – disease subtype with stool pattern: 25% constipation; 75% diarrhoea 26% of the peppermint oil group had persistent symptoms compared with 65% of the placebo group - Relative risk – 0.43% (95% CI).	3 studies - Jadad scale >4 relative risk 0.40; 0.29 to 0.55) No statistical significant heterogeneity	Peppermint oil superior to placebo

Ruepert <i>et al.</i> , 2011	Systematic Review 56 studies	Bulking agents – 12 T, antispasmodics - 29 T, 5 studies of peppermint oil were included. 187 to 225 mg peppermint oil per single dose, 2-6 single doses per day, divided in two to three times daily.  Antidepressants – 15T	Total - 3725 pt Antispasmodics - 2333	IBS	Primary:  Improvement of symptoms of abdominal pain;  Improvement of patients overall global assessment;  Improvement of IBS-symptom score.  A statistically significant effect for improvement of IBS symptom score for peppermint oil (RR 1.94; 95% CI 1.09 to 3.46; 269 patients)	A statistically significant effect for improvement of global assessment for peppermint oil (RR 2.25; 95% CI 1.70 to 2.98; 225 patients);	Different types of antispasmodics found statistically significant. Benefits and clinically relevance for cimetropium/ dicyclomine, peppermint oil, pinaverium and trimebutine.
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Khanna, 2013	Systematic review and meta-analysis RCT, RPCT with minimum treatment duration of 2 weeks and Crossover studies that provided outcome data before the first cross-over.	Peppermint oil 0.1-0.2ml, peppermint oil 225mg Minimum 2 weeks – 12 weeks 1 study in children	726 pt	IBS	<p>Global improvement of IBS symptoms, improvement in abdominal pain, and adverse events.</p> <p>Peppermint oil was found to be significantly superior to placebo for global improvement of IBS symptoms (5 studies, 392 patients, relative risk 2.23; 95% confidence interval, 1.78-2.81) and improvement in abdominal pain (5 studies, 357 patients, relative risk 2.14; 95% confidence interval, 1.64-2.79).</p>	Cochrane Collaboration software Review Manager (RevMan 5).	Statistically significant benefit for peppermint oil relative to placebo for improvement in abdominal pain and global IBS symptoms.
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### **4.3. Clinical studies in special populations (e.g. elderly and children)**

#### Peppermint leaves

A double-blind crossover study was performed in thirty (30) infants attending IMIP, Recife, Brazil. They were randomised to use formulation of leaves of the *Mentha piperita* (liquid drops; 1 drop per Kg body weight) or simethicone (liquid drops; 2.5 mg per Kg body weight) daily for a period of 7 days (no information about the preparation of *Mentha piperita* leaves) in the treatment of infantile colic with either drug. This study was carried out using a crossover double-blind design. Each child aged from 8 to 56 days (33±11.1) underwent an intervention for 14 days.

Primary outcomes were mother's opinion about responses to the treatment, number of daily episodes of colic, and time spent crying, measured by a chronometer. Mann-Whitney and chi-square tests were used to compare the results. This study was previously approved by the Ethical Committee in Research at IMIP.

At baseline daily episodes of infantile colic were 3.9 (±1.1) and the mean crying time per day was 192 minutes (±51.6). At the end of the study daily episodes of colic fell to 1.6 (±0.6) and the crying duration decreased to 111 (±28) minutes. All mothers reported decrease of frequency and duration of the episodes of infantile colic and there were no differences between responses to *Mentha piperita* and simethicone (Alves *et al.*, 2012).

#### Peppermint oil

##### **Clinical studies in children**

In a randomised, double-blind controlled trial of two weeks, forty two (42) children and adolescents (8 to 17 years old) with irritable bowel syndrome were given pH dependent enteric coated peppermint oil capsules (187 mg), or placebo. The patients weighing more than 45 kg received 2 capsules, 3 times a day. The smaller children, who weighed 30 kg to 45 kg, received 1 capsule 3 times a day. After two weeks, for 75% of those receiving peppermint oil reduced severity of pain associated with the IBS, but not the other symptoms, like heartburn, gas, urgency of stools, belching, stool pattern or stool consistency, was reported. No adverse events were reported (Kline *et al.*, 2001).

##### **Systematic review**

Abstracts and full texts of 57 randomised controlled trials on recurrent abdominal pain (RAP) in children were evaluated; 10 of them met the inclusion criteria involving children aged 5 to 18 years, diagnosis of RAP, randomization and controlled study. Famotidine, Pizotifen, cognitive-behavioural therapy, biofeedback and peppermint oil enteric-coated capsules (1 study) showed a decrease in measured pain outcomes compared to the control (Weydert *et al.*, 2003).

### **4.4. Overall conclusions on clinical pharmacology and efficacy**

#### Peppermint leaves

The clinical studies are mainly related with combinations and the clinical study in children gives no information about the preparation used. For these reasons only the traditional use is justified.

#### Peppermint oil

##### **Oral administration**

##### **IBS**

IBS is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit, and with features of disordered defecation (Longstreth *et al.*, 2006).

The Rome foundation team diagnostic criteria of Irritable Bowel Syndrome always presumes the absence of a structural or biochemical explanation for the symptoms and is made only by a physician.

After a consensus approach, the Rome Foundation team considering the available evidence and multinational expert opinions revised the Rome II diagnostic criteria for the functional bowel disorders, and updated diagnosis and treatment recommendations for the Rome III (Drossman *et al.*, 2006, Longstreth *et al.*, 2006).

The Rome process is a dynamic one, thus in June 2016, there was another update and the Rome IV criteria for diagnosing functional gastrointestinal (GI) disorders was published. Rome IV has several changes in how functional bowel disorders are described and diagnosed. Previous versions of Rome considered functional bowel disorders such as IBS, functional diarrhoea, functional constipation, and functional distension (Rome I) as separate entities. Later it was recognised that these disorders could overlap (Rome II-Rome III). However, in the clinic it may not be possible to confidently separate disorders into separate entities. Such is the case of IBS with predominant constipation (IBS-C) from functional constipation or IBS-D from functional diarrhoea. Thus, Rome IV considers that these disorders exist as a continuum rather than as single entities (Schmulson and Drossman, 2017).

Rome III Criteria for Diagnosing IBS: <sup>a</sup>	Rome IV Criteria for Diagnosing IBS: <sup>c</sup>
<p>Recurrent abdominal pain or discomfort<sup>b</sup> at least 3 days per month in the last 3 months associated with two or more of the following:</p> <ul style="list-style-type: none"> <li>• Improvement with defecation</li> <li>• Onset associated with a change in frequency of stool</li> <li>• Onset associated with a change in form (appearance) of stool</li> </ul>	<p>Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with two or more of the following criteria:</p> <ul style="list-style-type: none"> <li>• Related to defecation</li> <li>• Associated with a change in frequency of stool</li> <li>• Associated with a change in form (appearance) of stool.</li> </ul>
<p><sup>a</sup>Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. <sup>b</sup>“Discomfort” means an uncomfortable sensation not described as pain.</p>	<p><sup>c</sup>Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.</p>

Pain is still an essential part of the diagnosis, but the word “discomfort” has been removed.

The frequency of abdominal pain has been slightly increased, from 3 days per month to 1 day per week.

In terms of IBS subtypes, IBS is mainly classified according to the predominant bowel habit for IBS-C (constipation), IBS-D (diarrhoea), IBS with mixed bowel habits, and unclassified IBS. In Rome IV, bowel habits are based on stool forms only during days with abnormal bowel movements (more than one-fourth: 25% of bowel movements).

This is in contrast to Rome III in which the 25% threshold was determined based on the total number of bowel movements irrespective of whether they were normal or not. In fact this led to a

predominance of unsubtyped IBS using Rome III as it was the case in several epidemiological studies the USA and Latin America (Schmulson and Drossman, 2017).

The pathogenesis of IBS seems to be multifactorial, with several factors, such as heritability and genetics, dietary/intestinal microbiota, low-grade inflammation and disturbances in the neuroendocrine system of the gut, playing a central role. The diagnosis is based on clinical assessment and the Rome III criteria, which in general is not used by most clinicians consulted by IBS patients, who seek advice and require more clinical investigation to achieve the correct diagnosis (El-Salhy, 2012).

It affects more women than men and is more common in patients 30 to 50 years of age (Hadley and Gaarder, 2005).

Throughout the world, about 10%–20% of adults and adolescents have symptoms consistent with IBS. IBS symptoms come and go over time, often overlap with other functional disorders, impair quality of life and result in high health care costs. (Longstreth *et al.*, 2006).

According to the "Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97 Rev. 1, Set 2014), "there is still a lack of adequately studied and more so of licensed medications in Europe, and a certain unmet medical need for IBS has still to be realised. Moreover, there is a wide history of unsuccessful drug development programmes in the field, and the number of Marketing Authorisation Applications for the indication has been very low during the past decade".

Pharmacological options are usually recommended if non-pharmacological methods alone have proven to be ineffective. Most of the current pharmacological therapies aim at treating the symptoms with the rationale of modulating intestinal motility and/or secretion, decreasing visceral sensitivity or treating associated disorders, such as anxiety and/or depression.

The general recommendation is to use the Rome III criteria for inclusion, and to add a relevant diagnostic work-up for the most relevant potential other diseases.

This Guideline recommends, for the time being, assessing the main symptomatology in, at least, partially validated scales/outcome parameters. Because the main symptoms in IBS are considered to be abdominal pain/discomfort, along with abnormalities in defecation (consistency and frequency of stools), and there is ongoing controversy on whether abdominal discomfort is a symptom distinctly different from abdominal pain (and whether it should be evaluated together or separately), the main endpoints are now recommended along with the Rome III definitions. The two components included in the proposed primary endpoint should therefore be the evaluation of abdominal pain and the evaluation of stool frequency for IBS-C (based on the number of complete spontaneous bowel movements (CSBMs) per week), and the evaluation of stool consistency for IBS-D, based on the Bristol Stool Form Scale. For other subtypes of IBS, and for "global" development programmes intending to treat two or more subtypes, the use of the global assessment is, however, still recommended. The primary endpoint should be evaluated primarily as responder rate. The numerical evaluation of changes in scales is regarded to be a secondary endpoint. For the evaluation of abdominal pain, the use of a 11-point NRS-scale has at least been partially validated for use in IBS, and is therefore regarded to be acceptable. However, the previously recommended use of other scales for pain can also still be accepted, if adequately justified. As previously requested, scales (other than the 11-point NRS) should be open to change in both directions.

In cases of weekly evaluations of the primary endpoints, a minimally required number of valid diary entries should be defined in order to be evaluative as responder, and define patients below this threshold as non-responders.

In development programmes, where the global evaluation of the symptomatology is not included as primary endpoint (choices a) and b)), a global symptom assessment should be defined as the main secondary endpoint. The choice of a scale measuring improvement and deterioration is clearly recommended. The global assessment can also, likewise, be based on daily or weekly responder rates as recommended for the primary endpoint.

The epidemiology of IBS according to sex shows an overall predominance of women with a pooled Odds Ratio in prevalence of 1.67. The development of drug candidates for one gender only is considered fully acceptable, if indeed a differential therapeutic response with greatly reduced effects in one of them can be expected.

IBS in children – for the conduct of clinical studies – should be defined on the current proposals of the Rome Committee (Rome III criteria) unless otherwise adequately justified (Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome” (CPMP/EWP/785/97 Rev. 1, Set 2014).

Some studies in the literature show methodological problems, such as: use of no validated scales; the randomisation procedure being not clear; lack of adequate washout period; limited treatment period (2-4 weeks) and no data on repeated use; have small sample sizes and unclear diagnostic criteria. Despite this, some interventions with peppermint oil have been shown to be clinically effective in the treatment of symptoms of IBS, in several randomised well designed controlled trials, for a 3 month period. A variety of outcome measures have been used, making it difficult to compare the results of the trials.

In a systematic review of diagnostic criteria on the clinical studies for IBS, the literature was selected according to three periods of time (Rome I era from 1992 to 1999, Rome II era from 2000 to 2006 and Rome III era from 2007 to 2011). The first stage of the systematic review identified only 14 published studies validating diagnostic tests for IBS (with three studies evaluating more than one criterion). There were eight validations for Manning, three validations for Kruis, four validations for Rome I, three validations for Rome II, and no validation for Rome III. In the second review of utilization of Rome criteria, only 25.7% of published IBS papers used Rome III criteria during the Rome III era (Rome II was used most in 64.8% of studies). According to the author, this review identified that comparator groups varied widely between studies making comparison of criteria impossible (Dang *et al*, 2012).

The meta-analysis by Pittler and Ernst reported that the role of peppermint oil in the symptomatic treatment has not been established and more studies are needed to clarify. The difference in the diagnosis criteria in the clinical studies, may justify part of the problems encountered in the comparator groups in the meta-analysis.

The review by Cochrane about IBS treatment (2011) found a statistically significant effect for improvement of global assessment and at the meta-analysis from Khanna *et al.*, (2013), peppermint oil demonstrates to be clinically safe and effective short-term treatment for IBS.

The review from Wall *et al.*, (2014) include peppermint oil in an algorithm to guide practicing clinicians to treat IBS in the first line, as well as dicyclomine, pinavarium and trimebutine for “Abdominal pain with mixed bowel symptoms (IBS-M)”, for 4-6 weeks.

The American College of Gastroenterology (Ford, 2014) considered the quality of evidence as moderate, concluding that in specific formulations, which may not be universally available, peppermint oil is effective in IBS.

The dose of peppermint oil in the individual studies was in the range of 0.6 ml to 1.2 ml per day in gastro resistant capsules, divided in 2- 6 single doses for adolescents and adults and of 0.6 ml daily for children, divided in 3 single doses.

## **Antispasmodic**

During endoscopy and colonoscopy, the topical intraluminal administration of peppermint oil, was used as antispasmodic agent in several studies, with superior efficacy than placebo and hyoscine-N-butylbromide, with less adverse reactions too.

## **Post-operative nausea, sleep/alertness action and respiratory action**

The studies on post-operative nausea were performed with an experimental design, those on sleep/alertness in healthy subjects, not providing enough support for the efficacy of the indications. Just the TU can be accepted using the inhalation route for the relief of symptoms of cough and cold, according to the historical record of 30 years.

## **Tension headache**

The tension-type headache (TTH) is classified at the International Classification of Headache Disorders, 3<sup>rd</sup> edition (beta version).

This kind of primary headache is very common, ranging from 30 to 78% in several studies. It was first considered as psychogenic, but recent studies suggest a neurobiological basis, especially for the more severe cases. The last edition of *The International Classification of Headache Disorders* further subdivided episodic tension-type headache, into an *infrequent* subtype with headache episodes less than once per month and a *frequent* one. Another difference in this edition is noted regarding the use of precranial muscles' disorder, for the subdivision by assessing the tenderness on manual palpation and not the surface EMG or pressure algometry (The International Classification Of Headache Disorders, 2013).

This indication is mentioned in the ESCOP monograph. The Commission E monograph only includes the indication "muscle and neuralgic complaints".

The peppermint oil, by laboratory tests, seems to exert some actions on mechanisms associated with the pathophysiology of tension headache, producing an analgesic affect, after administering a 10% solution of peppermint oil on the forehead and the temples of the patients.

The comparative clinical study with 1000 mg acetaminophen, demonstrated no significant difference between both products on the relief of the pain. The numbers of patients in the studies were small; the inclusion criteria are not well defined with a broad range of ages. The characteristics of the pain described – 4.99 days per month for 14.12 years – fulfil the diagnostic criteria of the *Frequent episodic tension-type headache* (ICHD-II) and *Episodic tension-type headache* (IHS code).

No clinical trials were found for other preparations with peppermint oil for this indication.

# **5. Clinical Safety/Pharmacovigilance**

## ***5.1. Overview of toxicological/safety data from clinical trials in humans***

### **Oral administration**

#### **Peppermint leaves**

No data available for peppermint leaves.

#### **Peppermint oil**

In a literature search peppermint oil was found to cause the typical GI effects like heartburn and anal / perianal burning or discomfort sensations; 16 clinical trials investigating 180–200 mg enteric-coated

peppermint oil in irritable bowel syndrome (IBS) or recurrent abdominal pain in children (1 study) with 651 patients enrolled were identified (Grigoleit and Grigoleit 2005b).

Adverse effects were reported in six trials, in the verum treatment, such as heartburn, perianal burning blurred vision, nausea and vomiting. The frequency ranged from 11% to 36% (Pittler and Ernst, 1998).

The meta-analysis from Khanna *et al.*, (2014), evaluated seven hundred twenty six (726) patients from nine studies. The adverse events that were reported in the placebo-controlled studies were of mild and transient nature. The adverse events included heartburn, dry mouth, belching, peppermint taste, peppermint smell, rash, dizziness, headache, increased appetite and a cold perianal sensation.

In the review from the American College of Gastroenterology (Ford *et al.*, 2014), the 5 RCTs (peppermint oil ) included involving 492 patients and using an enteric-coated preparation of peppermint oil employed in doses ranging from 187 to 225 mg/caps, (2-3 times daily, 2-6 caps per day) not higher in peppermint oil groups compared to placebo (RR of experiencing any adverse event =1.26, 95% CI 0.75– 2.12) adverse events were reported.

No certain cases of liver damage caused by peppermint oil or mint oil have been reported (EMA/HMPC/138386/2005).

### Menthol

A case of asthma due to menthol was reported in a 40-year-old woman with no history of asthma or any other allergy. The aetiology was suggested by the history of exposure. The diagnosis was confirmed by the clinic history and by skin tests (Santos, 2001).

A form of stomatitis and glossitis with extremely prominent circumvallated papillae was described in patients who consumed excessive amounts of mint-flavoured sweets (Rogers, 1995).

### Pulegone and menthofuran

A literature review of cases of human intoxication with pennyroyal oil (*Mentha pulegium* containing pulegone content 62-97%) indicate that ingestion of 10 ml (corresponding to ca 5.4-9 g pulegone, ca 90-150 mg/kg bw for a 60 kg person; calculated with a relative density of 0.9 as for peppermint oil) resulted in moderate to severe toxicity while ingestion of greater than 15 ml (corresponding to ca 8-13 g pulegone, ca 130-215 mg/kg bw for a 60 kg person) resulted in death. The clinical pathology was characterised by massive centrilobular necrosis of the liver, pulmonary edema and internal haemorrhage (SCF, 2002, cited in EMA/HMPC/138386/2005 Rev. 1). A non-urgent information request was sent out to the member states concerning the use and association of licensed herbal medicinal products containing pennyroyal oil, peppermint oil and mint oil with reports of liver damage.

The toxicity of pulegone and menthofuran have been evaluated by HMPC and presented in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1).

### **Inhalation**

Some reports about auricular fibrillation after the inhalation and ingestion of excessive amounts of mentholated products were published in medical journals (Thomas, 1962)

Inhalation of large doses of menthol was reported to cause dizziness, confusion, muscle weakness, nausea or double vision (Natural Standard Research Collaboration 2005).

**Table 5:** Clinical safety data from clinical trials

<b>Type (aim) and objective(s) of Study Reference</b>	<b>Study Design and Type of Control Study duration (if available)</b>	<b>Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment</b>	<b>Number of Subjects (including age, sex, drop out)</b>	<b>Healthy Subjects or Diagnosis of Patients (inclusion criteria)</b>	<b>Adverse reactions</b>	<b>Comments on clinical relevance of results</b>
Grigoleit and Grigoleit 2005b	Review 2-11 weeks 6 months (1 open study) 9 studies rand. db. Cross over with or without run in and/or wash out 5 rand db parallel group 2 open	Capsules of 180-200 mg 2-11 weeks In most studies 1 to 2 capsule t.i.d. were administered	651 pt 1 study children	IBS or recurrent abdominal pain in children (1 study).	Heartburn (n=14) Anal/perianal burning (n=26),	Mild and transient symptoms
Pittler and Ernst 1998	Meta-analysis of 5/8 studies	0.2-0.4ml 3 times daily 2-6 weeks. 1 open study - 26 W	295 pt 18 dropouts	IBS	Heartburn, perianal burning, blurred vision, nausea and vomiting. The frequency ranged from 11 to 36% (mean 20%) of the patients studied.	Mild and transient symptoms
Khanna, 2013	Systematic review and meta-analysis RCT, RPCT	Peppermint oil 0.1-0.2ml, 225mg Minimum 2 weeks - 12 weeks 1 study in children	726 pt	IBS	Adverse events reported in the placebo-controlled trials include: heartburn, dry mouth, belching, peppermint taste, peppermint smell, rash, dizziness, headache, increased appetite, and a cold perianal sensation. Total - 218 per 1000 (160 to 297) in 474 patients (7 studies)	Safe and effective short-term treatment for IBS.
Ford, 2014	Review	Peppermint oil 187-	492	IBS		The adverse events

American College of Gastroenterology	5 RCT	225mg t.i.d.			RR of experiencing any adverse event =1.26, 95% CI 0.75- 2.12	were not higher on peppermint oil groups compared to placebo
Kline, 2001	RDBCT	Peppermint oil 187mg 1-2 capsx3 2 weeks 8-17 years	42 pt	IBS	No adverse reactions	Safe treatment

## 5.2. Patient exposure

### Peppermint leaves

Peppermint leaves and extract can be used in cosmetic formulations as fragrance ingredients. Peppermint water can be used as a flavouring agent or, also, as a fragrance component.

### Peppermint oil

Peppermint essential oil is widely used in flavouring, cosmetic formulations and skin-conditioning agents. In general peppermint oil is considered as safe ingredient for use in dietary supplements and common as a folk medicine.

The FDA calculated the estimated human exposure from cosmetic use, based on the concentration of use information supplied by industry. Using a body splash product containing 0.2% peppermint oil and assuming 100% absorption over a body surface of 17,000 cm<sup>2</sup> and a daily application of 1 mg/cm<sup>2</sup> (17 ml of the product), the FDA estimated an exposure of 34 mg/day. For a 60 kg person, this amounted to an estimated daily dose of 0.6 mg/kg/day (FDA 1997) (Final report on the Safety Assessment of *Mentha piperita*, 2001).

### Menthol

In 1976, FAO/WHO Joint Expert Committee on Foods Additives (JECFA) established an ADI of 0-2 mg/kg body weight/day for menthol. In 2000, an ADI of 0- 4mg/kg of body weight/day was allocated (WHO 2000).

### Pulegone and menthofuran

Maximum levels for pulegone in foodstuff and beverages to which flavourings or other food ingredients with flavouring properties have been added: 25 mg/kg in foodstuff, 100 mg/kg in beverages, with the exception of 250 mg/kg in peppermint or mint flavoured beverages and 350 mg/kg in mint confectionery (Annex II of Directive 88/388/EEC). Pulegone may not be added as such to foodstuff. Committee of Experts on Flavouring Substances (CEFS) of the Council of Europe (1997): Menthofuran is the proximate hepatotoxin of pulegone. Tolerated daily intake (TDI) of menthofuran and pulegone was set to 0.1 mg/kg bw, based on a no effect level (NOEL) of 20 mg/kg bw/d in the 28 days oral toxicity study in rats (Thorup *et al.*, 1983 a,b) with a safety factor of 200. Menthofuran is listed in the register of chemically defined flavouring substances laid down in Commission Decision (1999/217/EC, 2002/113/EC).

In addition to the use in medicine, humans are exposed to pulegone as part of the essential oil in flavourings, confectionery, and cosmetics (Karousou *et al.*, 2007; Barceloux, 2008 cited in Public statement on the use of herbal medicinal products containing pulegone and menthofuran, draft 1, Nov 2014). According to JECFA, the estimated per capita intake of pulegone is reported as 2 µg/day and 0.04 µg/kg bw/day for Europe, and 12 µg/day and 0.03 µg/kg bw/day for the USA (IPCS, 2001, cited in Public statement on the use of herbal medicinal products containing pulegone and menthofuran, EMA/HMPC/138386/2005 Rev. 1, 2014).

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Foods (SPFA, 2005) noted that in certain cases the maximum permitted levels of pulegone in food may lead to high intakes in subjects consuming regularly mint flavoured beverages or confectionery. For example, 500 ml/day of mint flavoured beverage and 100 g/day of mint confectionery could lead to 128 intakes of respectively 4.2 mg/kg bw and 1.2 mg/kg bw for a 30 kg child (SPFA, 2005 cited in Public statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1, 2014).

In conclusion, humans are exposed to pulegone and menthofuran in herbal medicinal products and food, and as part of the essential oil in flavourings, confectionery, and cosmetics. Estimates of per capita intakes are widely variable.

The highest recommended daily dose in medicinal products in EU is 1.2 ml peppermint oil i.e. 1099 mg peppermint oil, which contains maximum 120 mg pulegone + menthofuran (Ph Eur). For a 60 Kg person this would correspond to a daily intake of 2.4 mg/kg. In the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1), the HMPC concludes that an intake of pulegone + menthofuran up to 37.5 mg/person/day, for an adult of 50 kg body weight, can be accepted for herbal medicinal products as a lifetime intake. For children, the daily amount of pulegone + menthofuran has to be adjusted to the body weight of the age group: e.g. body weight of 20 kg would lead to an acceptable daily intake of 15 mg/day.

### **5.3. Adverse events, serious adverse events and deaths**

#### Peppermint leaves

Peppermint teas contain only a low amount of menthol and menthone. In adults, the adverse reactions are, in general, related with a high intake of menthol by other products, as confectionary or pharmaceuticals.

There are no reports of serious adverse effects with the normal and prolonged use of peppermint tea, but the gastroesophageal reflux may be worsened by taking it, such as peppermint relaxes the lower oesophageal sphincter. Due to this effect, it is not recommended to people with hiatal hernia and gastroesophageal reflux.

Peppermint may stimulate the production of bile. In case of cholangitis, gallstones and other biliary disorders this product should be used with caution and under the supervision of a medical doctor.

#### Assessor's comment:

*The following text will be included in section 4.8 'Undesirable effects' of the monograph on peppermint leaf: "The gastroesophageal reflux may worsen and heartburn may increase. The frequency is not known."*

#### Menthol and methyl salicylate

There is a report of full thickness skin and muscle necrosis and interstitial nephritis in an elderly patient after topical application of a preparation containing menthol and methyl salicylate, followed by prolonged use of an electrical heated pad. (Heng 1987, Bowen and Cubbin, 1992).

#### Peppermint oil

Anaphylactic shock has been reported (BfArm, Germany).

Topical preparations of peppermint oil have been used to calm pruritus and relieve irritation and inflammation. Their frequent application to impaired skin could contribute to the sensitization rates seen. Numerous allergic contact dermatitis reactions to peppermint oil, many of which are linked to both perioral and intraoral disorders, have been described. Although peppermint oil is known for its many properties, its role as a sensitizer should be recognised so as to aid in the diagnosis of both dermatitis and oral conditions and to allow the initiation of proper avoidance measures (Herro and Jacob, 2010).

A report of 12 cases of contact sensitivity to the flavouring agents, menthol and peppermint oil, in patients presenting with intra-oral symptoms in association with burning mouth syndrome, recurrent

oral ulceration or a lichenoid reaction is noted. The patients were referred from the Glasgow Dental Hospital over a 4-year period for assessment of the possible contribution of contact sensitivity to their complaints. 5 patients with burning mouth syndrome demonstrated contact sensitivity to menthol and/or peppermint, with 1 patient sensitive to both agents, 3 positive to menthol only and 1 to peppermint only. 4 cases with recurrent intra-oral ulceration were sensitive to both menthol and peppermint. 3 patients with an oral lichenoid reaction were positive to menthol on patch testing, with 2 also sensitive to peppermint. 9 of the 12 cases demonstrated additional positive patch test results. After a mean follow-up of 32.7 months (range 9-48 months), of the 9 patients that could be contacted, 6 patients described clearance or improvement of their symptoms as a consequence of avoidance of menthol/peppermint (Morton *et al.*, 1995).

Positive reactions were observed in 7 of 450 dermatitic patients tested with a patch of 2% Peppermint oil in yellow soft paraffin. Other study revealed reaction on in 6 of 86 dermatitic patients (Ernst, 2000).

Clinical dermal testing demonstrated that 8% Peppermint oil was not a sensitizer and 2% gave a small number of positive reactions in dermatitic patients (Final report on the Safety Assessment of *Mentha piperita*, 2001).

There are some reports referring allergic contact dermatitis after topical application on the skin of peppermint oil. These reactions are the most of the time transient and of mild to moderate sensitivity (Ernst, 2000).

Assessor's comment:

*The following adverse events will be listed in section 4.8 'Undesirable effects' of the WEU monograph on peppermint oil:*

Oral use

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.

Cutaneous use

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.

*The following adverse events will be listed in section 4.8 'Undesirable effects' of the TU monograph on peppermint oil:*

Inhalation

Apnoea, broncho- and laryngoconstriction in hypersensitive patients have been reported. The frequency is not known.

Oral and oromucosal use

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.

Cutaneous and transdermal 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. The frequency is not known.

Irritation of the skin and mucosa of the nose is possible, after local application.

#### **5.4. Laboratory findings**

No data available.

#### **5.5. Safety in special populations and situations**

##### **5.5.1. Use in children and adolescents**

###### Use in children

Importantly, the content of pulegone and menthofuran must comply with the safe limits recommended in the Public Statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1).

The nasal mucosa is an autonomic reflexogenic organ, which has a remote action to the heart, lungs and circulation and may lead to sudden apnoea and glottal constriction. The children less than 2 years old particularly present this reflex, so all the substances with a strong odour must be avoided (Dost and Leiber, 1967).

The occurrence of jaundice in babies exposed to menthol is mentioned in one report at the Medline, advising patients with G6PD deficiency to use menthol cautiously (Natural Standard Research Collaboration, 2005).

According to the SmPCs for herbal medicinal products in EU, the pharmaceutical form suppositories containing the essential oils eucalyptus oil, peppermint oil, mint oil and camphor, cineol, menthol, should not be used in children under the age of 30 months and in children with a history of seizures (febrile or not).

The use of peppermint preparations in open skin areas of small children, especially on the nose, face and chest, is not recommended.

The use in children is described further in the sections 5.5.2. 'Contraindications' and 5.5.3. 'Special warnings and precautions for use'.

##### **5.5.2. Contraindications**

###### Peppermint leaves and peppermint oil

People with hypersensitivity to peppermint preparations or menthol should not use/ take this medicinal product.

###### Peppermint oil

###### **WEU**

Oral use

Patients with liver disease, cholangitis, achlorhydria, gallstones and any other biliary disorders.

###### **TU**

Children under 2 years of age, because menthol can induce reflex apnoea and laryngospasm.

There is no information available regarding the direct relationship of seizures with the inhalation of peppermint oil alone at the dosage recommended in the monograph. For safety reasons HMPC decided to retain as a contraindication the administration to children with history of seizures (febrile or not).

#### Oral and oromucosal use

Hypersensitivity to peppermint oil or menthol.

### **5.5.3. Special warnings and precautions for use**

#### Peppermint leaves

Patients with gastroesophageal reflux (heartburn) should avoid peppermint leaf preparations because heartburn may increase.

Patients with gallstones and any other biliary disorder should be cautious using peppermint leaf preparations.

The use in children under 4 years of age is not recommended due to lack of adequate data.

#### Peppermint oil

Other products containing peppermint oil (e.g. other medicinal products, beverages, confectionery, and chewing gum) 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.

#### Oral use (WEU)

The use in children under 8 years of age is not recommended due to 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.

#### Cutaneous use (WEU)

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.

#### Inhalation, cutaneous use (nasal application), oral and oromucosal use (TU)

The use in children between 2 and 11 years of age has not been established due to lack of adequate data.

#### Oral and oromucosal use (TU)

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.

Patients with gallstones and any other biliary disorder should be cautious using peppermint oil.

Peppermint oil should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract.

#### Cutaneous and transdermal use (TU)

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.

### **5.5.4. Drug interactions and other forms of interaction**

#### Peppermint leaves

Not reported for peppermint leaves.

#### Menthol

A case report describes a possible interaction of menthol cough drops (the active ingredient is menthol) with warfarin, in a 57 year white male waiting for cardioversion for atrial fibrillation. The warfarin dose was adjusted to 7 mg daily to stabilise the INR values. One week later it fell from 2.28-2.68 to 1.45. The patient just used menthol cough drops to treat a flu-like illness. The values returned after stopping the drops (Kassebaum *et al.*, 2005).

Another case report describes the probable interaction of cough menthol drops with warfarin. A reduction on the INR value was observed on a patient taking 50 mg/week of warfarin, from 2.6 to 1.6 and remains stable despite incremental increases of the warfarin dose. The patient reported that he was taking 8-10 menthol cough drops per day during the time period that the INR decreased. Five days after discontinuing the drops, the INR increased to 2.9 (Coderre K, 2010).

#### Assessor's comments

*The dose of menthol responsible for these cases is not known, so it is not possible to consider the relevance for the peppermint oil preparations covered by this report.*

#### Peppermint oil

Use of food or antacids administered at the same time could cause early release of the enteric coated capsules 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.

### **5.5.5. Fertility, pregnancy and lactation**

Adequate data on the use during pregnancy and lactation is not available.

Some studies were performed to assess the prevalence and pattern of herbal medicines use during pregnancy, in each trimester (Bishop *et al.*, 2011; Nordeng *et al.*, 2011, Glover *et al.*, 2003, Pallivalapila *et al.*, 2015), but no safety data about the intake of peppermint oil was included.

In a review of the literature on safety and efficacy of the most commonly used herbs to enable midwives to give evidence-based information to pregnant women a total of 578 expectant mothers at least 20-weeks pregnant were enquired. It was concluded that there is limited documentation on the safety and efficacy of many herbs commonly used during pregnancy. Scientific documentation of the safety and efficacy of peppermint in pregnancy is not available (Holst *et al.*, 2011).

Despite the uncertainties about their safety and effectiveness, herbal preparations and other modalities of complementary and alternative medicine products are widely used during the pregnancy. More studies should be performed to assess their safety on fertility, pregnancy and lactation to provide the health professionals of more reliable information in order to give a scientific based advice to expectant mothers.

Some references report that peppermint may dry up milk secretions (Mills and Bone, 2005).

HMPC concludes that safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. However, in the WEU indication "Herbal medicinal product for the symptomatic relief of mild tension type headache", the use during pregnancy and lactation is not recommended, unless medical advice proposes that the benefit outweighs the potential risk.

No fertility data is available.

### **5.5.6. Overdose**

#### Peppermint leaves

Not reported for peppermint leaves.

An intoxication of a 9 years boy with a menthe (carvone) infusion prepared with 30 leaves is reported. The symptoms were tachycardia and agitation, relieved after 24 hours (Augiseau *et al.*, 1987).

#### Peppermint oil

Oral overdose may cause severe gastro-intestinal symptoms, diarrhoea, 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 massive overdose, the stomach should be emptied by gastric lavage. Observation should be carried out with symptomatic treatment if necessary (MedlinePlus Medical Encyclopedia, 2017).

Inhalation of large doses of menthol may lead to dizziness, confusion, muscle weakness, nausea and double vision (Natural Standard Research Collaboration, 2005).

A near fatal suicidal case due to ingestion of toxic dose of oral peppermint oil is being reported. The patient came in a comatose state and was in shock. She was managed with mechanical ventilation and ionotropes. Her vital parameters reached normal within 8 hours and became conscious by 24 hours. The quantity ingested was not mentioned on the article (Nath *et al.*, 2012).

#### **Drug abuse**

One case of fulminant pulmonary oedema following i.v. injection of 5 ml of peppermint oil was described in a patient with a history of drug abuse (Behrends *et al.*, 2005).

### **5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability**

No studies on the effect on the ability to drive and use machines have been performed.

### **5.5.8. Safety in other special situations**

Not applicable

## 5.6. Overall conclusions on clinical safety

### Peppermint leaves

There is a long experience on the use of preparations of peppermint leaves in adults, with no reports on interactions and overdose. Patients with gastroesophageal reflux (heartburn) should avoid peppermint leaf preparations, because heartburn may increase.

Patients with gallstones and any other biliary disorder should be cautious about using peppermint leaf preparations.

There is no adequate data available with the use in children under 4 years old, pregnancy and lactation. Therefore is not recommended.

### Peppermint oil

The adverse events reported in the doses recommended for the therapeutic indications, in non-allergic adults were generally mild and transient.

When used orally, it may cause heartburn, perianal burning, blurred vision, nausea and vomiting. Heartburn is related with the release of the oil in the upper GI tract, which relaxes the lower oesophageal sphincter, facilitating the reflux. The same occurs in the cases of hiatal hernia. This particular undesirable effect is minimised by an appropriate pharmaceutical formulation administration.

People with gallbladder disease, severe liver damage, gallstones and chronic heartburn should avoid the intake of peppermint oil.

Menthol and peppermint oil caused burning mouth syndrome, recurrent oral ulceration or a lichenoid reaction, by contact sensitivity in the intra-oral mucosa, in sensitive patients.

When applied on the skin, it may cause allergic reactions, as skin rashes, contact dermatitis and eye irritation.

Use in infants or children is not recommended, when inhaled, taken by mouth or if applied on open skin areas, the face or chest, due to the potential toxicity of the product.

Because there is a lack of information about the safety during pregnancy and breastfeeding, the use is not recommended.

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.

## 6. Overall conclusions (benefit-risk assessment)

### Peppermint leaves

*Mentha piperita* leaves is a well-known traditional herbal medicinal product used for centuries inside and outside the European countries.

There is enough literature evidence over a period of 30 years to demonstrate its use for the symptomatic treatment of digestive disorders.

Preparations of peppermint leaves demonstrated a relaxant and antispasmodic effects on gastrointestinal tissue and antinociceptive effect on animal models. Mixed flavonoids showed choleric activity in dogs. Also the peppermint oil present a similar action in animal and clinical studies. The carminative effect is due to a reduction in the tonus of the esophageal sphincter.

These pharmacological actions supports the traditional use on digestive disorders and the therapeutic indication proposed on this assessment report for the monograph – symptomatic relief of digestive disorders such as dyspepsia and flatulence.

According to the Ph. Eur., the whole drug contains a minimum of 12ml/kg of essential oil (EO) and a minimum of 9ml for the cut drug. Considering the density of essential oil (based on relative density 0.9-0.916 g/cm<sup>3</sup> according Ph. Eur. version 8.1 (2014)) ref.: 0405 the content of EO is of 10.992g/kg leaves.

Some articles mention that the infusions may contain 20-28% of EO. Given the relative amount of pulegone (<3%) and menthofuran (1-8%) present in the essential oil, we may find a minimum of 0.0216mg/g and a maximum of 0.3386mg/g of leaves in the infusion, of both.

Administering the posology for peppermint leaf infusions proposed, a minimum of 0.0972mg/day (4.5g of leaves) and a maximum of 3.047mg/day (9g) for adults and a minimum of 0.065mg/day (3g) and 1.693mg/day (5g of leaves) for children of pulegone+menthofuran can be found.

There is no information on the content of pulegone and menthofuran in the extracts.

Toxicity studies and clinical information gives no reason for concern, with the recommended dosage range for oral use, reflecting the dose limit of pulegone and menthofuran proposed. The special warnings advise patients with cholangitis, gallstones and any other biliary disorders to be cautious using peppermint leaf preparations.. Patients with gastroesophageal reflux (heartburn) should avoid peppermint leaf preparations.

There are no reports on interactions.

There is no adequate data available with children under 4 years old and in fertility, pregnancy and lactation.

There are no adequate tests for reproductive toxicity, genotoxicity and carcinogenicity for peppermint leaves preparations. Therefore an EU list entry cannot be supported.

#### Peppermint oil

##### WEU

Peppermint oil has been used widely since many decades ago as a digestive and carminative. As an authorised medicinal product for oral use, peppermint oil has been prescribed under the approved indications "for the symptomatic relief of symptoms related with irritable bowel syndrome" or "for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain". It has also been used topically, as a medicinal product, for the symptomatic treatment mild to moderate tension headache.

According to the preclinical and clinical data assessed and presented in this report, peppermint oil demonstrated an antispasmodic action of the smooth muscle of the GI tract, relieving minor spasms, flatulence and abdominal pain.

The treatment of IBS is complex, with unpredictable periods of relapse and remission, presenting a variety of symptoms. There is a lack of adequately studied and licensed medications in Europe for this indication. Moreover, there is a wide history of unsuccessful drug development programmes in the field, and the number of Marketing Authorisation Applications for the indication has been very low during the past decade (Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome EMA/CHMP/60337/2013).

Some studies on IBS in the literature show methodological problems, such as use of non-validated scales, the randomization procedure is not clear, lack of adequate washout period, limited treatment period (2-4 weeks), small sample sizes and unclear diagnostic criteria. Despite this, some interventions with peppermint oil have been shown to be clinically effective in the treatment of symptoms of IBS, in several randomised well designed controlled trials.

The peppermint oil, by laboratory tests, seems to exert some actions on mechanisms associated with the pathophysiology of tension headache, producing an analgesic effect, after applying a 10% solution on the forehead and the temples of the patients. The clinical studies are small but the results demonstrated the efficacy of peppermint oil on the episodic tension-type headache, according to the IHS classification.

## TU

There is a lack of clinical studies to confidently conclude about the efficacy on the treatment of cough and colds for *Mentha x piperita*, folium, as well as for peppermint oil. The symptomatic relief of localised muscle pain and pruritic conditions of the intact skin are not supported by clinical studies, allowing just the traditional use. There is enough information on the time of use, posology and method of administration to assure safe use of the product.

Humans are exposed to pulegone and menthofuran in herbal medicinal products and food, and as part of the essential oil in flavourings, confectionery, and cosmetics. Estimates of per capita intakes are widely variable.

According to the conclusions of the "Public statement on the use of herbal medicinal products containing pulegone and menthofuran, EMA/HMPC/138386/2005 Rev. 1, the HMPC concludes that an intake of pulegone + menthofuran up to 37.5 mg/person/day, for an adult of 50 kg body weight, can be accepted for herbal medicinal products as a lifetime intake.

For children, the daily amount of pulegone + menthofuran has to be adjusted according to the body weight of the age group: e.g. body weight of 20 kg would lead to an acceptable daily intake of 15 mg/day, (life-long exposure) or 30 mg/day for a short-term exposure (less than 1 year).

For treatment durations of less than 1 year an intake (pulegone + menthofuran) of 75.0 mg/day can be accepted. In the case of intermittent dosing, the acceptable daily intake should be based on the total number of dosing days instead of the time interval over which the doses are administered. For example, a drug administered once per week for 5 years (i.e., 260 dosing days) would have an acceptable intake per dose of 75.0 mg.

No quantitative data concerning absorption of pulegone and menthofuran through the skin exist although it is known that pulegone has been used as a "penetration enhancer". It is to ensure that the sum of pulegone and menthofuran within the daily dose is <37.5 mg for adults. The short term use (maximum 14 days) is restricted to intact skin. Higher contents within the products would be possible if for the relevant product (means the relevant matrix, because absorption might be greatly influenced by the excipients, for instance essential oils as enhancers) low absorption rates can be shown, not exceeding the daily intake of 37.5 mg for adults (EMA/HMPC/138386/2005 Rev. 1).

The calculations on the content of pulegone+menthofuran were assessed according to the posology found as plausible for traditional use and based on the clinical studies for well-established use.

## **Pulegone/Menthofuran content according to the posology**

### **Traditional use**

## Inhalation and oromucosal use

TRAD Adolescents, adults	total daily dose (ml)	Total daily dose (g) <sup>1)</sup>	Pulegone/menthofuran intake (mg) <sup>2)</sup>	EMA/HMPC/138386/2005 Rev. 1 1 mg	EMA/HMPC/138386/2005 Rev. 1 1 mg
<u>Inhalation</u>				37.5 long term (life long)	75 Up to one year from one given MP
0.08 - 0.16 ml of essential oil up to three times daily	0.24-0.48	0.22-0.454	24-50		
Oromucosal use					
0.08 - 0.12 ml essential oil, 3 - 4 times per day (0.2 - 0.5 ml)	0.32-0.48	0.288-0.454	32-50		

<sup>1)</sup> relative density is 0.900-0.916

<sup>2)</sup> Ph. Eur.: menthofuran 1-8%, pulegone maximum 3% (g/g) = total 11% = 11g/100g = 0.11 g/gr = 110 mg/gr

## Conclusion

The recommended dose is within the limits set by EMA/HMPC/138386/2005 Rev. 1.

The recommended dose is within the limits if the specifications of oil are set at 37.5/50 x 11% = 8.25% for menthofuran + pulegone. If limits are set for menthofuran at 1.0-5.25% and pulegone maximum 3% the oil is still in compliance with the Ph Eur monograph.

## Cutaneous use

### Ointment tube with mouth with diameter of 0.5 cm

- **1 cm of the ointment** corresponds to 0.196 cm<sup>3</sup> ~ 0.2 cm<sup>3</sup> which **corresponds to 0.18 g** (if we calculate with relative density 0.9; relative density of olive oil is 0.913)

	<b>Ointment 20% - 1 cm of the ointment = 4 mg of pulegone and menthofuran</b>	
	Daily dose	Single dose
Adult (50 kg) 37.5 mg pulegone+menthofuran/day	9.375 cm	3.125 cm

	<b>Ointment 15% - 1 cm of the ointment = 3 mg of pulegone and menthofuran</b>	
	Daily dose	Single dose
Adolescent 12 years (~35 kg of body weight) 26.25 mg pulegon+menthofuran /day	8.7 cm	2.9 cm

	<b>Ointment 10% - 1 cm of the ointment = 2 mg of pulegone and menthofuran</b>	
	Daily dose	Single dose
Child 4 years (~ 15 kg of body weight) 11.25 mg pulegone+menthofuran /day	5.6 cm	1.9 cm

### Ointment tube with diameter of 0.6 cm

- 1 cm of the ointment corresponds to 0.2826 cm<sup>3</sup> which corresponds to 0.254 g

	Ointment 20% - 1 cm of the ointment = 4 mg of pulegone and menthofuran	
	Daily dose	Single dose
Adult (50 kg) 37.5 mg pulegone+menthofuran/day	6.7 cm	2.2 cm

	Ointment 15% - 1 cm of the ointment = 3 mg of pulegone and menthofuran	
	Daily dose	Single dose
Adolescent 12 years (~ 35 kg of body weight) 26.25 mg pulegone+menthofuran /day	6.2 cm	2.1 cm

	Ointment 10% - 1 cm of the ointment = 2 mg of pulegone and menthofuran	
	Daily dose	Single dose
Child 4 years (~ 15 kg of body weight) 11.25 mg pulegone+menthofuran /day	4 cm	1.3 cm

### Conclusion

The posology for inhalation (liquid preparation) and oromucosal use is acceptable as the recommended doses are within the limits set by EMA/HMPC/138386/2005 Rev. 1.

The same safe limit is applied to the daily dose of the preparations for cutaneous and transdermal use. In this case, the amount of the preparation of the single dose can be controlled by, for example, an appropriate device, to prevent the possibility of exceeding that limit.

### Well Established Use

#### Oral use

WEU Adults and adolescents	total daily dose (ml)	Total daily dose (g) <sup>1)</sup>	Pulegone/menthofuran intake (mg) <sup>2)</sup>	EMA/HMPC/138386/2005 Rev. 1 mg	EMA/HMPC/138386/2005 Rev. 1 mg
0.6 – 1.2 ml daily of essential oil divided in 2 - 3 single doses	0.6-1.2	0.54-1.1	59-121	37.5 long term (life long)	75 Up to one year from one given MP

<sup>1)</sup> relative density is 0.900-0.916

<sup>2)</sup> Ph. Eur.: menthofuran 1-8%, pulegone maximum 3% (g/g) = total 11% = 11g/100g = 0.11 g/gr = 110 mg/g

The recommended doses are only within the limits set by EMA/HMPC/138386/2005 Rev. 1 if the specifications of oil are set at  $75/121 \times 11\% = 6.82\%$  for menthofuran + pulegone.

If limits are set for menthofuran at 1-3.82% and pulegone maximum 3% the oil is still compliance with the Ph. Eur. monograph.

For lifelong intake the limits should be set at  $37.5/121 \times 11\% = 3.4\%$  of menthofuran + pulegone.

For lifelong intake the limits should be set at  $37.5/59 \times 11\% = 6.9\%$  of menthofuran + pulegone.

WEU Children 8-12 years	total daily dose (ml)	Total daily dose (g) <sup>1)</sup>	Pulegone/menthofuran intake (mg) <sup>2)</sup>	EMA/HMPC/138386/2005 Rev. 1 mg	EMA/HMPC/138386/2005 Rev. 1 mg

0.2 ml of essential oil three times daily	0.6	0.54	59	15 mg 20 kg/bw long term (life long)	30 mg 20 kg/bw Up to one year from one given medicinal product
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The recommended dose is only within the limits set by EMA/HMPC/138386/2005 Rev. 1 if the specifications for the oil are set at  $30/59 \times 11\% = 5.5\%$  for menthofuran + pulegone.

For life-long intake the limits should be set at  $15/59 \times 11\% = 2.79\%$  of menthofuran + pulegone.

In the safety evaluation proposed in the "Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97 Rev. 1, Set 2014), "because treatment of IBS will require intermittent or continuous long-term use of medication, it is necessary to have long-term safety data with an observation period of at least 12 months available in adequate numbers to accurately assess the safety of the medicinal product. For products intended for long-term continuous use, this will mean the observation of 12 months on active treatment, whereas for compounds with an intermittent use, the time on active drug can be reduced to a period of at least 6 months, with the documentation of at least 12 months of observation (whichever comes first). Safety data collected in sub-populations of IBS patients may not support authorisation in a wider patient population. The safety evaluation in clinical trials for IBS is in general not different from other investigational products under development and should be focused according to the pharmacology of a compound. The main focus should be on the evaluation of gastrointestinal events (...). The focus may however change, depending on the primary pharmacology of a compound (...)."

The adverse effects of peppermint oil enteric coated capsules were generally mild and transient in the clinical studies as well as in pharmacovigilance the reports. Nevertheless, the preclinical data on pulegone and menthofuran requires an alerted pharmacovigilance of peppermint oil products with regard to potential toxicity.

The content of 75 mg of pulegone+menthofuran in medicinal products has the time limit of intake of 1 year. This recommendation is not adequate for a condition such as "minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome", which requires intermittent or continuous long-term treatment. The pulegone+menthofuran limit of 37.5 mg, which allows a lifetime intake, assures a safer treatment of the symptoms related with IBS, providing a positive benefit-risk assessment.

For adults and adolescents, the content of the maximum daily dose (1.2ml) requires peppermint oil with a limit of 3.4% of menthofuran + pulegone. The minimum dose (0.6ml) requires peppermint oil with the limit of 6.9% of menthofuran + pulegone.

In children, the limit for a lifetime intake of 0.75 mg/kg/day of menthofuran + pulegone can be accepted. However, at the proposed posology (0.6ml/day) included in the monograph, the peppermint oil would need to be restricted to batches complying with a limit of 2.79% of menthofuran + pulegone. It is evident from data of commercial batches (supplied in confidence by EDQM) that most batches from currently available commonly traded natural peppermint oils would exceed such a maximum limit for menthofuran + pulegone. Whilst HMPC recognises that for this reason use in children may not be feasible, it has decided to include children in the posology as the use is supported by clinical trial data and selection of suitable peppermint oil batches may be possible.

For the traditional use, the posology proposed for oromucosal, inhalation (0.08- 0.48 ml/day) and cutaneous use (from 1-20%) depending on the preparation or age, as there are no proven beneficial effects, should comply with the safe limit for life intake of pulegone and menthofuran, proposed on the

“Public statement on the use of herbal medicinal products containing pulegone and menthofuran, EMA/HMPC/138386/2005 Rev. 1, for long term intake, in adults and children.

The List Entry, for safety reasons, should be limited to cutaneous use, respecting the safe limit proposed in the “Public statement on the use of herbal medicinal products containing pulegone and menthofuran, EMA/HMPC/138386/2005 Rev. 1, for adults and children.

The indications proposed, for well-established use are:

#### Indication 1)

Oral use

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.

Proposed ATC code: A03AX

#### Indication 2)

Cutaneous use

Herbal medicinal product for the symptomatic relief of mild tension type headache

Proposed ATC code: N01BX

The indications proposed, which demonstrated plausibility for traditional use, are the following:

Cutaneous and transdermal use:

- I. For the relief of symptoms in coughs and colds;
- II. For symptomatic relief of localised muscle pain;
- III. For the symptomatic relief of localised pruritic conditions in intact skin.

Inhalation:

- I. For the relief of symptoms in coughs and colds.

Oral and Oromucosal use:

- I. For the relief of symptoms in coughs and colds.

## **Annex**

### ***List of references***