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

Draft – 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)	*Mentha x piperita* L. Whole or cut dried leaf of *Mentha x piperita* L.
Herbal preparation(s)	<u>*Mentha x piperita*, 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>*Mentha x piperita*, aetheroleum</u> (TU and WEU) Essential oil (obtained by steam distillation from the fresh aerial parts of the flowering plant).
Pharmaceutical form(s)	<u>*Mentha x piperita*, 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>*Mentha x piperita*, aetheroleum</u> (TU) Herbal preparations in liquid or solid dosage forms for oral and oromucosal use.

	Herbal preparations in liquid dosage forms for inhalation.
	Herbal preparations in liquid or semi-solid dosage forms for cutaneous or transdermal use.
	Mentha x piperita, aetheroleum (WEU)
	Herbal preparations in solid gastro–resistant dosage forms for oral use.
	Herbal preparations in liquid or semi-solid dosage forms for cutaneous use.
Rapporteur(s)	Helena Pinto Ferreira
Peer-reviewer	Ioanna Chinou

Note: This draft assessment report is published to support the public consultation of the draft revised European Union herbal monographs on _Mentha x piperita_, folium and _Mentha x piperita_, aetheroleum. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monographs. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monographs .

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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 90cm.

According to the European Pharmacopoeia, it contains a minimum of 12 mL/kg of essential oil for the whole drug and minimum 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 & Loomis 1973).

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

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 (maxim 3%), carvone (maximum 1%) . The ratio of 1,8-cineole content to limonene content is 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 (Mackay, 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 min (tea preparation with boiling water).

In a publication of Wiśniewski (1962), the determined content of essential oil in Menthae folium (the herbal substance) was 1.5%. In decoctions, upon the modified method described in the Supplement 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 by the first time in peppermint tea. These findings could be attributed to the different analytical approach employed, mainly to 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 ($C_{18}H_{16}O_8$; M_r 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 sensation of cold.

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 (maxim 3%), carvone (maximum 1%) and isopulegol (maximum 0.2%). The ratio of 1,8-cineole content to limonene content is 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 , toxline) 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, in special 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 of **peppermint leaf**

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
Tincture 1:20 *Mentha x piperita* L. folium, extraction solvent ethanol 90% V/V containing 65mg/g peppermint oil	Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence	20 oral drops 3x/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 Registered since 1995
Tincture 1:20 *Mentha x piperita* L. folium, extraction solvent ethanol 90% V/V, also contain Mentha piperitae aetheroleum 59 mg/g	Symptomatic relief in case of gastro-intestinal disorders (dyspepsia and flatulence).	Adults and adolescents from 12 years, 10 -15 drops max 3 times per day. Children 8- 12 years 8-10 drops max 3 times per day.	WEU Latvia since 1970
Peppermint leaf for herbal tea (infusion)	Traditional herbal medicinal product for the symptomatic relief of digestive disorders	**A)** 2 g in 100 ml of boiling water as a herbal infusion	Poland Before 1980

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	such as dyspepsia and flatulence	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 of **peppermint oil**

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
Peppermint oil	*Internal use:* Treatment of gastrointestinal disorders like flatulence, mild spasm of the gastrointestinal and bile tract, irritable bowel syndrome	*Elderly, adults and adolescents:* *Oral use:* 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.

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	Intake or inhalation: Treatment of cough and cold symptoms of the upper respiratory tract *External use:* Rheumatic symptoms and myalgia; treatment of the symptoms of itching and urticaria in case of sensitive skin.	*Inhalation:* 2-3 times 3-4 drops daily into 300 ml hot water. *Cutaneous use:* 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 spray 4 times daily a spray = 0.125 mg of essential oil	TU, France since 2005 THMP since 2012
Peppermint oil	Symptomatic treatment	Gastro-resistant	WEU, Belgium

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	of minor spasm of the gastrointestinal tract, flatulence and abdominal pain.	capsule, soft (0.2 ml per Capsule PO) Child >12 years, adult, elderly: Oral use, 1 capsule, 1-3x/day, if necessary max 2 capsules, 3x/day Children 8 – 12 years: 1 capsule, max 3x/day	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 symptoms in coughs and colds. Cutaneous use: Symptomatic treatment of neuralgic pain and muscle pain.	a) Oral use (100% essential oil): a + b) 3-4 drops 2-3 times/day Inhalation (100% essential oil):: 3-4 drops in 300ml hot water, 2-3 times/day Cutaneous use (100% essential oil):: Some drops locally	WEU/MA, Germany since 1978
Peppermint oil	Oral use:	a, b, c) 3-4 drops of	Standardzulassung

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	a) Symptomatic relief of minor spasms of the gastrointestinal and biliary tract. b) For the relief of symptoms of coughs and colds. c) Inflammation of the oral mucosa Inhalation: Relief of symptoms in coughs and colds. Cutaneous use: a) Symptomatic treatment of neuralgic pain and muscle pain. Coughs and colds.	essential oil (100%) in a glass of warm water or on a sugar cube 2-3 times/day Inhalation: 3-4 drops of essential oil (100%) in hot water Cutaneous use: Some drops to be applied locally.	Germany, since 1982
Peppermint oil	Symptomatic relief of minor spasms of upper intestine	Coated tablet adults adolescents: 1-2 tablets (37.5-75 mg) 3 times/day	WEU, Germany 1978-2008
Peppermint oil	Symptomatic treatment neuralgic pain, in mild to moderate tension headache	Cutaneous liquid local application of the forehead with an applicator every 15 min up to 3 times /day	WEU/MA Germany since 1996
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 /day	WEU Germany 1978-2011
Peppermint oil	Symptoms of IBS like abdominal pain, flatulence, repletion, obstipation and diarrhea.	Gastro-resistant capsule, soft adults and adolescents: 1 capsule (182 mg essential oil) 3 times /day	WEU/MA, Germany since 1983
Peppermint oil	Symptomatic relief of minor spasms of the gastrointestinal and	gastro-resistant capsule, soft adults and adolescents:	WEU/MA, Germany, since 1991

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	biliary tract.	1 capsule (182 mg essential oil) 3 times /day	
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 15min until 2 h or 3 times /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 x 3 times daily when discomfort is severe. Duration of use 1-2 weeks . Not to be used longer than 2- 3 months per course.	WEU/MA Ireland Since 1985 WEU/MA Czech Republic since 1997
Peppermint oil	Herbal medicinal product for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain	Gastro-resistant soft capsule Gastro-resistant soft capsule (0.2 ml per capsule peppermint oil) For oral use Adolescents over 12 years of age, adults and elderly 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. Children between 8 to 12 years of age 1 capsule (0.2 ml in gastro-resistant	WEU/MA, Netherlands since 2012

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		Duration of use: 2-4 weeks . Not be used longer than 3 months per course .	
Peppermint oil	Symptomatic treatment of spasmodic gastro-intestinal complaints, flatulence and abdominal pain, especially in patients with irritable colon disease.	Gastro-resistant capsule, soft (0.2 ml per capsule peppermint oil) Oral use; Children aged 8 to 12 years: 1 capsule (182 mg *Menthae piperitea aetheroleum*) up to 3 times daily, before meals; Adolescents , adults and elderly: 1 to 2 capsules up to 3 times daily before meals. 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.	WEU/MA Poland, before 2000
Peppermint oil	The product is indicated for the treatment of discomfort, abdominal pain and distension in patients with irritable bowel syndrome	Gastroresistant capsules (187 mg peppermint oil) Oral use; adults and adolescents 1 capsule 3 times daily to be used 30 to 60 minutes before meal; Up to 2 capsules 3 times daily. Not to be taken longer than 2 to 3 months	Austria, since 1986 WEU/MA
Peppermint oil	Symptomatic relief of minor spasms of the GI tract, flatulence and abdominal pain, especially in patients with irritable bowel	1 capsule contains 200 µl = 187 mg *Menthae pip. Aetheroleum* Oral use adults, adolescents:	WEU, Austria, since 2005

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	syndrome	3 x daily 1-2 capsules; children 8-12 years: up to 3 x 1 capsule daily	

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[1]	2-4 y	0.2	2
Children and adolescents[1]	5-9 y	0.3	3
Adolescents[1]	10-14 y	0.6	6
Adolescents and adults [1,2]	≥ 14 y	1.2	12

[1] 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.
[2] 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 20

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 since 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

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
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 grams) 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	ESCOP, 2nd edition, 2003, Wichtl (2002) and Bradley 1992 (adults) and Dorsch et al. 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/day	Germany (Blumenthal published 30.11.85, amended 13.3.90 and 1.9.90)
Infusion Tincture (1:5, 45% ethanol)	Symptomatic treatment of dyspepsia, flatulence and intestinal colic.	1.5-3 g (one tablespoon) dried leaves in 150ml water, 3 times daily before meals 2-3 ml three times daily	WHO monographs on *Menthae piperitae 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 (where relevant) 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.	Oral use Digestive disorders: 0.02-0.08ml (1-4 drops up to three times/daily in dilute aqueous preparations (e.g. peppermint water or emulsion) , or as drops on a lump of sugar. For IBS: 0.2-0.4 ml three times daily in enteric coated capsules Children Oral use: for digestive disorders, proportion of adult dose according to body weight	ESCOP monograph 2nd edition 2003, citing Stahl-Biskup, 1993, British herbal Ph 1983 Hansel 1999, Fintelman et al 1993,
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	Relief of coughs and colds;	Inhalation 3-4 drops added to hot water	ESCOP monograph 2nd edition 2003, citing

	Tension-type headache; Symptomatic relief of rheumatic complaints; Pruritus, urticaria and pain in irritable skin conditions.	10% solution rubbed on to the skin of forehead and temples. 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 to the affected area.. Children 4-10 years Semi-solid preparations 2 -10%; hydroethanolic preparations 2-4% - Children 10-16 years Semi-solid preparations 5 - 15%; hydroethanolic preparations 3 – 6%	Stahl-Biskup, 1993, Hansel 1999, Gobel 1996, Dorsch et al 2002, Gilchrest 1982
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 0.15-1.25ml, or *aqua* in doses of ½ - 1 Libra	Indian Materia Medica by Dr K. M. Nadkarni's (3rd 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	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	WHO monographs 2002

	treatment of catarrh and coughs	By inhalation: 3– 4 drops essential oil in hot water. Lozenges: 2– 10 mg essential oil per lozenge	

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, being a popular remedy inside and outside European countries, for its antispasmodic, choleretic 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**

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Herbal substance or Comminuted herbal substance	Dyspepsia, flatulence, intestinal colic, biliary disorders	Usually prepared with one or two teaspoons (1.5 to 3.0 grams) 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	**A)** 2 g in 100 ml of boiling water as a herbal infusion Children aged 4 to 12 years: 100 ml of herbal infusion 1-2 times daily; Adolescents 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	Poland Before 1980

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		daily; Children –adolescents aged 10 to 16 years: 200 ml of herbal infusion 2-3 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 to 2.0g 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- 6g

Adults, elderly

Herbal tea: 1.5 to 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 (PO) 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/day	Germany, MA, since 1978
Peppermint oil	For the relief of coughs and colds	Inhalation 0.08 - 0.16 ml of essential oil up to three times daily Daily dose 0.08 – 0.48 ml Oral and oromucosal use 0.08 - 0.12 ml essential oil, 3 - 4 times per day Daily dose 0.24 - 0.48 ml Cutaneous use *Adults and elderly* 5– 20% essential oil in dilute, semisolid or oily	Blumenthal et al 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	*Internal use:* Treatment of gastrointestinal disorders like flatulence, mild spasm of the gastrointestinal and bile tract, irritable bowel syndrome *Intake or inhalation:* Treatment of cough and cold symptoms of the upper respiratory tract *External use:* Rheumatic symptoms and myalgia; treatment of the symptoms of itching and urticaria in case of sensitive skin.	*Adolescentsadults and Elderly,:* <u>Oral use</u>: Average daily dose: 6-12 drops (2-3 times daily 3-4 drops). <u>Inhalation</u>: 2-3 times 3-4 drops daily into 300 ml hot water. <u>Cutaneous use</u>: Several drops should be applied directly to the affected skin parts	TU Hungary Since 14.06.1991 as a healing product Since 26.05.2005 as TU.
Peppermint oil	Oral use: d) Symptomatic relief of minor spasms of the gastrointestinal and biliary tract. e) For the relief of symptoms of coughs and colds. f) Inflammation of the oral mucosa Inhalation: Relief of symptoms in coughs and colds. Cutaneous use: b) Symptomatic treatment of neuralgic pain and muscle pain.	<u>Oral use</u> a, b, c) 3-4 drops of essential oil (100%) in a glass of warm water or on a sugar cube 2-3 times/day <u>Inhalation</u>: 3-4 drops of essential oil (100%) in hot water <u>Cutaneous use</u>: Some drops to be applied locally.	Standardzulassung Germany Since 1982

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Coughs and colds.		

Table 3c: Overview of evidence on period of medicinal use of **peppermint oil (PO) 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	Oral use: 187 mg gastro-resistant capsules: 1 capsule contains 200 µl = 187 mg Menthae pip. Aetheroleum oral; adults: 3 x daily 1 capsule	Austria, MA, 1986, 2005 Ireland, MA, 1985
		children 8-12 years: up to 3 x 1 capsule daily	Austria, WEU, 2005
		182 mg essential oil (=0.2 ml) (gastro-resistant capsule) oral; adolescents and adults: 3 x daily 1 capsule	Germany, MA, 1983
Peppermint oil (PO)	Symptomatic treatment neuralgic pain, in mild to moderate tension headache	Cutaneous use PO in ethanol solution in an applicator, treatment of the forehead every 15 min, 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 safety profile and are in accordance with the traditional use, based on the literature and on the 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 have the conditions required for the WEU are discussed in the chapter 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 (EMEA/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 choleretic activity

<u>Peppermint leaves</u>

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/litre 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_{50}, 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 (by Schermann 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. 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 choleretic activity in dogs. Flavomentin, a flavonoid preparation from peppermint leaf, stimulated bile secretion and the synthesis of bile acids 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).

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

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

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 was also tested, taking out three components. 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$_3$ receptors (serotonin receptor subtype) three different *in vitro* models were used : [14C]guanidinium influx into N1E-115 cells which express 5-HT3 receptors, isotonic contractions of the isolated rat ileum and equilibrium competition binding studies using a radioactively labelled 5-HT3 receptor antagonist ([^{3}H]GR65630) (3-(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1-propanone). Both peppermint oil and (-)-menthol inhibited [14C]guanidinium influx through 5-HT$_3$ receptor channels as well as contractions of the ileum induced by serotonin. Neither the peppermint oil nor (-)-menthol, however, was able to displace [^{3}H]GR65630 from 5-HT$_3$ binding sites. It may be concluded that peppermint oil and (-)-menthol exert their antiemetic effect at least partly by acting on the 5-HT$_3$ 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$_{50}$ was 83-91 mg/L (Reiter & Brandt, 1985)

Peppermint oil emulsified with tween, 1% in aqueous solution, relaxed chemically contracted guinea pig taenia coli (I$_{50}$: 22.1 µg/mL) and inhibited spontaneous activity in the guinea pig colon (I$_{50}$: 25.9 µg/mL) and rabbit jejunum (I$_{50}$: 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 to inhibit non-competively 5 –hydroxytriptamine (serotonin) and the substance P induced smooth muscle contraction (Hills et al, 1991).

Both menthol and peppermint oil inhibited specific [3H] nitrendipine and [3H] 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 $^{45}Ca^{2+}$ uptake experiments. Binding of menthol and peppermint oil, studied at 78 µg/ml, was competitive against [3H] nitrendipine in both smooth muscle and synaptosome preparations. The data indicate that both menthol and peppermint oil exert Ca^{2+} channel blocking properties which may underlie their use in irritable bowel syndrome. The authors conclude that Ca^{2+} channel antagonism may not be the only pharmacological effect of menthol and peppermint oil contributing to intestinal smooth muscle relaxation (Hawthorn et al, 1988).

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 anaesthetized 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 min 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

To characterize the effects of peppermint and caraway oil individually and in combination on the visceral nociception in a rat model of post-inflammatory hyperalgesia, a study was performed. 28 male Lewis rats were randomized 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 was found of up to 50 % compared to placebo. Individually both oils had no significantly 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 to 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 (1mg of menthol/kg added to the water vaporizer, corresponding to systemic absorption of not over 20 µg/kg body weight) was given to rabbits anesthetised 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 &, 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 piperitae* leaves showed a high oxygen radical absorbance capacity.

Water-soluble extracts from the *Mentha* species among which *M. piperita* were 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-catalyzed 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 & 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 & 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 4-8mg/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 $MIC_{50} \pm 100 \mu g/ml$ (Mahady et al, 2000).

In a study by Baszczyk at 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 (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 titters 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 reduced 82% and 92% respectively. Higher concentrations reduced virus titters for more than 90%. The 50% inhibitory concentration (IC_{50}) 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 antiplasmid activity, demonstrating a synergistic additive interaction with oxytetracycline (Schelz et al. 2006).

In a study by Mimica-Dukic et al (2003), is described 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. The content of essential oils expressed in percentage 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 determined by GC-MS and TLC. The most powerful antibacterial activity was demonstrated by *M. piperita*, in particular against multiresistant strain of *Shigella sonei* and *Micrococcus flavus* ATTC 10240. All tested oils showed significant fungistatic and fungicidal activity, considered higher than those of Bifonazol.

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 an effect, which was dose-dependent, 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 3µg/ml. The water, 50% ethanol eluate, separated by column chromatography also shows a similar effect at a dose of 1µg/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 (Inoue et al, 2001).

Following these results, the same authors 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-7-0-rutinoside showed a dose-related inhibitory effect of an antigen induced nasal response at doses of 100 and 300 mg/kg.

CNS action

<u>Peppermint leaves</u>

An aqueous extract of peppermint leaf (50 g of dried leaf infused for 10 min 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 in rats, in the behavioural tests, a biphasic effect with initial stimulation, followed by depression. 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

<u>Peppermint oil</u>

The effect of pre-treatment with essencial oils administered 60 minutes prior to intraperitoneal injection of a lethal dose of pentylenetetraol-(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. No seizures 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

<u>Peppermint leaves</u>

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 logia et al, 1990).

Chemopreventive effects

<u>Peppermint leaves</u>

In studies where some agents induced the carcinogenicity, peppermint showed a preventive and a reduction effect. A study was performed comparing a powdered tobacco mixture (15g) with and without 15g 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/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 on 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 & Ashok (2001), on the papillomagenesis of the skin induced by 7,12-dimetylbenz (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 were evaluated by using 9-week medium term model of benzo[*a*]pyrene (BP)-induced lung tumors in new born 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), 1g/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 at 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 1g/Kg peppermint extract, within 20 days post-irradiation at 8 Gy (Mckay& 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 administrated to group III at the same 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 high 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 ($P = 0.001^{**}$). The authors 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 these 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, administrated after an initiating 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 refer 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. Further, 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 Shama et al (2006). Pre and post treatment of *Mentha* with arsenic alters the biochemical parameters in the liver, declining 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

<u>Peppermint oil</u>

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 effectivity may be modified. (Hawthorn, 1988)

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

In another study the influence of acute and chronic intake of peppermint oil (PO – *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 PO were 0.1 and 0.2 mL/kg. The authors report that chronic PO intake (in both doses) led to significant decrease of analgesic effect of codeine, while acute intake of PO did not change this effect. Acute PO pretreatment in higher dose caused significant prolongation of pentobarbitone-induced sleeping time, while it was significantly shortened by chronic PO pretreatment at the same dose. Midazolam effect was enhanced and prolonged significantly by chronic PO intake at higher dose, while acute intake of PO did not change this effect. Gut motility was increased only by acute intake of higher PO dose. Regarding the fact that PO produces changes in tested drug effects, the authors concluded that the interaction between drugs and phytopreparations containing PO should be additionally followed/confirmed in humans (Samojlik et al, 2012).

3.1.5. Conclusions

<u>Peppermint leaves</u>

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 on bile secretion in dogs have 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 carminative effect appears to be related with a reduction in the tonus of the oesophageal sphincter, by peppermint leaf extracts.

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

<u>Peppermint oil</u>

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. 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, according to the authors.

Peppermint oil

Dermal absorption

The absorption rate for peppermint oil was measured after the application of eserine in a peppermint oil vehicle, to a 2.2cm^2 shaved area on the abdomen of mice. The latent period between application and the eserine-induced signs, gave the absorption rate of peppermint oil, which was of 58 minutes (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 min 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*. Metabolites isolated and characterized from the urine of rats after oral administration (800 mg/kg of body weight/day) of l-menthol were the following: p-menthane-3, 8-diol (II), p-menthane-3, 9-diol (III), 3, 8-oxy-p-menthane-7-carboxylic acid (IV), and 3, 8-dihyroxy-p-menthane-7-carboxylic acid (V). *In vivo*, the major urinary metabolites were compounds II and V. 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) reduced their levels considerably, 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 O2. 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 I-menthol to compound II in the presence of NADPH and O2. L-Menthol elicited a type I spectrum with control (Ks = 60.6 microM) and PB-induced (Ks = 32.3 microM) microsomes whereas with 3MC-induced microsomes it produced a reverse type I spectrum (Madyastha and Srivatsan , 1988).

One randomized 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 determined the pharmacokinetics of felodipine and dehydrofelodipine. 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 (100mg/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 I-menthol in rats indicated about equal excretion in feces and urine. The main metabolite identified was menthol-glucuronide. Additional metabolites are mono- or di-hydroxylated menthol derivatives (Grigoleit & Grigoleit, 2005a).

<u>Pulegone and menthofurane</u>

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 Rev1).

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 in feces and urine of essential oil compounds. 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 Rev1).

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_{50} of peppermint oil U.S.P. in fasted Wistar male rats after 24 h was found to be 4441 ± 653 mg/kg and after 48h 2426 mg/kg (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 ($p<0.01$), on 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 was investigated. AST and ALT activities were increased, but not statistically significant 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. The histopathological changes were observed, slight on 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 Rev1.

Menthone

In a 28 days study rats were dosed orally with 0, 200, 400 and 800 mg menthone/kg bw/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 seen histopathologically 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/day (HED = <32 mg/kg) (Madsen et al., 1986).

3.3.3. Genotoxicity

Peppermint oil (PO)

Salmonella strains TA1537, TA98, TA1535 and TA100 were used to test PO at concentrations of 800, 160, 32 and 6.4 µg per plate. No mutagenic properties were observed until 160 µg per plate. 800 µg PO/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 i*n 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).

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 Rev1).

<u>Menthol</u>

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)

<u>Menthone</u>

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)

<u>Pulegone and Menthofuran</u>

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

<u>Peppermint oil</u>

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/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 reduced initially in animals of the 16-mg/kg/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$_1$ 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 Rev1).

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 (200-250g) were randomized in four groups of 12 each. The experimental group was given 20 g/L *M. piperita* tea, or 20g/L *M. spicata* tea or 40g/L *M. spicata* tea. The group control had commercial drinking water. The follicle-stimulating hormone and luteinizing hormone had increased and total levels of testosterone had decreased, comparing with the control group, being statistically significant. The Johnsen testicular biopsy scores were different but not statistically significant (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/day, respectively, were not observed teratogenic effects in mice, rats and hamsters (FAO/WHO expert on Food Additives, 2000).

3.3.6. Local tolerance

Poppermint 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 described 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 a very high dose levels (1250 mg/kg/day), peppermint did increase mortality and reduce survival time in the host resistance assay, on 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 Fragance Materials, 1996).

3.3.8. Conclusions

Toxicological studies on peppermint leaves and peppermint oil are scarce.

The oral LD_{50} of peppermint oil U.S.P. in fasted Wistar male rats after 24 h was found to be 4441±653 mg/kg and after 48h 2426 mg/kg.

Peppermint oil was negative in , the Ames test (up to 160 µg/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/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. 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 pulegone administrated orally, 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 /d (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$_1$ 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/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 bilirrubin were dose dependent, after levels of 0, 200, 400 and 800 mg/kg bw/day. The non-observable- effect-level (NOEL) for menthone in this study was lower than 200 mg/kg bw/day. A NOEL of 400 mg/kg bw/day was reported in a 28 day toxicity study in rats.

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 content in essential oil .

Stimulation on 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 possible 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 PO, 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 Rev1).

The highest daily dosage of of peppermint oil is 1.2 ml i.e. 1080-1099 mg (based on relative density 0.9-0.916 g/cm^3 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/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/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, (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 for an adult of 50 Kg body weight (e.g. for children with a body weight of 20 kg 30mg/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 Rev1).

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 Rev1).

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 & 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 & McNally, 1969).

An aqueous suspension of peppermint oil injected along the biopsy tract in 20 patients prevented the colonic spasms that 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 administered intraluminally by the endoscope. Also, the effects of a placebo solution i.m. were compared with those of a peppermint oil solution administred intraluminally. 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± 11.4) than in the hyoscine-N-butylbromide group (185.9±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 studies, 269 healthy subjects or patients underwent exposure to peppermint oil (PO) either by topical intraluminal (stomach or colon) or oral administration by 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 0.1-0.24ml of PO/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 PO of the smooth muscles of the gastrointestinal tract. This effect commences as early as 0.5 min after topical (intestinal tract) application and may last up to 23 min.

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 PO to maintain the short lasting effect a sustained release formulation is needed to secure constant exposure of the organ to constant concentrations of PO (Grigoleit & Grigoleit, 2005a)

Heartburn, one of the major adverse events of oral PO 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 & 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 & Spilker, 2003).

160 patients scheduled for outpatient colonoscopy were randomized 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 PO group (102 seconds) than the control group (137 seconds) – $p=0,045$ (Sanaka Madhusudhan et al, 2004).

The effect of acute PO 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 PO (182 mg) or placebo was administered during the studies in a randomized 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 decreased significantly after PO 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 PO 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 PO treatment, as compared with placebo (p = 0.01). Postprandial VAS scores were similar between PO 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 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 (ESCOP monographs, 2003 , citing Hansel R et al. 1984, 1999, Haen 1989, Schilcher H 1986) and decongestant in the nose (ESCOP 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 EJ (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, gave 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 & Rajabi, 2013).

Sleep/alertness action

Twenty-one 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 then 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 local 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 inhibit in the brain stem (Fachinfo Euminz, 1997).

The application to the forehead of PO plus ethanol (10% PO in ethanol 90%).showed on the EMG activity, a significant reduction of the M temporalis wave, as a pronounced increase in blood flow through the capillaries of the skin, as compared to the ethanol solution in the study 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 pericraneal musculature was significantly reduced by 27% (p<0.1) by the combination of PO plus ethanol (10% PO 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 PO to get a prolonged effect and avoid the inappropriate release of the oil in the upper GI tract, causing adverse effects like heartburn.

The choleretic, 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 menthol

External use effects

The topical application of PO stimulates the cold sensitive receptors, exerting a local and a probably segmental inhibition of pain, giving an analgesic effect, The experimental laboratory findings point to the possible mechaniss 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

Hurrel 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 dose dependent potent 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 (^{55}Fe or ^{59}Fe) into erythrocytes. Compared with a water control meal, inhibition by back tea was 79-94%, peppermint tea 84%, pennyroyal 73%, cocoa 71%, vervain 59%, lime flower 52% and camomile 47%. At higher polyphenol concentrations (about 200mg/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 & 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 metabolized, 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 & Gaarder, 2005).

In a randomized placebo-controlled study performed in 24 healthy male Japanese volunteers randomly assigned, an L-menthol preparation, NPO-11 sprayed directly onto gastric mucosa was assessed for tolerability and pharmacokinetics (PK) 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 glucoronide 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 randomized, double blind, two way crossover study with eleven subjects, comparing the kinetics and effects of a single oral dose of felodipine ER tablet (Plendil 10 mg), with menthol (test) or placebo (reference), was studied the effect of menthol on the pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. The results concluded that the pharmacokinetics parameters of felodipine and dehydrofelodipine were not markedly during the measurements (Gelal, 2002).

After ingestion of enteric coated PO a patient suffering from achlorhydria described by Rhodes (1976), (cited by Grigoleit & 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, after skin application of camphor, menthol and methyl salicylate, the systemic absorption was examined. Concentration time profiles were erratic and variable and the half-lives relatively shorts (Martin et al, 2004).

Excretion

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, , containing each a total of 0.4 ml of PO in a cross over study. Urine was collected in 2-hourly intervals up to 14 h plus one 10 h sample up to 24 h. Total 24 h 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 delayed-release form of peppermint oil is released to a significant

extent in the lower digestive tract and in the colon, where the antispasmodic effects are expected. The gelantine capsule release pattern does not meet the therapeutic requirements. (Sommerville, 2004)

Pharmacokinetic studies reveal that fractionated urinary recovery of menthol is dependent on the kind of formulation used for the application of PO. Optimal pH triggered enteric coated formulations start releasing PO in the small intestine extending release over 10-12 h thus providing PO 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 & Grigoleit, 2005a)

It is unknown if peppermint oil constituents are he 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

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, more eligible for conclusions.

Liu et al (1997) conducted a prospective, randomized, double-blind, placebo-controlled clinical study in 110 outpatients (66 men/44 women; 18-70 years of age) with symptoms of IBS. Fifty-two patients on PO (one capsule containing 187mg 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 PO (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 PO were significantly better than after placebo ($P < 0.05$; Mann-Whitney U-test). One patient on PO 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 PO and 6 on placebo drop-out. On this study the random sequence generation was not described. The expected outcomes were reported.

Capanni et al (2005) included 178 consecutive patients with IBS in a randomised, double blind controlled trial, using the Rome II diagnostic criteria, to evaluate the efficacy of PO 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), psychical discomfort, in 34/91 (37%) vs 16/87 (18%) patients (p<0.05), and socio-familiar impact, in 69/91 (76%) vs 37/87 (43%) patients.(p<0,04). The authors found a statistically significant benefit for PO 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 without small intestinal bacterial overgrowth, lactose intolerance and celiac disease (randomisation computer generated) with IBS 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 patient's 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 was used from 0 to 4 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. Twenty-four 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). With peppermint oil at T(4) and at T(8) compared with T(0) a statistically significant reduction of the total irritable bowel syndrome symptoms score was found (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. (* χ2-test). The authors concluded that there is a stastically significant benefit for PO 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 randomized double-blind placebo-controlled study on 90 outpatients with IBS (Rome II criteria).. The symptoms and quality of life was evaluated after the first, fourth, and eighth weeks.

Patients were randomized 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 min 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 PO group and from 0 to 6 in controls (p<0.001). The severity of abdominal pain was also reduced significantly in the PO 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, as compared to

controls, showed statistically significant improvement in the SF-36 domains of bodily pain, general health, general health, social functioning, and role limitations due to emotional problems. 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 PO for relieving the symptoms and changes of QoL in diarrhea predominant IBS, through a prospective double blind randomized placebo-controlled study during 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 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 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 statistically highly 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 reliving only abdominal pain in diarrhea predominant IBS transiently. As there is no adequate information about the dose, no conclusion can be achieved for this monograph.

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

72 patients, PO (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 ≥ 4 on a 0–10 scale and a Total IBS Symptom Score (TISS) of ≥ 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, fecal 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 utilized via a central randomization centre.

The primary endpoint was changed from baseline in the TISS 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 h 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, diarrhea, 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 PO used in this study consists of a triple-coated microsphere formulation with sustained release of PO in the small intestine, to improve the tolerability

At 4 weeks, PO was associated with a 40 % reduction in the TISS from baseline (mean change -1.16, SD ± 0.807), superior to the 24.3 % decrease (mean change -0.70, SD ± 0.737) observed with placebo (P = 0.0246). The decrease in the TISS of 19.6 % (mean change -0.55, SD ± 0.613) in the PO group at 24 h was also significantly larger than placebo (-10.3 %, mean change -0.27, SD ± 0.342) (P = 0.0092). At trial completion, patients in the PO group experienced greater improvement in multiple individual gastrointestinal symptoms as well as in severe or unbearable symptoms, compared to placebo. PO was well tolerated with few adverse events. Withdrawals were rare, with more than 94 % of randomized subjects completing the trial. The 4 individual IBS symptoms that were more responsive to PO (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-h efficacy and has not been previously validated.

The authors explained that this scale was chosen based on its previous use in a trial of PO in patients (Cappello, 2007) with IBS as well as the fact that there is no specific regulatory guidance regarding endpoints for a randomized controlled trial including patients with more than one IBS subtype.

Reviews/Meta-analysis

In the review of **Grigoleit & Grigoleit** (2005b) 16 clinical trials in the literature search using 180-200 mg enteric-coated peppermint oil (PO) in irritable bowel syndrome (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 randomized double blind cross over trials with (n = 5) or without (n = 4) run in and/or wash out periods, five had a randomized double blind parallel group design and two were open labelled 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 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 & 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 PO 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. The most of them for reasons unrelated with the study. Other reasons were (n=6 worsening of symptoms, PO or placebo; n=2 nausea and vomiting by PO; n=3 perianal burning by PO; n=2 peppermint taste and pyrosis).

Adverse events reported were generally mild and transient, but very specific. PO 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 PO trials, concludes the authors (Grigoleit, & 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 & Grigoleit 2005b).

Caracteristics of the studies reviewed by Grigoleit & 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 et al. (1982)	db,co,randomized,wash out?	One to two capsules t.i.d.d	Placebo	2/treatment	20
3 Dew et al. (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 et al. (1986)	db,co,no wash out, randomized	Two capsules t.i.d.a	Placebo 2 capsules t.i.d.	2/treatment	41
5 Munst et al. (1987)	db,co,wash out, double dummy, randomized	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,randomized	One capsule t.i.d.a	Placebo,1 capsule t.i.d.	3	60
7 Lawson et al. (1988)	db,co,no wash out	One capsule t.i.d.b	Placebo,1 capsule t.i.d.	4	25
8 Lech et al. (1988)	db,pg,randomized	One capsule t.i.d.d	Placebo,1 capsule t.i.d.	4	47
9 Wildgrube (1988)	Matched pairs, db pg, randomized	Capsules	Matching placebo capsules	2	40
10 Carling et al. (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, randomized	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,randomized	Not specified	Alverine citrate	11/treatment	18
14 Shaw et al. (1991)	Open, pg, randomized	One capsule t.i.d.a	Stress management program, median 6 psychotherapy sessions of each 40 min/patient	24	35
15 Liu et al. (1997)	db,pg,randomized	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,randomized	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.
B Enteric-coated PO capsule.

C Mentacur
D Unspecified PO formulation.
(Grigoleit & Grigoleit, 2005b).

Summary of "overall success" data for peppermint oil (PO) in IBS in the studies by Grigoleit & 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 PO (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 PO
		Hyoscyamine	38	P<0:01; placebo and hyoscyamine p>0:05
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 & Ernst (1998) performed a statistical meta-analysis of eight 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, 1974, Lech et al, 1988, Nash et al, 1986, Rees et al,1979). Three 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 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 & 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 et al. [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 et al. [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 et al. [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 et al. [17]	4	double-blind cross-over	41	8	Colpermin® [3 × 0,4 ml]/ placebo	2	N	13/33 vs 17/33
Rees et al. [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 et al. [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 et al. [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 et al. [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 trials using the global improvement of symptoms as an endpoint. Two 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 favor 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.
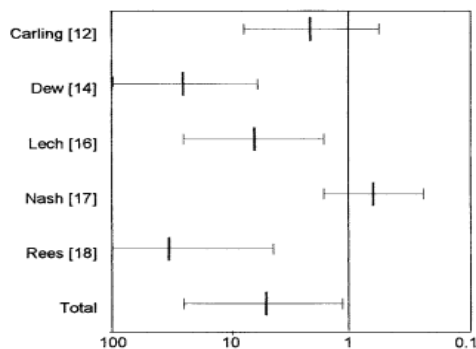
Three of eight trials (Dew et al. 1984, Nash et al. 1986, Schneider & Otten 1990) failed to define any inclusion criteria for patients with IBS. Thus, a definitive classification of 44% of the patients studied is

impossible. The autors 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 & Ernst 1998)

A systematic review and meta-analysis performed by **Ford** (2008) of randomized controlled trials using databases as Medline, Embase, Cochrane controlled trials register u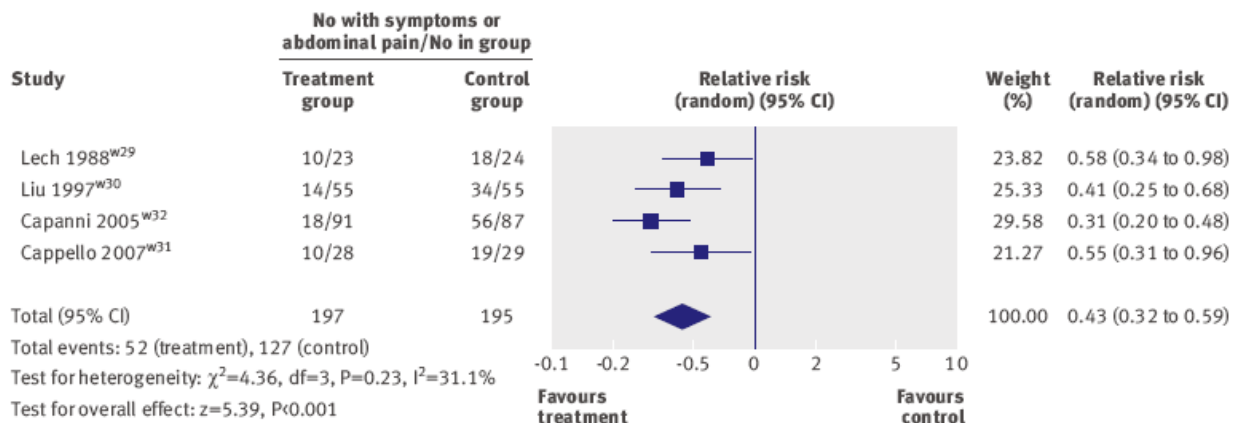p to April 2008, to determine the effect of fibers, antispasmodics and PO in the treatment of IBS was performed. The comparison used was the placebo or no treatment and the minimum duration of therapy considered was one week. The studies had to report either a global assessment of cure of or improvement in symptoms, or cure of or improvement in abdominal pain (primary outcomes).

In this report just the results involving PO are referred.

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 ($I2=31.1\%$, $P=0.23$). 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 ($I2=22.0\%$, $P=0.28$)

Study	No with symptoms or abdominal pain/No in group		Relative risk (random) (95% CI)	Weight (%)	Relative risk (random) (95% CI)
	Treatment group	Control group			
Lech 1988[w29]	10/23	18/24		23.82	0.58 (0.34 to 0.98)
Liu 1997[w30]	14/55	34/55		25.33	0.41 (0.25 to 0.68)
Capanni 2005[w32]	18/91	56/87		29.58	0.31 (0.20 to 0.48)
Cappello 2007[w31]	10/28	19/29		21.27	0.55 (0.31 to 0.96)
Total (95% CI)	197	195		100.00	0.43 (0.32 to 0.59)

Total events: 52 (treatment), 127 (control)
Test for heterogeneity: $\chi^2=4.36$, df=3, P=0.23, $I^2=31.1\%$
Test for overall effect: z=5.39, P<0.001

-0.1 -0.2 -0.5 0 2 5 10
Favours treatment — Favours control

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 has still 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 cimteropium/ dicyclomine, peppermint oil, pinaverium and trimebutine. (Ruepert et al., 2011)

Another systematic review and meta-analysis (**Khanna** et al., 2013) 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 randomized 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 analyzed using an intention-to-treat approach. Study quality was evaluated using the Cochrane risk of bias tool.

Nine studies that evaluated 726 patients were identified. Data were analyzed 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 PO)(5 studies), Mint oil (225g PO)(3 studies) and one unspecified, against placebo.

Six of the 8 trials included in the Pittler and Ernst review had treatment periods of ≤1month. 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.
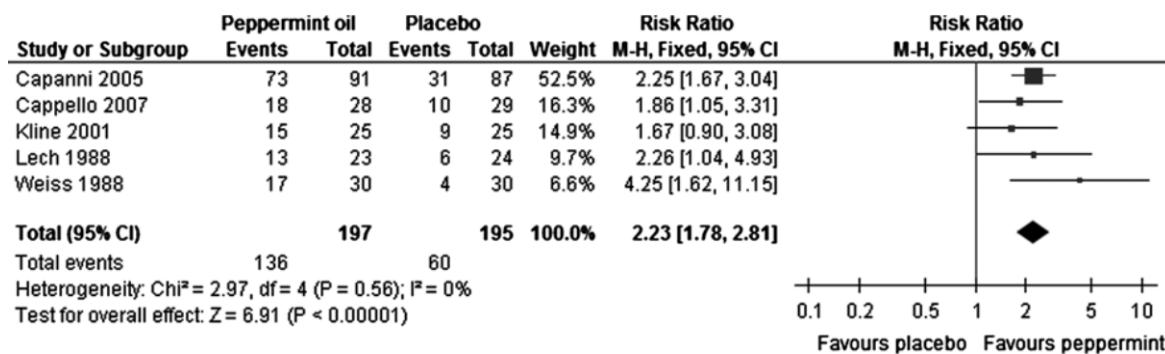
The authors conclude that PO is a safe and effective short-term treatment for IBS.

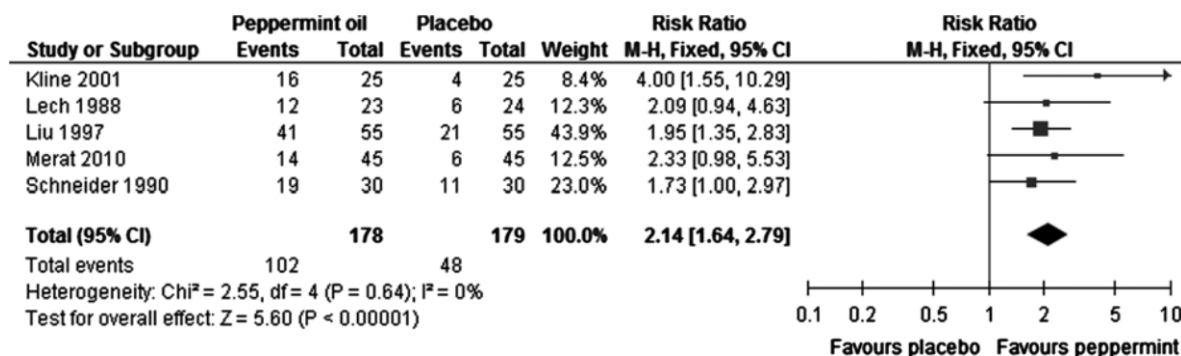Characteristics of included studies (Khanna et al., 2014):

References	No. Patients	Country No. Centers	Interventions	Duration of Therapy (wk)	Methods
Alam et al[9]	74	1 country 1 center	Peppermint oil (unspecified) or placebo	6	Double-blind
Capanni et al[33]	178	1 country 1 center	Peppermint oil (Mintoil) 2 capsules tid or placebo	12	Double-blind
Cappello et al[34]	57	1 country 1 center	Peppermint oil (Mintoil) 225 mg peppermint oil) 2 capsules bid or placebo	4	Double-blind
Kline et al[37]	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 et al[35]	47	1 country 1 center	Peppermint oil (Mintoil) 50 mg capsules 4 capsules tid or placebo	4	Double-blind
Liu et al[36]	110	1 country 1 center	Peppermint oil (Colpermin) 187 mg peppermint oil 1 capsule tid or qid or placebo	4	Double-blind
Merat et al[8]	90	1 country 1 center	Peppermint oil (Colpermin) capsules 0.2 mL/capsule 1 capsule tid or placebo	8	Double- blind
Schneider and Otten[7]	60	1 country 1 center	Peppermint oil (Colpermin) capsules 0.2 mL/capsule (tid) or placebo	6	Double-blind Cross-over
Weiss and Koelbl[6]	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:

Study or Subgroup	Peppermint oil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Capanni 2005	73	91	31	87	52.5%	2.25 [1.67, 3.04]
Cappello 2007	18	28	10	29	16.3%	1.86 [1.05, 3.31]
Kline 2001	15	25	9	25	14.9%	1.67 [0.90, 3.08]
Lech 1988	13	23	6	24	9.7%	2.26 [1.04, 4.93]
Weiss 1988	17	30	4	30	6.6%	4.25 [1.62, 11.15]
Total (95% CI)		197		195	100.0%	2.23 [1.78, 2.81]
Total events	136		60			

Heterogeneity: Chi² = 2.97, df = 4 (P = 0.56); I² = 0%
Test for overall effect: Z = 6.91 (P < 0.00001)

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

Study or Subgroup	Peppermint oil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
Total (95% CI)		178		179	100.0%	2.14 [1.64, 2.79]
Total events	102		48			

Heterogeneity: Chi² = 2.55, df = 4 (P = 0.64); I² = 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

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk	Corresponding Risk			
	Control	Peppermint Oil vs. Placebo			
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 recent 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 yet exist. 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 randomized 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
Alosteron is effective in females with IBS-D.	8	4,987	0.79 (0.69–0.90)	8 (5–17)	Weak	Moderate
Mixed 5-HT_4 agonists/5-HT_3 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
Linaclotide 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_3, serotonin subtype 3; 5-HT_4, 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 were included for peppermint oil (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/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 PO 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 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/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 & Cardozo, 1990).

In a double blind, randomized, placebo controlled, multicentre, 4-week trial, 39 patients with dyspepsia (non ulcerative), with 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 & 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 h, filled with sugar, and adminiistered 30 minutes before they received their chemotherapy treatment, again four h after first capsule and finally four h later in home) for all patients, independent of their age or weight. No significant side effects were found when increasing the dose.

Fifty 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) .

Postoperative Nausea

A study was performed with 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 32 healthy subjects in a double blind placebo-controlled, randomized, four-fold crossover study. Neurophysiological, psychological and experimental algesimetric 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 significant clinical reduction of the pain intensity continued 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 randomized, placebo-controlled double-blind crossover study. The preparation was tested against both the reference substance acetaminophen and to 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 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 was allowed with possible effect on the symptoms. 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 respected. 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 standardized category rating scale - 0 (no pain) to 4 (severe). Compared to the application of placebo, the 10% peppermint oil in ethanol solution significantly reduced the clinical headache intensity already after 15 minutes ($p < 0.01$). This significant clinical reduction of the pain intensity continued over the one hour observation period. Acetaminophen, too, proved to be efficient compared to placebo ($p < 0, 01$). There was no significant difference between the efficacy of 1,000 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 local of application, by the stimulation of the cold-sensitive receptors, giving an analgesic effect.

Safety data were available for 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 **IBS**							
Rees et al. 1979	Double-blind placebo cross-over study, wash out perior 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 PO group overall assessment significantly better - $P<0,001$ PO 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 PO group overall assessment significantly better - P<0,001 PO group better for abdominal pain P<0,001 No effect on the number of bowel actions.	Rating scale (0-4) for the severity of symptoms recorded daily by he 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 x 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 et al. 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 PO/ 26% for placebo	Fisher test	Clinically relevant .
Carling 1989	Double blind-cross over study 3 groups	Peppermint oil 1-2 capsules 0,2ml 3x/day hyoscyamine 0.2 mg placebo 2 weeks	40 patients 14 males 26 females mean age 44 yrs 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 x day not further specified	50 patients 18-69 yrs 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 et al 1997	Double blind study, randomised, parallel group	1 capsule 187 mg (0.2 ml) 3 or 4 x day 4 weeks	110 patients 40% female; 18-70 years of age 52 patients on PO and 49 on placebo completed the study 9 drop-outs – 3 on PO and 6 on placebo.	IBS symptoms	Mean improvement values of symptoms Symptom improvements after PO 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 peppermint oil and 45 mg of excipient;	178 patients Drop out:5	IBS diagnosis, according to the Rome II criteria	Global IBS symptoms assessed by a validated questionnaire.	Chi-square test	Results are considered clinically relevant concerning the efficacy and

| | | Placebo: 225 mg of maltodextrin with mint flavour

2 capsules, 3 times a day, before meals for 3 months | Test group:

91 patients (22 M, 69 F); mean age 41 years old; range 18-72 years old)

Placebo group:

87 patients (23 M, 64 F; mean age 44 years old; range 21-74 years old). | | 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 ($p < 0.01$), psychical discomfort, in 34/91 (37%) vs 16/87 (18%) patients ($p < 0.05$), and socio-familiar impact, in 69/91 (76%) vs 37/87 (43%) patients ($p < 0.04$)]. | | safety of peppermint oil in patients with IBS. |

| Cappello 2007 | Randomized double-blind placebo-controlled, | Two enteric-coated capsules (225mg) twice per day or placebo) for 4 weeks | 57 patients

76% female

Mean age 42 years

28 taking peppermint oil and 29 taking a placebo.

7 dropouts (3 on each group, excluded from the study)

One patient in the peppermint group withdrew due to intense heartburn after taking the medication | IBS

Rome II criteria | Assessment T0, T4 and T8 of symptoms:

Abdominal pain, continuous;

IBS-symptom score, continuous and dichotomous;

symptom intensity and frequency from 0 to 4 were scored

A P-value ≤0.05 was considered statistically significant.

75 % of the patients in the PO group showed a >50 % reduction of basal (T0) total irritable bowel syndrome symptoms score compared with 38 % in the placebo group (p<0.009) | chi-square test

Student's t-test for paired data

Mann–Whitney U test (two-tailed) | Stastically significant benefit for PO and clinically relevant for IBS symptoms. |

Merat et al. (2010)	Randomized double-blind placebo-controlled	- 187 mg or 0.2 ml peppermint oil; - three times daily, 30 min before each meal; - oral use (capsules) - 8 weeks	90 patients, 45 in test group, 45 in placebo group. Drop out: 30 Finished study: 33 in placebo; 27 in test group; 15 male, 45 female	Patients diagnosed according the Rome II criteria. Major complains: abdominal pain, distension and flatulence.	Week 1, 4, 8 Primary outcome: absence of abdominal pain or discomfort at week 8 Secondary outcomes Score with the SF-36 form for assessment of QOL Score with a non validated patient questionnaire Score with a non validated researcher questionnaire The number of subjects free from abdominal pain or discomfort changed from 0 at week 0 to 14 at week in the PO group and from 0 to 6 in controls (p/0.001). The severity of abdominal pain was also reduced significantly in the PO group compared to controls	ITT analysis - No P-values of 0.05 were considered significant. .	The study evidences improvement of abdominal pain and discomfort. However, almost 30% of subjects did not complete the study (no ITT analysis). Low number of subjects. Questionnaires were not validated The clinical relevance of the results is questionable
Alam et al. 2013 The abstract is available, only	Double blind placebo controlled study	Peppermint oil (unspecified) 3 x day for 6 weeks	74 9 drop out	Patients with IBS (who fulfilled the ROME II	Efficacy in relieving the symptoms, changes of quality of life (QOL) in diarrhea	Paired and unpaired T-Test P<0.01 for abdominal pain at 6 weeks	Improvement after six weeks , but worsening after 8

				criteria)	predominant IBS		Other symptoms and QoL did not improve significantly.	.
Cash, 2016	Randomized, double-blind, placebo-controlled clinical trial	Peppermint oil (180mg), tricoated capsules 3 x 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 PO 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 PO and placebo groups. Paired t tests were usedto 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 **Endoscopy-induced spasm**								
Asao,et al. 2001	Prospective. placebo controlled. Only a preliminary study (N=71) was randomized.	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)	Inclusion criteria for colonoscopy: positive test for occult blood in feces, an abnormal barium enema, or surveillance	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 t test was used for evaluation of differences. A p 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.

			56.8 ± 11.3 / Age Range: 25-89 Control group: N=36 Male/Female 26/10 Age average: 55.2 ± 11.9 Age range: 21-76	after previous polypectomies. 9 Patients with a history of colectomy or severe colitis were excluded			
Asao et al. 2003	Prospective trial on the efficacy of peppermint oil during double-contract barium enema (DCBE)	Peppermint solution (100ml water, 8mL peppermint oil, 0.2mL Tween 80) Buscopan 20mg	383 consecutive patients 4 groups: Peppermint oil in barium (91) Peppermint oil in tube (90) Buscopan (105) No-treatment(97)	Patients undergoing DCBE who had positive results from occult blood test	Evaluation of the presence of colonic spasms on a series of spot films Buscopan+PO had less spasms then the no-treatment group (p<0.0005) No significant difference between Po and Buscopan	Chi-square or Mann-Whitney U test. P<0.05 was considered significant	Similar results for both preparations. Maybe useful for the barium enema.
Hiki 2003	Prospective, Double-blind, double-dummy controlled trial	Peppermint oil solution admnistered intraluminally vs hyoshine-N-butylbromide by intramuscular injection	100 patients	Patients undergoing upper endoscopy. Exclusion criteria was used	Primary outcomes – opening and contraction ratios Determination of gastric relaxation to a statistically significant extent with minmal side effects compared with hyoshine-N-butylbromide	Mann-Witney U test: compare the antispasmodic effects Wilcoxon test: contraction ratios before and after the administration p<0,001 for PO and p<0,05 for hyoshine-N-butylbromide	Contraction ratio was significantly smaller after PO than after Hyoscimine injection (p<0,0001)

					p<0,001 for PO and p<0,05 for hyoshine-N-butylbromide		
Imagawa, et al. 2012	non-randomized prospective study	20 ml of a 1.6 % peppermint oil solution administered directly tothe 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 (esophagogas troduodenosc opy). Patients with clinical evidence of severe disease were excluded (ex. American Society of Anesthesiolog ists 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 ± 0.925) did not significantly differ from that of groups HB and GL Placebo group score: 3.846 ± 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,et al. 2007	randomized, two-way crossover study	0.64 ml of peppermint oil with a test meal (200 kcal per 200 ml) Control group:	N=10 asymptomatic male volunteers with no history of gastrointestinal	Healthy patients	Time required for gastric emptying estimated by scintigraphy (50% of the labeled	Wilcoxonsigned-rank test. Level of significance: P < 0.05	No clinical relevance: dimension of the

		meal without peppermint oil. Second way test separated by 7 days	disease.		meals; ^{13}C-acetic acid breath test) Peppermint oil enhances gastric emptying.		sample; sex distribution; healthy volunteers; no ITT.

Review of Clinical Studies for <u>Children</u>

Kline, 2001	RDBCT	PO enteric-coated capsules 187 mg 1-2 cpsx3 Children and adolescents 8-17 years 2 weeks The patients weighing more than 45kg 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 - 17yrs 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 categoric data analysis; Cochran- Armitage test for the data (χ^2[6, $N = 42$] = 12.6; $P < .001$)	No change in the type of symptoms but change in the severity reported by patients. Clinically relevant especially for abdominal pain

Mint leaves

Alves et al. 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 od colic, time spent crying Secondary: number of milk regurgitation,vomiting, diarrhoea, constipation and drowsiness.	Mann-Whytney and chi-square tests	No difference Self limiting disease

Review of Clinical Studies for <u>Tension Headache</u>

Gobel et al, 1996	Randomized, double blind, placebo controlled, fourfold crossover study/placebo and acetaminophen	PO 10% in ethanol repeated after 15 and 30 min / 500mg acetaminophen	41pt 18-65 years old, both sexes. 164 headache attacks	Tension type headache HIS classification	Intensity of the headache. Standardised category rating scale - assessment after 15, 30, 45 and 60 min by the patients Significant reduction of the intensity during 1 hour of observation similar to acetaminophen. P<0,01	T test Standardized pain rating scale (0-4)	Promising results. Clinically relevant
Gobel et al, 1994, 1995	Double blind placebo controlled randomised , four-fold crossover study	PO 10% in ethanol Four different topic preparations,	32 healthy subjects	Healthy subjects	Neurophysiologic, psychological and experimental algesimetric 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
Review of Clinical Studies for **Other indications**							
Barnick 1990	PCDB	PO 187 mg 2 caps 3xday – 5 days	69 woman Age 20-66 yrs	Abdominal distension and dyspepsia after gynaecological surgery	Abdominal distension Dyspepsia	**Mann-** Whytney U test	No difference between the groups.Not relevant for the monograph
Tayarani-Najaran et al, 2013	RDBCT	PO/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		Safe and effective option. Not relevant for the monograph

					M.Spicata and PO		
					P<0,05		
					Intensity of nausea was significantly reduced during 24h		
					p>0,05		

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 & Grigoleit 2005b	Review 2-11 weeks 6 months (1 open study) 9 DBCT 5 DB parallel 2 open studies	Capsules of 180-200mg 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- PO efficacy in the range from 39% to 79% (mean 58%).	PO 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>PO in 6 months 2 trials – PO similar to placebo on pain relief	Overall significant Benefit on three of the five DBPCT. Methodological flaws in some of the studies.
Ford et al, 2008	Meta-analysis 4 studies- PO/placebo	PO, fibers, antispasmodic 4 weeks-3 months 187 to 225 mg per single dose, 2-6 single doses/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 PO 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 stastitical significant heterogeneity	PO superior to placebo

| Ruepert et al. 2011 | Systematic Review 56 studies | Bulking agents – 12 T, antispasmodics - 29 T, 5 studies of peppermint oil were included. 187 to 225 mg PO per single dose, 2-6 single doses/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 *PO* (RR 1.94; 95% CI 1.09 to 3.46; 269 patients) | A statistically significant effect for improvement of global assessment for *PO* (RR 2.25; 95% CI 1.70 to 2.98; 225 patients; | Different types of antispasmodics found statistically significant. Benefits and clinically relevance for cimteropium/ dicyclomine, peppermint oil, pinaverium and trimebutine. |

| 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. | PO 0.1-0.2ml, PO 225mg
Minimum 2 weeks – 12 weeks
1 study in children | 726 pt | IBS | Global improvement of IBS symptoms, improvement in abdominal pain, and adverse events.

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. | 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. |

4.3. Clinical studies in special populations (e.g. elderly and children)

<u>Peppermint leaves</u>

A double-blind crossover study was performed with 30 infants attending IMIP, Recife, Brazil. They were randomized 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 each 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).

<u>Peppermint oil</u>

Clinical studies in children

In a randomized, double-blind controlled trial of two weeks, 42 children and adolescents (8 to 17 years old) with irritable bowel syndrome were given ph dependent enteric coated peppermint oil capsules (187 mg), versus placebo. The patients weighing more than 45kg received 2 capsules, 3 times a day. The smaller children, who weighed 30Kg to 45 kg, received 1 capsule 3 times a day. After two weeks, 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. No adverse events were reported (Kline et al., 2001).

Systematic review

Abstracts and full texts of 57 randomized 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, controlled study. Famotidine, Pizotifen, cognitive-behavioral 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

<u>Peppermint leaves</u>

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

<u>Peppermint oil</u>

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 criticism 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, so in June 2016, there was another update and the Rome IV criteria was published for diagnosing functional gastrointestinal (GI) disorders. 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 diarrhea, functional constipation, and functional distension (Rome I) as separate entities. Later it was recognized that these disorders could overlap (Rome II-Rome III). However, in the clinic it may be 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 diarrhea. Thus, Rome IV considers that these disorders exist as a continuum rather than as in isolation (Schmulson,& Drossman, 2017).

Rome III Criteria for Diagnosing IBS:[a]	Rome IV Criteria for Diagnosing IBS:[c]
Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following: • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool	Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with two or more of the following criteria: • Related to defecation • Associated with a change in frequency of stool • Associated with a change in form (appearance) of stool.
[a]Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. [b]"Discomfort" means an uncomfortable sensation not described as pain.	[c]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

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

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

In terms of IBS subtypes, IBS is mainly classified according to the predominant bowel habit for IBS-C (constipation), IBS-D (diarrhea), 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,& Drossman, 2017).

The pathogenesis of IBS seems to be multifactorial, with several factors playing a central role, like heritability and genetics, dietary/intestinal microbiota, low-grade inflammation and disturbances in the

neuroendocrine system of the gut. 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, which 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 & 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 are 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 evaluable 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 is 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 randomized 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 & Ernst reported that the role of peppermint oil in the symptomatic treatment has not been established and more studies are needed to clarify the issue. The difference in the diagnosis criteria in the clinical studies, may justify part of the problems found in the comparator groups in the meta-analysis.

The review from 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), PO demonstrates to be clinically safe and effective short-term treatment for IBS.

The review from Wall et al, (2014) include PO on 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 also than hyoscine-N-butylbromide, with less adverse reactions

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

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

Tension headache

The tension-type headache (TTH) is classified at the International Classification of Headache Disorders, 3rd 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* subdivided episodic tension-type headache further, into an *infrequent* subtype with headache episodes less than once per month and a *frequent* subtype. Another difference in this edition is related with the disorder of the precranial muscles, using now for the subdivision 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 PO on the forehead and the temples of the patients.

The comparative clinical study with 1,000 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 large 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 PO 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 (PO)

PO were found to cause the typical GI effects like heartburn and anal / perianal burning or discomfort sensations in a literature search; 16 clinical trials investigating 180–200 mg enteric-coated peppermint oil (PO) in irritable bowel syndrome (IBS) or recurrent abdominal pain in children (1 study) with 651 patients enrolled were identified (Grigoleit & Grigoleit , 2005b).

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

The meta-analysis from Khanna et al (2014), evaluated 726 patients from nine studies. The adverse events that were reported in the placebo-controlled studies were mild and transient in nature. The

adverse events included are 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 (PO) included involving 492 patients, 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/day), reported adverse events not higher in PO groups compared to placebo (RR of experiencing any adverse event = 1.26, 95% CI 0.75– 2.12).

No certain cases of liver damage caused by peppermint oil or mint oil have been reported (EMEA/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 stomatites and glossites 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 and 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 Rev1). A non-urgent information request was sent out to the member states concerning 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 Rev1).

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

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)	Adverse reactions	Comments on clinical relevance of results
Grigoleit & 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 180-200mg 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 & 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	PO 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 American College of	Review 5 RCT	PO 187-225mg t.i.d.	492	IBS	RR of experiencing any adverse event	The adverse events were not higher on

Gastroenterology					= 1.26, 95% CI 0.75– 2.12	PO groups compared to placebo
Kline, 2001	RDBCT	PO 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 agent. In general PO 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 cm2 and a daily application of 1 mg/cm2 (17 ml of the product), the FDA estimated an exposure of 34 mg/day. For a 60kg 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 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 medication, 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 120mg pulegone +menthofuran (Ph Eur). For a 60Kg 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 Rev1), 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, 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 & 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 have been described, many of which are linked to both perioral and intraoral disorders. Although peppermint oil is known for its many properties, its role as a sensitizer should be recognized so as to aid in the diagnosis of both dermatitis and oral conditions and to allow the initiation of proper avoidance measures (Herro & Jacob, 2010).

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. 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 sensivity (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 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 Rev1.

The nasal mucosa is an autonomic reflexogen organ, which has a distance action to the heart, lungs and circulation and may lead to sudden apnoea and glottal constriction. The children less than 2 years old present particularly this reflex, so all the substances with a strong odour must be avoided (Dost & 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 relation of seizures with the inhalation of peppermint oil alone, on the dosage recommended on 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. Patients with liver disease, cholangitis, achlorhydria, gallstones and any other biliary disorders.

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 the 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 a lack of data on safety and efficacy.

The gastro-resistant solid dosage forms should be swallowed whole, i.e. not broken or chewed, because this would release the peppermint oil prematurely, possibly causing local irritation of the mouth and oesophagus.

Patients, who already suffer from heartburn or hiatal hernia have sometimes an exacerbation of this symptom after taking peppermint oil. Treatment should be discontinued in these patients.

*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, 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 was described of possible interaction of menthol cough drops (the active ingredient is menthol) with warfarin, on 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 50mg/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/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

T*he dose of menthol responsible for these cases is not known, so it is not possible to consider the relevance for the PO 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 PO 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).

Even being uncertain 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 appoint that peppermint may dry up milk secretions (Mills & 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 benefit is higher than 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

<u>Peppermint leaves</u>

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 using peppermint leaf preparations.

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

<u>Peppermint oil (PO)</u>

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

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 minimized by an appropriate pharmaceutical formulation.

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, on 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)

<u>Peppermint leaves</u>

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 to demonstrate its use for the symptomatic treatment of digestive disorders, over a period of 30 years.

Preparations of peppermint leaves demonstrated a relaxation and antispasmodic effects on gastrointestinal tissue and antinociceptive effect on animal models. Mixed flavonoids showed choleretic 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 esfincter.

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^3 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.

Giving 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 not to take these preparations without medical supervision. 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 a EU list entry cannot be supported.

Peppermint oil

WEU

Peppermint oil has been used widely since many decades as a digestive and carminative. As an authorized 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 been also 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 exacerbation 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 randomized 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 affect, after administering 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.

<u>TU</u>

There is a lack of clinical studies to conclude about the efficacy on the treatment of cough and colds for *Mentha x piperita*, folium, as well for peppermint oil The symptomatic relief of localized muscle pain_ and of 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 a 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 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 Rev1).

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)[1]	Pulegone/ menthofuran intake mg)[2]	EMA/HMPC/138386/2005 Rev1 mg	EMA/HMPC/138386/2005 Rev1 mg
Inhalation				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		

[1] relative density is 0.900-0.916

[2] Ph. Eur.: menthofuran 1-8%, pulegone max 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 Rev1.

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 max 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^3 ~ 0.2 cm^3 which **corresponds to 0.18 g** (if we calculate with relative density 0.9; relative density of olive oil is 0.913)

	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	9.375 cm	3.125 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 pulegon+menthofuran /day	8.7 cm	2.9 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)	5.6 cm	1.9 cm

11.25 mg pulegone+menthofuran /day		

Ointment tube with diameter of 0.6 cm

− 1 cm of the ointment corresponds to 0.2826 cm^3 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 Rev1.

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)[1]	Pulegone/ menthofu ran intake mg)[2]	EMA/HMPC/138 386/2005 Rev1 mg	EMA/HMPC/13838 6/2005 Rev1 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

[1] relative density is 0.900-0.916
[2] Ph. Eur.: menthofuran 1-8%, pulegone max 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 Rev1 if the specifications of oil are set at 75/121 x 11%= 6.82% for menthofuran + pulegone.

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

For lifelong intake the limits should be set at 37.5/121x11%= 3.4% of menthofuran + pulegone.

For lifelong intake the limits should be set at 37.5/59x11%= 6,9% of menthofuran + pulegone.

WEU Children 8-12 years	total daily dose (ml)	Total daily dose (g)[1]	Pulegone/menthofuran intake mg)[2]	EMA/HMPC/138386/2005 Rev1 mg	EMA/HMPC/138386/2005 Rev1 mg
0.2 ml of essential oil three times daily	0.6	0.54	59	15 mg 20kg/bw long term (life long)	30mg 20kg/bw Up to one year from one given medicinal product

The recommended dose is only within the limits set by EMA/HMPC/138386/2005 Rev1 if the specifications for the oil are set at 30/59 x 11%= 5.5% for menthofuran + pulegone.

For life-long intake the limits should be set at 15/59x11%= 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 the reports of pharmacovigilance. Nevertheless, the preclinical data on pulegone and menthofuran requires an alerted pharmacovigilance of peppermint oil products 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 37.5mg, 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 PO with a limit of 3.4% of menthofuran + pulegone. The minimum dose (0.6ml) requires PO with the limit of 6.9% of menthofuran + pulegone.

In children, the limit for a lifetime intake of 0.75mg/kg/day of menthofuran + pulegone can be accepted. However, at the proposed posology (0.6ml/day) included in the monograph, the PO would need to be restricted to batches complying with a limit of 2.79% of menthofuran + pulegone. It is evident from data on commercial batches (supplied in confidence by EDQM) that most batches from currently available commonly traded natural POs 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 PO batches may be possible.

For **the traditional use**, the posology proposed for oromucosal, inhalation (0.08- 0.48mL/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:

Cutaneousl use:

   I.   For the relief of symptoms in coughs and colds;
   II.   For symptomatic relief of localized 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