European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT ON

MENTHA X PIPERITA L., AETHEROLEUM

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I. REGULATORY STATUS OVERVIEW

MA: Marketing Authorisation;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status			
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Finland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Ireland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: Food supplements
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: Natural products
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Malta	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Portugal	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
United Kingdom	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:

II. ASSESSMENT REPORT FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH WELL-ESTABLISHED USE

Mentha x piperita L., aetheroleum

BASED ON ARTICLE 10A OF DIRECTIVE 2001/83/EC AS AMENDED

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Mentha x piperita* L., aetheroleum
Herbal preparation(s)	Menthae piperitae aetheroleum
Pharmaceutical forms	Liquid dosage forms
Rapporteur	Dr Helena Pinto Ferreira Dr Ana Paula Martins

1 INTRODUCTION

Peppermint is believed to be a hybrid of spearmint (*Mentha spicata* L.*)* and water mint (*Mentha aquatica* L.*)* (Murray, Lincoln and Marble, 1972).
It has been a popular domestic remedy for at least two centuries. The essential oil is obtained from the fresh leaves of *Mentha piperita L.* by steam distillation and its most active product available in most parts of the world for flavouring, cosmetic and medicinal uses.

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"

The activity of peppermint oil and of its major constituent, menthol, have been subject to a series of pharmacological and clinical studies. Several medicinal products have been authorized for the relief of digestive disorders, to reduce spasms of the smooth muscles, for neuralgic pains and for colds and coughs, given orally or topically.

This monograph gives the result of the literature available on the efficacy and safety of peppermint oil, for well-established use.

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

- Herbal substance(s)[1] [2]:

Mentha x piperita L., aetheroleum

- Herbal preparation(s)[1] [2]:

Menthae piperitae aetheroleum

- Combinations of herbal substance(s) and/or herbal preparation(s)[3]

1.2 Information on period of medicinal use in the Community regarding the specified indication

2 NON-CLINICAL DATA

For all studies cited, it should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.

2.1 Pharmacology

2.1.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

[1] According to "Note for guidance on Quality of herbal medicinal products" (CPMP/QWP/2819/00…)
[2] According to "Note for guidance on Specifications: Test procedures and acceptance criteria for herbal drugs, herbal preparations and herbal medicinal products" (CHMP/QWP/2820/00)
[3] According to the Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations (EMEA/HMPC/166326/2005)

Major chemical constituents

The major constituents are menthol (30-55%) and menthone (14-32%). Other monoterpenes present are limonene (1-5%), cineole (3, 5-14%), menthofuran (1-9%), isomenthone (1,5-10%), menthyl acetate (2,8-10%), pulegone (until 4%), carvone (until 1%) with a ratio of cineole content to limonene content greater than 2.

Antispasmodic action on the smooth muscle

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.

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-competitively 5 –hidroxitriptamine (serotonin) and the substance P induced smooth muscle contraction (Hills JM 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 45Ca2+ uptake experiments. Binding of menthol and peppermint oil, studied at 78 micrograms ml-1, was competitive against [3H] nitrendipine in both smooth muscle and synaptosome preparations. The data indicate that both menthol and peppermint oil exert Ca2+ channel blocking properties which may underlie their use in irritable bowel syndrome. The authors conclude that Ca2+ channel antagonism may not be the only pharmacological effect of menthol and peppermint oil contributing to intestinal smooth muscle relaxation (Hawthorn M et al, 1988).

Another study made experiments on male guinea pigs concerning the pharmacological activity of essential oils on Oddi`s sphincter. Oddi`s sphincter prolapses through i.v. injection of *Mentha piperita* L. **(**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 C., Guo Z., Pentz R, 1991).

Ant carminative activity

Peppermint oil 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 N., James K., Pugh W, 1978)

Analgesic action

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 B et al, 2006).

Studies have demonstrated that rodents who lay down in bedding that was soaked in peppermint oil show a pain relief response compared with those who lay in control bedding.

On another study in identified Helix neurons, the authors indicate a modulating action of external menthol on Ca inactivation (Hawthorn M et al, 1988)

Virucidal, antimicrobial and antiplasmid action

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. Not after penetration into the host cell (Dresser et al, 2002).

Peppermint oil showed antimicrobial and antiplasmid activity, demonstrating a synergistic additive interaction with oxytetracycline (Schelz Z, 2006).

Bronchomucotropic activity

Menthol

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).

On several old studies peppermint oil was reported to depress ciliary activity, but there are some other studies where PO markedly stimulated it (Das, Rathor, Sinha, Santal, 1970) .

Using VapoRub vapours in a study, where animals were exposed continuously to 30 times the relative peak clinical atmospheric concentrations of the product, no significant suppression of pulmonary bactericidal activity was observed (Jakab, Green, 1975).

Interactions

Peppermint oil has demonstrated competitive antagonism at calcium channels in animals and in vitro. On a theoretical point of view, the calcium channels blockers effectivity may be modified.

Peppermint oil was reported to inhibit cytochrome P450 3A (CYP3A) activity in rat and human liver microsomes and to enhance the oral bioavailability of the CYP3A4 substrate felodipine in people (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).

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

2.1.2 Assessor's overall conclusions on pharmacology

Peppermint showed in vitro and in vivo studies, to have antispasmodic activity on the gastrointestinal smooth muscle. The mechanism seems to be related to the reduction of the calcium influx and the block of non-competitive contraction induced by 5-hidroxytriptamine.

Peppermint appears to have antiseptic properties in vitro and cholagogic action in vivo, but had no significantly effect on post-inflammatory visceral hyperalgesia.

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

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

The reversible inhibition of cytochrome P450 3A was reported in vitro and in vivo, requiring further investigation.

Cyclosporine maximum concentration may increase, with the action of peppermint oil. Topically, peppermint oil increased the penetration of 5-fluorouracil.

2.2 Pharmacokinetics

2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

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 (Final report on the Safety Assessment of Mentha Piperita, 2001)

Inhalation

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 inhalated menthol and camphor were 35, 5 and 39,9min 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 l-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 (Hawthorn et al, 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).

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).

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 faeces and urine. The main metabolite identified was menthol-glucuronide. Additional metabolites are mono- or di-hydroxylated menthol derivatives.

2.2.2 Assessor's overall conclusions on pharmacokinetics

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

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

2.3 Toxicology

2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Toxicity

Peppermint, pulegone, menthofurane

Short-term toxicity studies demonstrated that peppermint oil (40 and 100 mg/kg b.w. day) and pulegone (80 and 160mg/kg b.w.day) induced brain lesions in rats at oral doses.

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. After 48h was 2426 mg/kg.

The interest in toxicity of pulegone, menthofuran and peppermint oil appears to have been provoked by three reports in the literature. It was reported that pulegone, when given to rats for 28 days, caused histopathological changes in the liver (vacuolisation) and the brain ("cystlike spaces") (Thorup et al. 1983a,b; Olsen and Thorup, 1984). The histopathological changes were seen in rats receiving 80 and 160 mg/kg/day of pulegone. However, all haematological and clinical chemical parameters were found to be within the normal range in all groups. There were neither obvious signs of clinical symptoms due to encephalopathy. Based on these studies the NOEL (no effect level) of pulegone was considered to be 20mg/kg bw/day. Later "confirmatory" studies by the same group, however, reported that there were no significant histopathological changes in the liver or the brain. The "cyst-like spaces" reported in the brain in the earlier studies were thus not confirmed and may have arisen from inadequate tissue fixation procedures (Molck et al. 1998). In this study the clinical biochemical examinations revealed increased plasma glucose, alkaline phosphatase and ALAT and a decreased creatinine in the dosed group. In later studies the liver toxicity of pulegone has been confirmed and a mechanism of action has been proposed based on its metabolism to menthofuran and other reactive metabolites, which are the ultimate hepatotoxins (see SCF report on Public statement on the use of HMP containing pulegone and menthofurane – EMEA/HMPC/138386/2005).

Menthone

The oral toxicity of menthone was evaluated in an animal model. The decrease in plasma creatinine and the increase in phosphatase alkaline and bilirubin were dose dependent, after levels of 0, 200, 400 and 800mg/kg b. w. /day. The NOEL for menthone in this study was lower than 200mg/kg b.w. /day (Madsen et al, 1986). A NOEL of 400 mg/kg b. w. /day was reported in a 28 day toxicity study in rats (Who, 2000).

Genotoxicity

Peppermint oil

Salmonella strains TA1537, TA98, TA1535 and TA100 at concentrations of 800, 160, 32 and 6,4 µg per plate were used to test peppermint oil. No mutagenic properties were observed[75]. Menthol and pulegone were also negative.

Peppermint oil was negative on a dose of 150µg/ml in a mouse lymphoma L5178Y TK +/- cell mutagenesis assay and, on a concentration of 155µg/ml, in an unscheduled DNA synthesis assay, on rat hepatocytes (Final report on the Safety Assessment of Mentha Piperita, 2001)

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

Menthone

Menthone exhibited mutagenic responses in several Salmonella tester strains, although responses were rather inconsistent in terms of concentration and requirement of S9. It was also positive in the wing somatic mutation and recombination tests (SMART) [105] 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). (Final report on the Safety Assessment of *Mentha piperita*, 2001)

Peppermint oil was negative in two validated tests of genotoxicity, the Ames test and the mouse lymphoma assay. Weak and inconsistent genotoxic responses in other non-validated tests are probably toxicologically inconsequential. There is more evidence for genotoxicity potential of menthol and there seems to be a discrepancy between peppermint oil and its most important constituent menthol. However, the present evidence points to a very weak or totally absent genotoxicity of peppermint oil.

Immunotoxicity

At a very high dose levels (1250mg/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 (Final report on the Safety Assessment of *Mentha piperita*, 2001)

Teratogenicity

Menthol

No teratogenic effects were noted after oral intubations of Brazilian menthol on pregnant mice, rats, hamsters and rabbits (Food and Drug Research Labs, 1973).

Carcinogenicity

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, on a two year study, in 1979. In female mice, was noted a dose related increased deaths.

After 20 weeks of oral dosing with 1% (-) menthol, was reported a significant inhibition of induced mammary gland carcinogenesis (*p<0,001*) (Russin et al).

3 CLINICAL DATA

- For all studies cited, it should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.

3.1 Clinical Pharmacology

3.1.1 Pharmacokinetics

3.1.1.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

Oral administration

Peppermint oil is relatively rapidly absorbed after oral administration and eliminated mainly via the bile.

Menthol

To determine the disposition kinetics and to examine subjective and cardiovascular effects of menthol, was conducted a crossover placebo-controlled study that compared pure menthol versus placebo, along with an uncontrolled exposure to menthol in food or beverage. 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 ($P < .05$). 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).

An aqueous suspension of peppermint oil was injected along the biopsy tract in endoscopic examinations. Colonic spasm was relieved within 30 seconds in each of 20 patients using this technique (Leicester, 1982).

After administration of peppermint oil to ileostomy patients, elimination of menthol glucuronide was less than after administration to healthy subjects, indicating that part of the absorption of menthol took place in the distal small intestine.

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

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 (Grigoleitt, 2005).

The excretion in the breast milk is undetermined.

3.1.1.2 Assessor's overall conclusions on pharmacokinetics

Peppermint oil is relatively rapidly absorbed after oral administration and eliminated mainly via the bile. Peppermint oil is highly fat soluble and rapidly absorbed at the proximal gut. However, some studies with ileostomy patients suggest that part of the absorption of menthol took place in the distal small intestine. Nevertheless pharmacokinetic studies reveal that fractionated urinary recovery of menthol is dependent on the kind of formulation used for the application of PO.

The systemic absorption after dermal application was examined and concentration time profiles were erratic and variable and the half-lives relatively shorts.

3.1.2 Pharmacodynamics

3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

Antispasmodic action on the smooth muscle

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

One study is an investigation about peppermint oil to reduce colonic spasms during endoscopy in 20 patients. Peppermint oil is injected along the biopsy channel of the colonoscope. Colonic spasm was relieved within 30 s (Sigmund, McNally, 1969).

The principal pharmacodynamic effect of peppermint oil relevant to the gastrointestinal tract is a dose-related antispasmodic effect on the smooth musculature, as we can see on the studies presented below, due to the interference of menthol with the movement of calcium across the cell membrane. The choleretic and antifoaming effects of peppermint oil may play an additional role in medicinal use.

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). 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).

A randomized double-blind, double dummy, controlled trial was conducted in 100 patients to compare the antispasmodic effects of hyoscine-N-butylbromide IM, and a placebo solution administered intraluminally by the endoscope, and also the effects of a placebo solution IM with those of a peppermint oil solution administered intraluminally. The percent change in diameter of the pyloric ring before and after the administrations was defined as the 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.

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 on the quality of the examination (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. 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.

The 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*) (Asao et al, 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 POS group (102 seconds) than the control group (137 seconds) – *p=0,045* (Goerg et al, 2003)**.**

3.1.2.2 Assessor's overall conclusions on pharmacodynamics

The pharmacodynamic studies demonstrated the spasmolytic effect on the smooth muscle of the intestinal tract. The different formulations may reach different target organs. An appropriate galenic formulation minimizes the adverse effects.

Peppermint oil shows activity on the relaxation of the Oddi's sphincter on the gallbladder, demonstrating some choleretic properties.

The relaxation of the oesophageal sphincter, plus the reduction in gastric and intestinal foam volume, observed in vitro, contribute to the carminative effect.

3.2 Clinical Efficacy Studies

3.2.1 Dose response studies

There are no dose-finding studies available.

The recommended dosage of 0.2 ml – 0,4ml for adults, elderly and children over 12 years (2 –3 times daily) is supported by clinical investigations as noted below, for the treatment of irritable bowel syndrome.

3.2.2 Clinical studies (case studies and clinical trials)

Oral administration

Irritable bowel syndrome

Non Controlled clinical studies

- When 50 patients suffering from irritable bowel syndrome were studied in an open multicentre trial, they received three peppermint oil capsules (of 0.2 mL) per day, each administered orally 30 minutes before a meal. Evaluation of all signs and symptoms, both pre- and post-treatment (after four weeks of treatment), confirmed a statistically significant decrease of symptoms.

Controlled clinical studies

- In two double blind, crossover studies of irritable bowel syndrome with 16 and 29 patients respectively, capsules containing peppermint oil (0.2 mL/capsule) were compared with placebo.

Patients received orally three times daily 1 or 2 capsules depending on the severity of symptoms. The overall assessment of each treatment period showed that patients felt significantly better ($p<0.01$) while taking peppermint oil capsules compared with placebo, and considered peppermint oil better than placebo in relieving abdominal symptoms ($p<0.005$).

- 34 patients with irritable bowel syndrome in whom pain was a prominent symptom were entered in a double blind clinical trial of peppermint oil (0.2 mL/capsule) versus placebo. Two capsules were taken orally three times daily. The patients' assessments at the end of two and four weeks of treatment showed no significant difference between peppermint oil and placebo in terms of overall symptoms.

- Enteric-coated capsules containing peppermint oil (0.2 mL/capsule, taken orally) were compared with placebo in a double blind, crossover trial involving 18 patients with irritable bowel syndrome. The patients received three capsules per day for 4 weeks and then changed to the alternative medication for a further 4 weeks. With peppermint oil, there was a small but statistically significant increase in frequency of defecation but no significant change in scores for global severity of symptoms or scores for the specific symptoms of pain, bloating, urgent defecation and the sensation of incomplete evacuation.

- In a double blind, crossover study, 40 irritable bowel syndrome patients were treated orally for 2 weeks with peppermint oil in enteric-coated capsules (0.2 mL/capsule), hyoscyamine (0.2 mg) or placebo. Treatment with peppermint oil tended to have a more pronounced effect on symptoms than placebo or hyoscyamine, but this was not statistically significant. (Krag,1985, Pittler, Ernst, 1998)

Reviews

On one review, 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, 2005).

Study no./Ref.	Design	Study drug(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 Mu¨ nst 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 Ko¨ lbl (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 ¼ double blind, co ¼ cross over, pg ¼ parallel groups. A Colpermins .
B Enteric-coated PO capsule.

C Mentacurs

D Unspecified PO formulation.

(Grigoleit, 2005).

Table 2. Summary of ‘‘overall success’’ data for peppermint (PO) oil in IBS [54-56]

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 symptoms, single symptoms all P<0:05
16	70	Placebo	43	Children/recurrent abdominal pain, p<0:002

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. Others (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[56].

The authors conclude 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[56].

Meta-analysis

A statistical meta-analysis of eight studies showed 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 methodologic problems including vague inclusion criteria for patients and treatment periods that were too short. 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 three of five trials, significant benefit over placebo for global improvement were reported ($p<0,001$). In the descritive 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. Overall, there was a significant benefit on four of the six double blind placebo controlled trials over a two to six weeks treatment period. (Pittler MH, Ernst 1998).

Dyspepsia

- A placebo controlled double-blind study has been studied in 69 woman in the treatment of abdominal distension and dyspepsia following routine gynaecological surgery, using Peppermint oil (Colpermin – Tillots Laboratories, St. Albans, Hertfordshire), in enteric coated capsules, 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[61].

- 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 (Enteroplant ®) 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 C.G., Cardozo, 1990).

Gallbladder – cholelitolytic, cholagogue, choleretic

In these clinical studies it was used a terpene preparation called Rowachol ® (Pinene 17mg, Camphene 5mg, Cineol 2mg, Menthone 6mg, Menthol 32mg, Borneol 5mg, Olive Oil 33mg – for each capsule of 100mg).

Uncontrolled study

It was given to19 of 31 patients with common bile duck stones, up to 7 capsules/day initially of Rowachol ®, and 3 capsules/day later. 8 (42%) patients had total stone disappearance in 3 to 48 months; Bile acid (chenodeoxycholic in 11, ursodeoxycholic in 4) was given also to 15, from 2 to 60 months, and within 18 months, 11 had complete stone dissolution (Somerville et al, 1985).

15 patients were treated with Rowachol ®, 3 capsules daily minimum. The treatment was effective in dissolving stones when administered in one year (Bell, Doran, 1979).

Controlled study

A human controlled study with two groups, evaluated the biliary lipid secretion and gall bladder bile composition. Rowachol ® enhanced the cholesterol solubility of gall bladder bile (*p<0,001*) and human T-tube (*p<0, 05*) bile after the ingestion of 2 capsules three times daily for 48 hours (Bell, Doran, 1979).

The Commission E monograph also describes a cholagogic action to peppermint oil.

Inhalation

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).

Respiratory action

According with ESCOP, inhalation of the oil for treating congestion due to common colds is believed to ease congestion, aiding respiration, by stimulating cold receptors in the respiratory tract.

A secretolytic action in the bronchi and decongestant in the nose were reported (ESCOP monographs, 2003).

Various studies did not demonstrate a change on inspiratory or expiratory nasal airway resistance, but enhances the sensation of nasal airway latency. It seems that menthol acts upon trigeminal sensory nerve endings within the nose (Eccles et al, 1988).

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 others 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 S, 1997)

External application

Tension headache

There is not clear clinical and pharmacological data to support this indication, but there are some studies, which enable an assessment of Peppermint oil for external use in tension headache, as follows.

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.

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 (Dresser, 2002).

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. 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. 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.

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

The application to the forehead showed on the EMG activity, a significant reduction of the M temporalis wave, as a pronounced increase in blood flow through the capillaries of the skin (Fachinfo Euminz, 1997)

Safety data were available for 150 Patients without AE´s.

Analgesic effect

Case study

Report of a post herpetic neuralgia 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).

3.2.3 Clinical studies in special populations (such as elderly and children)

Clinical studies in children

In a randomized, double-blind controlled trial of two weeks, 42 children (8 to 17 years old) with irritable bowel sd were given ph dependent enteric coated peppermint oil capsules, 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 Robert et al, 2001).

3.2.4 Assessor's overall conclusions on clinical efficacy

Oral administration

IBS

The Rome II 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.

Irritable Bowel Syndrome can be diagnosed based on at least 12 weeks (which need not be consecutive) in the preceding 12 months, of abdominal discomfort or pain that has two out of three of these features*:*

1. Relieved with defecation; and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool.

Other symptoms that are not essential but support the diagnosis of IBS:

- Abnormal stool frequency (greater than 3 bowel movements/day or less than 3 bowel movements/week);
- Abnormal stool form (lumpy/hard or loose/watery stool);
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
- Passage of mucus;
- Bloating or feeling of abdominal distension

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

According to the document "Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome" (CPMP/2003), considering the chronic character of this disease, it may be acceptable to conduct a number of studies with different designs to provide all the required efficacy data (dose response studies, efficacy with first use – 4 weeks duration, withdrawal/rebound effect, efficacy with repeated use). The trials must be long, considered as necessary 6 months of active treatment. Other studies should be justified. On short term studies of 4 weeks, would be required a 50% of the time on the response on the specified improvement in symptoms.

IBS is a complex disorder that affects many patients. Its treatment is also complex, because a variety of processes appear to be involved. So, it is difficult to find treatment suitable for all sort of IBS patients, but effective towards specific aspects. IBS is a chronic condition, with unpredictable periods of exacerbation and remission. Thus, clinical trials of only few weeks are of limited relevance to conclude about the effectiveness of the treatment.

Some studies in the literature show methodological problems, as use of no validated scales, the randomization procedure is not clear, there is lack of adequate washout period, limited treatment period (2-4 weeks), 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. A variety of outcome measures have been used, making it difficult to compare the results of the trials.

The meta-analysis by Pittler and Ernst reported that the role of peppermint oil in the symptomatic treatment has not been established and more studies are needed to clarify the issue.

Nevertheless, the clinical studies demonstrated a reduction in spasms during barium enemas and endoscopies, as smooth muscle relaxing properties, pointing peppermint oil as an antispasmodic agent on the GI tract, reducing abdominal pain. The enteric-coated capsules are generally recommended to reach the target organ and avoid undesirable effects like heartburn and oesophageal reflux.

The carminative properties attributed to peppermint were documented by the literature, helping to relief the flatulence.

Dyspepsia (non-ulcer)

Small number of controlled trials with a combination of peppermint and caraway oil shows some benefits on dyspepsia symptoms. It is not clear what constituent is the most effective.

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.

Cholagogic, cholelitolytic, and choleretic

Some studies appointed cholagogic, cholelitolytic, and choleretic properties, but some more trials are necessary, with a better design.

Tension headache

According to the IHS classification (ICHD-II) - International Headache Society 2003, tension type headache is classified as:

2. Tension-type headache (TTH)

2.1 Infrequent episodic tension-type headache

2.1.1 Infrequent episodic tension-type headache associated with pericranial tenderness

2.1.2 Infrequent episodic tension-type headache not associated with pericranial tenderness

2.2 Frequent episodic tension-type headache

2.2.1 Frequent episodic tension-type headache associated with pericranial tenderness

2.2.2 Frequent episodic tension-type headache not associated with pericranial tenderness

2.3 Chronic tension-type headache

2.3.1 Chronic tension-type headache associated with pericranial tenderness

2.3.2 Chronic tension-type headache not associated with pericranial tenderness

2.4 Probable tension-type headache

2.4.1 Probable infrequent episodic tension-type headache

2.4.2 Probable frequent episodic tension-type headache

2.4.3 Probable chronic tension-type headache

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 severed 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, 2004).

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 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 point A of the diagnostic criteria of the *Frequent episodic tension-type headache* (ICHD-II) and Episodic tension-type headache (IHS code).

More research is needed to conclude about the effectivity on this indication. In Finland the indication "herbal medicinal product for temporary headache" is authorized since 2003.

Also for the relief of headache, for adults and children over 6 years, a local application (100% oil) of the forehead with the aid of an applicator several times at intervals of 15 minutes, is proposed (Germany – MA, 1978)

3.3 Clinical Safety / Pharmacovigilance

3.3.1 Patient exposure

Peppermint essential oil widely used in flavouring, cosmetic formulations and skin-conditioning agent. In general 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 60-kg person, this amounted to an estimated daily dose of 0.6 mg/kg/day (FDA 1997) (Final report on the Safety Assessment of *Mentha Piperita*, 2001).

The highest recommended daily dose in EU is 1,2 ml peppermint oil i.e. 1080 mg peppermint oil, which contains maximum 140mg pulegone +menthofurane (Ph Eur). For a 60Kg person this would correspond to a daily intake of 2.3 mg/kg

Menthol

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

Pulegone and menthofurane

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): Menthofurane is the proximate hepatotoxin of pulegone. Tolerated daily intake (TDI) of menthofurane 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. Menthofurane is listed in the register of chemically defined flavouring substances laid down in Commission Decision (1999/217/EC, 2002/113/EC).

USA: Pulegone and menthofurane have FEMA GRAS status and are listed among the authorized synthetic flavouring substances. JECFA (Joint FAO/WHO Expert Committee on Food Additives, 2000): "No safety concern" was applied to (R)-(+)-pulegone and structurally related flavouring agents including (R)-(+)-menthofurane.

3.3.2 Adverse events

A total of 213 patients and healthy volunteers have been included in 8 studies where efficacy and safety in the use of peppermint oil were investigated. Oral administration in capsules or direct injection into the colon varied from a single dose to two and four weeks of treatment at daily doses of 3-6 x 0.2 mL of the oil. Peppermint oil, at concentrations of 20-50 μg/ml, evoked ion permeability of heart cell membranes.

PO caused 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 , 2005).

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

Menthol

A case of asthma due to menthol is 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 as by skin tests (Santos, 2001)

A form of stomatites and glossites with extremely prominent circumvallated papillae in patients who consumed excessive amounts of mint-flavoured sweets was described (Santos, 2001)

Pulegone

A literature review of cases of human intoxication with pennyroyal oil (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). 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 highest recommended daily dose in EU is 1.2 ml peppermint oil i.e. 1080 mg peppermint oil, which contains maximum 140 mg pulegone + menthofurane (Ph Eur). For a 60 kg person this would correspond to a daily intake of 2.3 mg/kg bw. Clearly, this recommended daily dose of peppermint oil in herbal medicinal products results in an intake of pulegone/menthofurane that exceeds the TDI (0.1 mg/kg) set for food by CEFS.

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

Inhalation

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

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

3.3.3 Serious adverse events and deaths

Anaphylactic shock is reported (Germany).

3.3.4 Laboratory findings

Not relevant

3.3.5 Safety in special populations and situations

3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

Contact sensitivity

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 (Goel, Lao, 2005).

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).

Use in children

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, 1966).

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 proposal of SPC for herbal medicinal products containing the essential oils Eucalyptus oil, Peppermint oil, Mint oil and Camphor, Cineol, Menthol, the product should not be used in children under the age of 2 years and in children with a history of seizures (febrile or not).

3.3.5.2 Drug interactions

Peppermint oil used on the skin with 5-fluouracil may increase the absorption rate of 5-fluouracil.

Use of food or antacids administered at the same time could cause early release of capsule content, if this is the pharmaceutical form used. Other medicinal products used for the normalization of the digestive function, should be avoided.

3.3.5.3 Use in pregnancy and lactation

Safety during pregnancy and lactation has not been established. As a precautionary measure, because of lack of data, use during pregnancy and lactation is not recommended.

3.3.5.4 Overdose

In animal studies, at 40 and 100 mg/kg body weight/day dose levels, histopathological changes in the cerebellum white matter were seen.

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 over usage, the stomach should be emptied by gastric lavage. Observation should be carried out with symptomatic treatment if necessary.

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

3.3.5.5 Drug abuse

One case of fulminant pulmonary oedema following IV injection of 5 ml of peppermint oil was described, on a patient with history of drug abuse (Matthias B. et al. 2005)

3.3.5.6 Withdrawal and rebound

Not relevant

3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

Not relevant

3.3.5.8 Contraindications

Hypersensitivity to peppermint and menthol.

Oral application

People with chronic heartburn, severe liver damage, and inflammation of the gallbladder, obstruction of bile ducts and other occlusive disorders of the GI tract should avoid it (Matthias B. et al. 2005)

People with gallstones should consult a physician before using peppermint oil (Sigmund DJ, McNally, 1969)

External application

Open skin areas of small children, especially on the nose, face and chest, are not recommended. Children under 2 years of age.

3.3.6 Assessor's overall conclusions on clinical safety

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 animals (rats), peppermint oil increases levels of cyclosporine in the blood, but this is not clear in humans.

On laboratory studies, peppermint oil is a moderately potent reversible inhibitor of in vitro CYP3A4 activity. The levels of drugs and supplements, which are processed by this enzyme, may be increased.

4. ASSESSOR'S OVERALL CONCLUSIONS

Peppermint oil has been use for generations as a digestive and carminative. More recently, as an authorized medicinal product for oral use, has been prescribed under the approved indication for the symptomatic relief of the irritable bowel syndrome. It has been also used topically, as a medicinal product, for the symptomatic treatment of neuralgic pain, in mild to moderate tension headache and for the relief of symptoms in cough and colds.

There are a lack of clinical studies to conclude about the efficacy of peppermint oil on the treatment of dyspepsia and on the treatment of cough and colds.

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

In general, the safety clinical studies showed transient and mild adverse effects. To minimise the adverse effects, like heartburn, the enteric-coated tablets are recommended. Some interactions were reported in vitro and in vivo studies, but more research should be done.

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. More research is needed to confirm these studies.

Nevertheless, this kind of indication needs the diagnosis of a medical doctor and must not be considered as a traditional medicinal product.

The indications proposed considered as proven, for well-established use are:

- Oral use

1. Herbal medicinal product for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome.

- Cutaneous use

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

ANNEXES

PROPOSED COMMUNITY HERBAL MONOGRAPHS FOR MENTHA X PIPERITA L., AETHEROLEUM

III. ASSESSMENT REPORT FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH TRADITIONAL USE

Mentha x piperita L., aetheroleum

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Mentha x piperitae* L., aetheroleum
Herbal preparation(s)	Menthae piperita aetheroleum
Pharmaceutical forms	Liquid dosage forms
Rapporteur	Dr Helena Pinto Ferreira Dr Ana Paula Martins

1 INTRODUCTION

Peppermint is an herbaceous plant highly aromatic, yielding a valuable essential oil widely used in flavouring, medicine and toiletries. Native to Europe, peppermint was much used to ancient times, having a long history of medicinal use, dating to ancient Egypt, Greece and Rome. Peppermint oil has been used historically for several health conditions, such as common cold conditions, cramps, headache, indigestion, joint pain and nausea, given orally or topically.

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

- Herbal substance(s)[4] [5]:

Mentha x piperitae L., aetheroleum

- Herbal preparation(s)[1] [2]:

Menthae piperita aetheroleum

2 TRADITIONAL MEDICINAL USE

- It should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.

2.1 Information on period of medicinal use in the Community regarding the specified indication

See point 2.3.1

2.2 Type of tradition, where relevant

European phytotherapy.

Ayurvedic medicine.

2.3 Bibliographic/expert evidence on the medicinal use

It is not certain if peppermint oil was produced in the Middle Ages (Gildemeister and Hoffman, 1900). One of the oldest specimens of peppermint is included in the herbarium of the English botanist John Ray (1628-1705).

There are reports of pharmacological and clinical studies published in medical, pharmacological and toxicological Journals since 1941. Oswald, N.C., in the British Medical Journal, concludes that the most desirable property of menthol is their pleasant smell because the main virtue of steam inhalation "is the expectorant effect of hot, moist hair".

According to Commission E, the uses proposed are:
Internal: Spastic discomfort of the upper gastrointestinal tract and bile ducts, irritable colon, catarrhs of the respiratory tract, inflammation of the oral mucosa.
External: Myalgia and neuralgia.

[4] According to "Note for guidance on Quality of herbal medicinal products" (CPMP/QWP/2819/00…)
[5] According to "Note for guidance on Specifications: Test procedures and acceptance criteria for herbal drugs, herbal preparations and herbal medicinal products" (CHMP/QWP/2820/00)

From ESCOP:
Internal use: Symptomatic treatment of digestive disorders such as flatulence; irritable bowel syndrome; symptomatic treatment of coughs and colds.
External use: Relief of coughs and colds; symptomatic relief of rheumatic complaints; tension-type headache; pruritus, urticaria and pain in irritable skin conditions.

There is a reference on Martindale The Extra Pharmacopoeia, 27th Edition, June 1977, that refers peppermint oil as "an aromatic carminative, relieving gastric and intestinal flatulence and colic and is employed with purgatives to prevent griping".

On the Indian Materia Medica by Dr K. M. Nadkarni's (3rd revised edition – 1976, reprinted 1999), peppermint is referred as a 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.

2.3.1 Evidence regarding the indication/traditional use

External use

1. For the relief of coughs and colds – WHO monographs; Germany 1978 (marketing authorization)
2. For symptomatic relief of muscle pain and of neuralgic pain, for example in mild to moderate tension headache – Germany – 1978, 1983 (marketing authorization)
3. Pruritus, urticaria and pain in irritable skin conditions – ESCOP monograph 2nd edition
4. Myalgia and neuralgia - Commission E Monographs

For inhalation

5. For the relief of symptoms in coughs and colds – Germany – 1978, 1983 (marketing authorization)

Traditionally used in cases of nasal congestion and common cold – France, Traditional Use 2005

6. Herbal medicinal products to treat symptoms of cold - Finland (marketing authorization, March 2003))

Oral use

7. Symptomatic treatment of coughs and colds – ESCOP monograph 2nd edition

   Treat symptoms of cold – Finland (marketing authorization, March 2003)

   Catarrhs of the respiratory tract, inflammation of the oral mucosa – Commission E Monographs

   Traditionally used locally (oromucosal spray solutions, lozenges) as an analgesic in conditions of the oral cavity and/or pharynx. - France, Traditional Use, 2005

8. Herbal medicinal product to balance mild, temporary and functional disorders in digestive tract - Finland (marketing authorization, March 2003)

On Ayurvedic medicine (Pudine, paparaminta):

External use: For muscle and joint stiffness

For cold, flu – *kapha*

2.3.2 Evidence regarding the specified strength

Peppermint oil should be used with caution. Doses of menthol over 1 g/Kg b.w. may be deadly.

The data from **Germany**, on the authorized products is mentioned:

Indication 2, 5% - 100% essential oil - cutaneous liquid

From **Martindale The Extra Pharmacopoeia**, 27th Edition, June 1977:

Peppermint water (U.S.N.F) – a saturated solution of peppermint oil in water.

Peppermint spirit (B.P.C.) – Spiritus Menthae Piperitae; Peppermint oil 10 ml, alcohol (90%) to 100 ml. Dose: 0, 3 to 2 ml.

From **Commission E Monographs**:

External use: Semi-solid and oily preparations 5-20%

In aqueous-ethanol preparations 5-10%

In nasal ointments 1-5% essential oil.

From **ESCOP**

External use:

Indication 3 – In dilute liquid or semisolid preparations equivalent to 1,1 – 1,0% m/m menthol or 1.25 – 16% m/m menthol.

- 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%

2.3.3 Evidence regarding the specified posology

For inhalation:

3 or 4 drops of the oil added to hot water, up to three times daily (Germany - authorized medicinal products, ESCOP, Commission E monographs)

2-3 drops spread on a stick and inhale – not more than three times/day- Finland (marketing authorization, March 2003) - not recommended for children under 12 years old.

4 x daily 4 spray nasal (2 in each nostril) or 4 buccal spray for adults and children over 6 years – France (TMP)

3-4 drops in hot water - Commission E Monographs

For oral use:

6 – 12 drops daily, that means: 2 – 3 times daily 3-4 drops - Germany (authorized medicinal products):

2-3 drops (0,08-0,12 ml) 3-4 times per day (0,2 – 0-5 ml) – Finland (marketing authorization, March 2003) - not recommended for children under 12 years old.

External use:

100% peppermint oil – some drops locally applied with the aid of an applicator several times at intervals of 15 minutes - Germany (authorized medicinal products)

Peppermint oil in ethanol solution in an applicator - Germany (authorized medicinal products)

2.3.4 Evidence regarding the route of administration

See point 2.3

2.3.5 Evidence regarding the duration of use

Finland – not recommended to use this product continuously over three months time.

Because of safety concerns the duration must be limited. If the symptoms persist during the treatment a medical doctor must be consulted.

2.4 Assessor's overall conclusion on the traditional medicinal use

Peppermint oil had 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, with more than 15 years in the EU countries, as more than 30 years on others.

2.5 Bibliographic review of safety data of the traditional herbal medicinal substances

2.5.1 Patient exposure

2.5.2 Adverse events

See point 3.3.2

2.5.3 Serious events and deaths

See 3.3.3

2.5.4 Intrinsic (including elderly and children)/extrinsic factors

See point 3.3.5.1

2.5.5 Drug-drug interactions and other interactions

Peppermint oil used on the skin with 5-fluouracil may increase the absorption rate of 5-fluouracil.

2.5.6 Use in pregnancy and lactation

2.5.7 Overdose

Inhalation of larges doses of menthol may lead to dizziness, confusion, muscle weakness, nausea and double vision [107].

For oral mucosal use see point 3.3.5.4.

2.5.8 Drug abuse

2.5.9 Withdrawal and rebound

Not relevant

2.5.10 Effects on ability to drive or operate machinery

Not relevant

2.5.11 Contra indications (hypersensitivity and allergic potential to be both covered)

It is contraindicated in cases of hypersensitivity to peppermint oil.

Use in children under 2 years old, because menthol can induce reflex apnoea and laryngospasm.

In children with history of seizures (febrile or not).

2.6 Non-clinical safety data

2.6.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

(e.g. single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, local tolerance, other special studies)

Assessor's overall conclusions on safe use

It is contraindicated in cases of hypersensitivity to peppermint oil and in children under the age of two years old because menthol can induce reflex apnoea and laryngospasm.

In children with history of seizures (febrile or not).

3 PHARMACOLOGICAL PROPERTIES[6]

3.1 Overview of pharmacological effects of herbal substance(s), herbal preparation(s) and relevant constituents thereof on the basis of long-standing use and experience

4 LITERATURE REFERENCES

5 ASSESSOR'S OVERALL CONCLUSIONS

Peppermint oil has been used historically for several health conditions, orally, topically and for inhalation, existing in countries of the EU as medicinal products with marketing authorization. The oral use for digestive complaints was subject to several pharmacological and clinical studies, giving sufficient data to be considered with a well-established use for the indication "Symptomatic relief of minor spasm of the gastrointestinal tract, flatulence and abdominal pain, experienced by patients with irritable bowel syndrome".

The indications proposed, which demonstrated traditional use and plausibility, according to the pharmacological properties, are the following:

External 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:

IV) For the relief of symptoms in coughs and colds.

Oramucosal use

V) For the relief of symptoms in coughs and colds

ANNEXES

PROPOSED COMMUNITY HERBAL MONOGRAPHS ON MENTHA X PIPERITA L., AETHEROLEUM

LITERATURE REFERENCES

[6] Not required as per Article 16c(1)(a)(ii) of Directive 2001/83/EC as amended