EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Lavandula angustifolia* Miller, aetheroleum and *Lavandula angustifolia* Miller, flos

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Lavandula angustifolia* Miller, flos
Herbal preparation(s)	• Lavandulae aetheroleum Essential oil obtained by steam distillation from the flowering tops of *Lavandula angustifolia* Miller • Lavandulae flos a) Comminuted herbal substance b) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 50-60% v/v
Pharmaceutical forms	• Lavandulae aetheroleum Herbal preparation in liquid dosage form for oral use and as a bath additive. • Lavandulae flos Herbal substance or comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid dosage form for oral use.
Rapporteur	Gert Laekeman

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Introduction

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

- Herbal substance(s)

Lavender flower consists of the dried flowers of *Lavandula angustifolia* Miller (*Lavandula officinalis* Chaix) (European Pharmacopoeia 2008a).

- Herbal preparation(s)

Essential oil obtained by steam distillation from the flowering tops of *Lavandula angustifolia* Miller (*Lavandula officinalis* Chaix) (European Pharmacopoeia 2008b).

The species is regularly confused with other lavender species *L. x intermedia* Emeric. (Lavandin) and *L. latifolia* MEDIK. (Spiklavender). If no detailed quality specifications are mentioned, the herbal substance consists of flowers from different flower species (Hänsel et al. 1993).

- 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.

- Constituents

Lavender flower contains not less than 13 ml/kg of essential oil, calculated with reference to the dried drug.

Lavender flower

- Essential oil (1-3%)

- Coumarin derivatives: umbelliferon, herniarine

- Flavonoids

- Sterols (traces): cholesterol, campesterol, stigamsterol, β-sitosterol

- Triterpenes (traces): mictomeric acid, ursolic acid

- Tannins: up to 13% in the herbal substance

- Phenylcarboxylic acids such as rosmarinic acid, ferulic acid, isoferulic acid, α-cumaric acid, p-cumaric acid, gentisinic acid, p-OH-benzoic acid, caffeic acid, melilotic acid, sinapinic acid, sytingic acid, vanillinic acid.

Lavender oil

The main components of the essential oil are monoterpene alcohols (60-65%) such as linalool (20-50% of the fraction), linalyl acetate (25-46% of the fraction). Others include cis-ocimen (3-7%), terpinene-4-ol (3-5%), limonene, cineole, camphor, lavandulyl acetate, lavandulol and α-terpineol, β-caryophyllene, geraniol, α-pinen. Non-terpenoid aliphatic components: 3-octanon, 1-octen-3-ol, 1-octen-3-ylacetate, 3-octanol (ESCOP 2009; Hänsel *et al*. 1993; Bruneton 1999).

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	See composition
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No mono preparations registered
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No mono preparations registered
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only flowers in herbal tea
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combined preparations registered
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	See detailed information
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information

Member State	Regulatory Status				Comments
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Licensed medicine

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'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

Composition of preparations

Member State	Regulatory Status	Comments
Austria	**BUCOSEPT Lavendel–Ölbad** 100 g solution contains 5 g essential oil from *Lavandula angustifolia.* Posology For a full bath 30 ml of the solution; duration of bath 15-20 minutes. Indication Supportive in case of exhaustion.	On the market since 1994
Denmark	2 products with Lavandulae herba as one of the components in herbal tea.	On the market since 1999
France	**Aromastress oleocapsule aromatique** (Pranârom–Natessence) Essential oils of *Origanum majorana*, *Lavandula hybrida*, *Citrus reticulata*, *Aloysia triphylla* Indication Stress, nervousness **Climarome voies respiratoires** (Cosbionat) Essential oils of *Lavandula angustifolia*, *Melaleuca viridiflora*, *Pinus sylvestris*, *Mentha arvensis*, *Thymus vulgaris* 33.6% - excipients qsp 100. Indication Prevention of respiratory tract infections. Adults and children ≥3 years: to be applied on tissue for inhalation or to be put on the throat or the thorax. **Perubore spray aromatique** (Mayoli spindler): essential	Capsule as food supplement. >30 years on the market >30 years on the market >30 years on the

Member State	Regulatory Status	Comments
	oils of *Thymus vulgaris*, *Rosmarinus officinalis*, *Lavandula officinalis*, *Cinnamomum zeylanicum*. Indication Cough, common cold, nose congestion. Adults and children >30 months: vaporise 2 to 3 puffs in the atmosphere or on tissue when the first symptoms of common cold occur. To be repeated several times daily. At nighttime 2 to 3 puffs on the pillow.	market
	Vivalessence (Motima) Essential oils of *Lavandula*, *Cinnamomum*, *Satureja*, *Eucalyptus* 4.8%, hydroalcoolic extract of *Avena*, ethanol – water qs. ad 100%. Indication Seasonal complaints. Adults, children >7 year: Seasonal complaints: during 15 days 30 to 50 drops daily in a glass of water (in the morning).	>30 years on the market
	Tetesept anti-stress Bad (Merz Pharma) essential oils of *Lavandula*, *Melissae indicum*, *Pinus*, *Rosmarinus.* Indication No indication mentioned. To be put in a bath.	On the market since 1996
	Tetesept Entspannungs Bad (Merz Pharma) essential oils of: *Citrus aurantium spp.*, *Cinnamomum*, *Lavandula* Indication No indication mentioned. To be put in a bath.	On the market since 1983
Germany	**Lavandulae aetheroleum** Under diluted form: 10% and 1% (mostly in olive oil) Anthroposophical use	On the market at least since 1949 Notified
	Lavandulae aetheroleum In soft capsules containing 80 mg Lavandulae aetheroleum Indication For treatment of anxious restlessness or For treatment of restlessness due to anxiety Posology 1x1 capsule per day For oral use in adults over 18 years Specific information Possible influence on medicinal products, which act via GABA-receptors (barbiturates, benzodiazepine). Clinical data are not available. Adverse events: eructation (7%); nausea (2%) No use in children and adolescents below the age of 18 years.	Authorised product since 2009 WEU

Member State	Regulatory Status	Comments
	Up to now, there was no need to undertake pharmacovigilance actions. **Lavandulae aetheroleum** All as bath additive Indication Traditionally used to improve feeling in state of exhaustion Posology For use in adults and adolescents over 12 years 1) 15-20 ml bath additive / full bath at 35-38° for 10-20 minutes 7 g Lavandulae aetheroleum / 100 g (= approximately 96 ml) bath additive 2) 15-20 ml bath additive / full bath at 35-38° for 10-20 minutes 7 g Lavandulae aetheroleum / 100 g (=95 ml) bath additive 3) 30 ml bath additive / 150-200 l water at 35-37° for 15-20 minutes 10 g Lavandulae aetheroleum / 100 g bath additive Specific information General contraindications to take a bath. Up to now, there was no need to undertake pharmacovigilance actions.	Authorised product at least since 1976 TU
United Kingdom	Oleum aethereum Lavandulae Dilution of 10%	Licensed product

1.3. Search and assessment methodology

For this assessment report the following sources were used:

- Allied and alternative medicine

- Biosis

- Chemical abstracts (since 1967)

- Current contents search - bibliographic records

- Derwent drug file

- Derwent drug file backfile

- Excerpta Medica

- International pharmaceutical abstracts

- Medline

- Pascal

- PubMed

- Standard reference books

These sources were searched on the following terms (alone or in combination):
Lavandula, *lavender*, *essential oil*, *stress*, *anxiety*, *relaxation*, *sleep*, *sleeping*, *disorder*

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

In the 15th century when the technique of steam distillation was developed, Hildegarde von Bingen, Matthiolus and Paracelsus described the use of distilled water saturated with the essential oil of lavender as a sedative (*'Nervinum'*) and against tooth- and headache (Kroeber 1935, Madaus 1938). The oil was traditionally used by evaporating it into rooms to calm 'excited' children. Even narcotic effects have been described when high concentrations were used (Guillemain *et al*. 1989). Rembertus Dodonaeus (1608) mentioned already the use of lavender water as a calming agent, even in case of epileptic seizures.

Pabst (1888) describes the oil as belonging to strongly toxic substances.

Indications can also be related to gastro-intestinal complaints and musculoskeletal disorders. Some sources mention posologies for oral use: five drops of essential oil on a cube of sugar, two times a day (Fischer 1939). Lavender is also used in behavioural therapy (Pelikan 1958).

Flowers and essential oil of *Lavandula officinalis* have been used for their sedative activity throughout Europe (Weiss & Fintelmann 1999). Leclerc (1966) has mentioned the use of lavender flowers in phytotherapeutic practice in France.

According to information on marketed products, lavender oil has been marketed for use as bath additive since 1976. Since 2009, soft capsules with lavender oil have been marketed as an authorised product in Germany. This practice has been preceded by a long-standing tradition of administering the essential oil as drops on a piece of sugar (ESCOP 2009; British Herbal Pharmacopoeia 1983, referring to the British Pharmaceutical Codex BPC 1973).

2.2. Information on traditional/current indications and specified substances/preparations

Peroral use

Soft capsules with Lavandulae aetheroleum have been authorised in Germany since 2009.

- Therapeutic indications: WEU
  For treatment of anxious restlessness or for treatment of restlessness due to anxiety.
- Posology
  For adults ≥ 18 years: soft capsules containing 80 mg, 1 capsule per day.

Use as bath additive

Bath additives with Lavandulae aetheroleum have been authorised in Germany since at least 1976.

- Therapeutic indications: TU
  Herbal medicinal product traditionally used to improve feeling in state of exhaustion.
- Posology
  For adults and adolescents over 12 years: 15 to 30 ml bath additive containing 7 to 10% (w/w) Lavandulae aetheroleum per full bath at 35-38°C during 10-20 minutes.

A bath additive with 5% Lavandulae aetheroleum has been on the market in Austria since 1994. The posology is the same as for the preparations in Germany.

Cutaneous use

There is a tradition for direct cutaneous use of lavender oil in diluted (mostly 10%) preparations. This use is for supportive treatment in conditions of nervous or physical tension which can show as:

- restlessness
- difficulties falling asleep
- gastro-intestinal (abdominal) complaints, e.g. cramps and wind (flatulence)
- periodic pains.

The product is a traditional herbal medicinal product for use in the specified indications exclusively based upon long-standing use in anthroposophic medicine in Germany.

There exists indeed a lot of written protocol data survey of cutaneous anthroposophic practice. This practice goes back more than 30 years and can be considered as traditional (Fischer 1939). The translation into exact instructions seems to be of a more recent date.

The first document mentioning a detailed use of the 10% lavender oil diluted with olive oil dates from 1999. Under posology, it reads:

... if no other instructions are given, 2-3 times per day 3-5 drops of essential oil should be gently rubbed on the skin area affected or applied on a gauze …

... in case of balance disturbance, difficulties to fall asleep and functional heart disease and circulatory difficulties, the left part of the thorax should be rubbed with essential oil …

... in case of flatulence the essential oil should be rubbed clockwise on the belly …

... in case of dysmenorrhoea the essential oil must be applied on the belly and in the lumbar region …

... for baby's and small children up to 5 years old, the essential oil should not be directly rubbed as a 10% preparation but applied on a gauze …

This information specifies the places where to rub the skin with the diluted (10%) lavender oil. It is even specified that in case of flatulence the rubbing should be done clockwise on the belly. There also does not seem to be an age limit.

With regard to the dose used for compresses the number of drops to be put on the gauze proposed cannot be retrieved in a written source.

Conclusion on the cutaneous use: there is a long-lasting tradition for cutaneous use. However the modalities cannot yet be considered as traditional, especially not for children.

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

According to the ESCOP monograph (2009)

- Indications

Mood disturbances such as restlessness, agitation or insomnia

- Posology

- Lavender flower

An infusion is made of 1-2 teaspoons (approximately 0.8 to 1.6 g) in 150 ml of water. The number of doses is not specified.

Tincture (1:5 in 50% v/v ethanol), 60 drops per day

- Lavender oil

1-4 drops (approximately 20-80 mg) e.g. on a sugar cube

According to Blumenthal et al. (2000) (referring to Commission E monographs)

- Indications

Internal use: restlessness or insomnia and nervous stomach irritation, Roehmheld's syndrome (stomach discomfort), meteorism and nervous intestinal discomfort.

For balneotherapy: treatment of functional circulatory disorders.

The German standard license for lavender tea lists it for restlessness, sleeplessness, lack of appetite, nervous irritable stomach, meteorism and nervous disorders of the intestines.

- Posology

Infusion: 1-2 teaspoons (approximately 0.8-1.6 g) in 150 ml water
Essential oil: 1-4 drops (approximately 20-80 mg) e.g. on a sugar cube
Bath additive: 20-100 g dried flowers for a 20 liter bath

According to the British Herbal Pharmacopoeia (1979 and the 1983 compilation)

- Posology

Internally as a tea: dried flowers 1-2 g by infusion 3 times daily
Tincture (1:5) in 60% ethanol, 2-4 ml 3 times daily
Lavender oil BPC (1973), 0.06–0.2 ml 3 times daily

According to Leclerc (1966)

Lavandulae flos is used in case of asthma, whooping cough, influenza and laryngitis. An infusion is made of 5 parts per 100 (w/w) and 4 cups a day are prescribed.

According to Valnet (since 1964)

- Indications

Internal use:

- Irritability, spasms, insomnia
- Fever blasts, infectious diseases
- Neurasthenia, melancholy
- Respiratory diseases: asthma, whooping cough, influenza, bronchitis due to whooping cough
- Oliguria
- Rhumatism

- Instability during childhood
- Atonic stomach or intestinal atony
- Migraine, vertigo, hysteria, sequellae of paralysis
- Typhoid enteritis (diarrhoea)
- Cystitis, blennorrhoea
- Dermal eruptions
- Intestinal parasites
- Metrorrhagia, leucorrhoea
- Hypertension

- Posology

Infusion: 1 teaspoon in a cup of boiled water, infusion during 10 minutes: 3 cups per day between meals.

Alcoholature: 40 drops 4 times daily in water (no detailed composition of alcoholature communicated).

Essential oil: 2-5 drops in honey or in an alcoholic solution. In case of anaesthesia: 1 g aids at mentally relaxing, without losing intellectual capacity.

Vaporisation: make a solution of 2% in water. To be vaporised in public rooms.

According to Madaus (1938)

- Indications

Internal use: Lavender mildly acts on the nervous system, especially in case of migraine. It is used against neurasthenia, vertigo, nervous tachycardia, general nervous tension, hysteria, spasms, weakness and sleeplessness. Lavender has been used against affections of the stomach like gastritis, against meteorism and oedema.

External use: Lavender flowers are used as a bath additive. Lavender oil is used for local massage in case of rheumatism, gout, neuralgia, ischias and scabies. Rinsing fluid is made in case of *fluor albus*.

- Posology

Essential oil: 8 drops (without further specification)

Tincture (strength not given): 10-15 drops

Infusion: 2-3 teaspoons (= 3-4.5 g) daily

3. Non-Clinical Data

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

- *In vitro* studies

Antimicrobial effects

Lavender oil had an antimicrobial activity against *Escherichia coli, Bacillus subtilis, Candida albicans* and *Staphylococcus aureus*, but not against *Pseudomonas aeruginosa*. The model used was the plate diffusion test. No details about the concentrations used are mentioned. Linalool was active against *Streptococcus mutans* with a MIC of 1600 µg/ml which is a rather high concentration (Kubo *et al.* 1993).

Eight essential oils were examined using the agar dilution method, including *Carum carvi, Citrus aurantium* var. *amara, Foeniculum vulgare dulce, Illicium verum, Lavandula angustifolia, Mentha arvensis, Mentha x piperita,* and *Trachyspermum copticum*. Doubling dilutions of the essential oils were tested against 12 species of intestinal bacteria, which represent the major genera found in the human gastrointestinal tract (GIT). *Carum carvi, Lavandula angustifolia, Trachyspermum copticum,* and *Citrus aurantium* var. *amara* essential oils displayed the greatest degree of selectivity, inhibiting the growth of potential pathogens at concentrations that had no effect on the beneficial bacteria examined. The most promising essential oils for the treatment of intestinal dysbiosis are *Carum carvi, Lavandula angustifolia, Trachyspermum copticum,* and *Citrus aurantium* var. *amara*. The herbs from which these oils are derived have long been used in the treatment of gastrointestinal symptoms and the *in vitro* results of this study suggest that their ingestion will have little detrimental impact on beneficial members of the GIT microflora. For lavender was among the oils displaying the highest degree of selectivity. Concentrations varied from 0.55 to 4.5% (v/v). More research is needed, however, to investigate tolerability and safety concerns, and verify the selective action of these agents (Hawrelak *et al*. 2009).

Spasmolytic effects

The ileum of the guinea-pig and the rat uterus and phrenic nerve diaphragm were used as an experimental model. These isolated organs contract when exposed to acetylcholine, histamine or noradrenaline or electrically stimulated (field stimulation). Lavender oil inhibited the contractions of the isolated ileum by about 50%. Pure linalool had similar effects. In contrast with lavender oil, a concentration-effect relationship was studied with linalool: $5x10^{-5}$ to $2x10^{-4}$ g/ml on the diaphragm and $4x10^{-6}$ to $8x10^{-5}$ g/ml was used on the isolated ileum; both organs were electrically stimulated. However no concentration-effect curves were displayed.

The inhibition of the electrically stimulated contractions by lavender of guinea-pig ileum appeared to be postsynaptic and not atropine-like, as lavender inhibited the contractile responses due to acetylcholine and to histamine to a similar degree. The relaxation effect by isoprenaline was potentiated by linalool, which may indicate a phosphodiesterase inhibitory activity (Lis-Balchin & Hart 1997 and 1999).

Experiments were designed to investigate the relaxation mechanism of linalyl acetate as the major ingredient of lavender essential oil in rabbit carotid artery specimens. Linalyl acetate produced sustained and progressive relaxation during the contraction caused by phenylephrine. The relaxation effect of linalyl acetate at a concentration near the EC_{50} was partially but significantly attenuated by nitroarginine as an inhibitor of nitric oxide synthase, 1H-(1,2,4) oxadiazolo (4,3-a) quinoxaline-1-one as an inhibitor of guanylyl cyclase, or by the denudation of endothelial cells. In specimens without endothelium, the phenylephrine-induced contraction and phosphorylation of myosin light chain (MLC) were significantly attenuated after the pretreatment with linalyl acetate. The relaxation caused by linalyl acetate in the endothelium-denuded specimens was clearly inhibited by calyculin A as an inhibitor of MLC phosphatase, although not by ML-9 as an inhibitor of MLC kinase. Furthermore, suppression of the phenylephrine-induced contraction and MLC phosphorylation with linalyl acetate was canceled by the pretreatment with calyculin A. These results suggest that linalyl acetate relaxes the

vascular smooth muscle through partial activation of the nitric oxide/cyclic guanosine monophosphate pathway, and partial MLC dephosphorylation via activating MLC phosphatase (Koto *et al.* 2006).

Other effects

Cultures of cerebellar granular cells from rat pups were exposed to neurotoxic concentrates of glutamate (10^{-7} M). The neuroprotective effect of a dry aqueous extract from lavender flower (DER approximately 5:1) was tested at concentrations of 10 µg/ml, 100 µg/ml, 1 mg/ml and 10 mg/ml. At 100 µg/ml and 1 mg/ml, the extract significantly reduced glutamate-induced neurotoxicity from 37% to 29% ($p<0.05$) and 21% ($p<0.001$) respectively (Büyükokuroglu *et al*. 2003).

A study on MCF-7 human breast-cancer cells (positive for oestrogen receptors) demonstrated that lavender oil is weakly oestrogenic in concentrations of 0.01 and 0.03% (V/V), treated for 18 h. In MDA-kb2 cells (positive for androgen receptors) lavender oil was revealed to be weakly anti-androgenic in concentrations between 0.0001 and 0.01% (V/V) treated for 24 h (Henley *et al*. 2007).

Lavender oil concentration-dependently inhibited histamine release from peritoneal mast cells ($p< 0.05$):
- stimulated by compound 48/80 (a synthetic phosphodiesterase and ATP-ase inhibitor) at dilutions of 1:500, 1:100, 1:10, 1:1 and undiluted
- stimulated by anti-dinitrophenyl IgE at dilutions of 1:100, 1:10, 1:1 and undiluted.

It also had a significant inhibitory effect on anti-dinitrophenyl IgE-induced TNFα secretion from peritoneal mast cells at 1:1000, 1:100, 1:10 and undiluted ($p<0.05$) (Kim & Cho 1999).

Assessor's comments:
The relevance of antimicrobial, spasmolytic as well as other effects is difficult to evaluate, as no detailed information about concentrations as such and concentration-effect relationship is available. For the inhibition of histamine release, highly concentrated dilutions or even pure oil have been used, which seems of poor relevance.

It is difficult to judge the human relevance of oestrogenic effects seen *in vitro.*

- *In vivo* studies

Anticonvulsive effects

Purpose	Species	Intervention	Outcome
to study the anticonvulsive effects of lavender (Atassanova-Shopova & Roussinov 1970)	female and male rats	electroshock- and metrazole-induced convulsions	Electroshock-induced convulsions were inhibited after single intraperitoneal doses of lavender oil at 138 and 140 mg/kg body weight respectively; metrazole-induced convulsions were also inhibited in 60-70% of the animals by intraperitoneal doses of 200-300 mg/kg.
to study the anticonvulsive effects of	male mice stimulated with pentetrazol,	Anticonvulsive effects of lavender oil inhalation (0.3, 0.5 and 1 ml of lavender oil soaked in cotton, in a glass cylinder) were studied	Compared to controls, lavender oil blocked convulsions induced by the lower dose of pentetrazol and by nicotine; no

Purpose	Species	Intervention	Outcome
lavender (Yamada *et al*. 1994)	nicotine or strychnine (groups of 3 to 7 mice per convulsive agent)	in mice; convulsions were induced by pentetrazol (50 and 100 mg/kg i.p.), nicotine (7.5 mg/kg i.p.), strychnine (2.5 mg/kg i.p.) or by electroshocks (80 V, 0.4 seconds). The convulsive agents or electroshocks were administered after inhalation of lavender oil for 15 minutes.	anticonvulsive effects were observed with strychnine, after electroshocks; lavender oil dose-dependently reduced tonic extensions and clonic convulsions.

Sedative effects

Purpose	Species	Intervention	Outcomes
to study the sleep prolongation (Atassanova-Shopova & Roussinov 1970)	rats	lavender oil administered i.p. to rats at 100 mg/kg, anesthetized with hexobarbital sodium (100 mg/kg i.p.) and alcohol (35%, 3.5 g/kg i.p.)	Duration of anaesthesia induced by hexobarbital sodium was doubled and anaesthesia induced by alcohol (35%, 3.5 g/kg i.p.) was prolonged almost two-fold; duration of the anaesthesia by chloral hydrate (300 mg/kg i.p.) was more than 1.5-fold longer.
to study locomotor activity (Atassanova-Shopova & Roussinov 1970)	male albino mice	lavender oil i.p. administered during the rotarod motor test	Lavender oil administered i.p. at 200-300 mg/kg reduced spontaneous locomotor activity, as well as locomotor activity increased by caffeine-sodium benzoate or amphetamine; in the rotarod test motor coordination was reduced with an ED_{50} of 248 mg/kg.
to study locomotor activity (Buchbauer *et al*. 1991; Buchbauer *et al*. 1993a)	6-month old female mice	exposure to an atmosphere containing the vapour of lavender oil or its constituents linalool and linalyl acetate Concentrations in the atmosphere were not measured.	Locomotor activity decreased remarkably and time-dependently in two studies, after 60 minutes of inhalation, motility was reduced by 43% and 78% with lavender oil, 15% and 73% with linalool, and 35% and 69% with linalyl acetate as compared to controls. Increase in activity of 160% after an injection of caffeine (0.1%, 0.5 ml i.p.) was reduced to 105%, 126% and 132%

Purpose	Species	Intervention	Outcomes
			respectively by inhalation of the vapour of lavender oil, linalool or linalyl acetate.
to study stress-induced hyperthermia (Akutsu *et al*. 2002)	male Wistar rats transmitter were implanted in order to make records of heart rate and body temperature	cages with a bedding that had been sprayed with 200 µl of a 0.03% solution of lavender oil, green leaf odour (mixture of hexenol and hexenal), α-pinene or the solvent only (triethyl citrate) as control (n=12 per group, except for the control: n=6)	Following transfer to this novel environment the body temperature of the rats increased by almost 1°C, indicating stress-induced hyperthermia; this was attenuated by green leaf odour and α-pinene, but not by lavender oil or solvent.
to study explorative behaviour and sleeping time (Delaveau *et al*. 1989), (Guillemain *et al*. 1989)	mice	four plates test with oral administration of lavender oil at 0.4 ml/kg bw (as a 1:60 dilution in olive oil) daily for 5 days; pentobarbital-induced sleeping time of 30 minutes; hole board test and the labyrinth test	Lavender oil increased in the number of explorations by 68%, indicating an anxiolytic effect; with the same single dose sleeping time was prolonged to 35-59 minutes (Delaveau *et al*. 1989). The same dose of lavender oil did not decrease motility in the hole board test nor increase the number of explorations in the four plates test or number of entries into open arms in the labyrinth test to statistically significant levels (in terms of anxiolytic effects), although modest increases were observed; pentobarbital-induced sleep latency was significantly shortened ($p<0.03$) and pentobarbital-induced sleeping time was increased ($p<0.05$) compared to a control group, indicating a sedative effect (Guillemain *et al*. 1989).
to study locomotor activity (Peana *et al*. 2003)	mice	linalool administered to mice subcutaneously at 25, 50, 75 and 100 mg/kg	Spontaneous locomotor activity increased by 95% ($p<0.05$ for 75 mg/kg) and 300% ($p<0.0005$ for 100 mg/kg) respectively, whereas 25 mg/kg produced a non-significant increase of 15%,

Purpose	Species	Intervention	Outcomes
			and 50 mg/kg a non-significant decrease of 34%.
to investigate the effects of lavender essential oil inhalation on gerbil behaviour (Bradley *et al*. 2007)	male and female gerbils	gerbil behaviour in the elevated plus maze test was observed and results compared with the effects of diazepam (1 mg/kg) i.p. after 30 minutes and 2-week administration; odour exposure was via an electronic vapouriser and aroma stone, placed into the animal holding room and the experimental suite, but out of reach of the animals, during behavioural testing; lavender oil was refreshed 3 times daily with 4 drops of the essential oil, to achieve the concentration commonly recommended by aromatherapists	Traditional measures of open entries showed an increasing trend over the 2 weeks exposure, whereas ethological measures indicative of anxiety (stretch-attend frequency and percentage protected head-dips) were significantly lower; exploratory behaviour and total head-dip frequency started to increase 24 h after lavender and lasted for the 2 weeks exposure. These results are comparable with diazepam administration; females showed a significant decrease in protected head-dips compared to both males and to female controls. In conclusion, exposure to lavender oil may have an anxiolytic profile in gerbils similar to that of the anxiolytic diazepam.
to study the anticonflict effects of lavender oil and identify its active constituents (Umezu *et al*. 2006)	ICR mice	two conflict tests in ICR mice were used and then the active constituents were identified; lavender oil produced significant anticonflict effects at 800 and 1600 mg/kg in the Geller conflict test and at 800 mg/kg in the Vogel conflict test, suggesting that the oil has an anti-anxiety effect; analysis using GC/MS revealed that lavender oil contains 26 constituents, among which alpha-pinene (0.22%), camphene (0.06%), beta-myrcene (5.33%), p-cymene (0.3%), limonene (1.06%), cineol (0.51%), linalool (26.12%), borneol (1.21%), terpinen-4-ol (4.64%), linalyl acetate (26.32%), geranyl acetate	Cineol, terpinen-4-ol, α-pinene and beta-myrcene did not produce any significant anticonflict effects in the Geller test; linalyl acetate did not produce any significant anticonflict effects in either test; both borneol and camphene at 800 mg/kg produced significant anticonflict effects in the Geller, but not in the Vogel conflict test; linalool, a major constituent of lavender oil, produced significant anticonflict effects at 600 and 400 mg/kg in the Geller and Vogel tests, respectively, findings that were similar to those of lavender oil; authors concluded that linalool is the major pharmacologically active

Purpose	Species	Intervention	Outcomes
		(2.14%) and caryophyllene (7.55%) were identified; effects of linalool, linalyl acetate, borneol, camphene, cineol, terpinen-4-ol, alpha-pinene and beta-myrcene were examined using the Geller and Vogel conflict tests in ICR mice	constituent involved in the anti-anxiety effect of lavender oil.
to establish a valid animal model of the effects of olfactory stimuli on anxiety, a series of experiments was conducted using rats in an open- field test (Shaw *et al*. 2007)	rats	effects of lavender oil were compared with the effects of chlordiazepoxide (CDP), as a reference anxiolytic with well-known effects on open-field behaviour rats were exposed to lavender oil (0.1-1.0 ml) for 30 min (experiment 1) or 1 h (experiment 2) prior to open-field test and in the open field or injected with CDP (10 mg/kg i.p.); in experiment 3 rats were pre-exposed during different durations (1 to 4 h) and during the field test; also in experiment 4 rats were exposed during the open field test, during 1 h entering the field, one half of them had also lavender oil in the field; in Experiments 3 and 4, various combinations of pre-exposure times and amounts of lavender oil were used	CDP had predicted effects on behaviour, and the higher doses of lavender oil had some effects on behaviour similar to those of CDP. In experiment 1, there was a significant decrease in peripheral movement and defecation for CDP and the highest doses (0.5 and 1 ml) of lavender oil; the same results were seen in experiment 2, and there was an additional significant stimulation of rearing with the same doses. In experiment 3 with sufficient exposure time and quantity of lavender, the same effects were obtained as in experiment 2, but for all doses; there was also an increase in immobility for lavender oil doses only; the same results were obtained in experiment 4; experiment 4 demonstrated that these behavioural effects of lavender could be obtained following pre-exposure, even if no oil was present in the open-field test. Together, these experiments suggest that lavender oil does have anxiolytic effects in the open field, but that a sedative effect can also occur at the highest doses.

Anti-inflammatory and analgesic effects

Purpose	Species	Intervention	Outcome
to study local anti-inflammatory activity (Kim & Cho 1999)	mice and rats	ear swelling induced by the standard compound 48/80 (200 µg/ear intradermally); pre-treatment with lavender oil (mice); passive cutaneous anaphylaxis induced by anti-dinitrophenyl IgE (rats) and topical or intradermal lavender oil (no further specifications about doses)	Swelling (ear - mice) was concentration-dependently inhibited by topical or intradermal pre-treatment with lavender oil at concentrations of 1:100, 1:10, 1:1 and undiluted ($p<0.05$); cutaneous anaphylaxis was also concentration-dependently inhibited following application of lavender oil topically (1:100 non-significant; 1:10; 1:1 and undiluted, $p<0.05$) or intradermally (1:100,1:10 and 1:1 non-significant; undiluted, $p<0.05$).
to study local anti-inflammatory activity (Yasukawa *et al*. 1989)	mice	linalool locally applied 30 minutes before the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear oedema test	2 mg of linalool inhibited oedema by 30% ($p<0.01$).
to study systemic anti-inflammatory activity (Pulla Reddy & Lokesh, 1994)	male Wistar rats	linalool administered by gavage at 100 and 200 mg/kg 3 h before injection of carrageenan (2.5 mg/kg body weight) in the carrageenan-induced paw-oedema test	Oedema was inhibited by 23 and 24% respectively.
to study systemic anti-inflammatory activity (Peana *et al*. 2002)	rats	the carrageenan-induced rat paw oedema test; linalool and linalyl acetate perorally administered	After 3 h: (-)-linalool at 25, 50 and 75 mg/kg b.w. inhibited oedema by 28, 29 and 33% respectively ($p<0.01$, $p<0.01$ and $p<0.005$); (±)-linalool at 50 and 75 mg/kg (but not at 25 mg/kg) inhibited oedema by 51 and 38% ($p<0.05$ and $p<0.05$); linalyl acetate at 64 and 96 mg/kg (but not at 32 mg/kg) inhibited oedema by 40 and 36% ($p<0.01$ and $p<0.05$) H-linalool is the naturally-

Purpose	Species	Intervention	Outcome
			occurring isomer, but the racemate (±)-linalool may be present in distilled or extracted essential oil.
to study the anti nociceptive effect (Peana *et al*. 2003)	mice	the acetic acid induced writhing test or the hot plate test; linalool subcutaneously injected	In the writhing test, linalool inhibited the response dose-dependently by 38% at 25 mg/kg subcutaneously (p=0.03) and by 52% at 50 mg/kg (p=0.01) and 47% at 75 mg/kg (p=0.03); the effect of linalool at 50 mg/kg was completely reversed by i.p.-administered naloxone (5 mg/kg) or atropine (5 mg/kg); in the hot plate test, linalool at 100 mg/kg significantly increased reaction time, by 45% after 2 h (p=0.004) and by 89% after 3 h (p=0.0001), while lower doses had no effect.
to study the anti-nociceptive effect (Peana *et al*. 2004a)	male Wistar rats	in the paw withdrawal test, unilateral subplantar injection of carrageenan and L-glutamate induced a hyperalgesic effect (decrease of thermal threshold) on the injection side, while prostaglandin E, induced hyperalgesia on both the injection and the contralateral side linalool was administered by abdominal subcutaneous injection 30 minutes before intraplantar injection of the hyperalgesic substances	In the first test, linalool (50, 100 or 150 mg/kg) significantly reduced withdrawal latencies induced by carrageenan (p<0.05 to p<0.001), with no effect on the contralateral paw; linalool at the highest dose (200 mg/kg intraplantar) prevented the reduction in paw withdrawal latency induced by L-glutamate (p<0.0005), demonstrating anti hyperalgesic and anti-nociceptive effects; an anti-nociceptive effect was also apparent in the contralateral paw (p=0.02) compared to the untreated control; in the test with prostaglandin E, linalool at 200 mg/kg antagonized paw withdrawal latency on the side contralateral to the prostaglandin E2 injection (p=0.032), but inhibition of withdrawal latencies on the side

Purpose	Species	Intervention	Outcome
			of the injection were non-significant.
to study the anti-nociceptive effect (Peana *et al*. 2004b)	male mice and Wistar rats	hot plate test with linalool administered subcutaneously; formalin test	Linalool significantly increased reaction time in the hot plate test with mice (p=0.005 at 100 mg/kg and p=0.003 at 150 mg/kg); linalool at 50 and 100 mg/kg s.c. caused a significant reduction in responses (-42%, p =0.013 and -37%, p=0.04 respectively) in the early acute phase of the formalin test, but not in the late tonic phase (rats); the highest dose (150 mg/kg) caused a significant anti nociceptive effect in both phases (early phase: 35%, p=0.048; late phase: 32%, p=0.0038); the anti-nociceptive effects of linalool were reduced by pre-treatment with atropine, naloxone, sulpiride and glibenclamide, but not by pirenzepine or SCH-23390 (a dopamine D1 receptor antagonist).
to study local anaesthetic effects (Ghelardini *et al*. 1999)	male New Zealand rabbits	rabbit conjunctival reflex test with lavender oil, linalool and linalyl acetate, 1 drop applied to the conjunctival sac	Local anaesthetic effects of lavender oil, linalool and linalyl acetate were demonstrated: 30-2500 µg/ml dose-dependently increased the number of stimuli necessary to provoke the reflex (p<0.01).

Enzyme-inducing effects

Purpose	Species	Intervention	Outcome
to study the influence on the enzyme content (Roffey *et al*. 1990)	male Wistar albino rats	enzyme activity after oral administration of linalool	Linalool administered at 1.5 g/kg b.w. for 5 days caused induction of peroxisomal bifunctional enzyme (2445 ng control protein/µg protein loaded vs. 1069 ng for controls; p<0.001) but not of cytochrome P450 IVA1 (1.76% of total P450 vs.

Purpose	Species	Intervention	Outcome
			2.43% for controls; non-significant).
to study the influence on liver enzyme content (Parke et al. 1974)	Wistar rats (4 week old)	linalool (500 mg/kg) as a solution in propylene glycol was administered by gavage for 64 days	Liver weight and relative liver weight were unaffected by linalool (500 mg/kg) up to day 30, but by day 64 there were slight but significant increases in these parameters compared to controls ($p<0.05$); microsomal protein concentration was unaffected up to day 14, but had increased by 20%, by day 30 ($p<0.02$) and remained elevated up to day 64; cytochrome P450 and cytochrome b concentrations showed a biphasic response, both being depressed on day 7 ($p<0.022$ in each case) but subsequently increased by 50% on day 30 ($p<0.01$); cytochrome P450 remained at this level, whereas cytochrome b, increased further to 70% on day 64 ($p<0.002$).

Other effects

Purpose	Species	Intervention	Outcome
to study the diuretic effect of lavender flower (Elhajili *et al*. 2001)	female Wistar rats	infusion of lavender flower (40 g/litre) was intragastrically administered	Infusion exerted significant diuretic effects ($p<0.01$) in rats 70 and 99 minutes after intragastric administration of 0.03 g/kg b.w.; at maximum diuretic response, urinary osmolarity (111 mosmol/kg) was significantly less ($p<0.01$) than that of the untreated control (195 mosmol/kg) and of the positive control, diosmin (162 mosmol/kg); sodium excretion was moderate.

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

Species	Intervention	Outcome
mice	exposure of mice to a lavender oil atmosphere	time-dependent increase in linalool plasma levels (approximately 0.9 ng/ml after 30 minutes, 2.7 ng/ml after 60 minutes and 2.9 ng/ml after 90 minutes) (Buchbauer *et al*. 1993a)
mice	1 h exposure to a medium containing the vapour of lavender oil (37.3% linalool and 41.6% linalyl acetate), linalool or linalyl acetate at 5 mg/l	Serum levels were 3 ng/ml for linalool and 11 ng/ml for linalyl acetate; after 1 h of exposure to linalool, the serum level was 8 g/ml, and after 1 h of exposure to linalyl acetate the level was 1 ng/ml and the serum linalool level 4 ng/ml (Buchbauer *et al*. 1993a; Jirovetz *et al*. 1990; Bickers *et al*. 2003).
rats	oral administration of labelled linalool to rats at 500 mg/kg b.w.	After oral administration of labelled linalool 55% was excreted in the urine as the glucuronic acid conjugate, while 23% was excreted in expired air and 15% in the faeces within 72 h; only 3% was detected in the tissues (Bickers *et al*. 2003).

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

Acute toxicity

The acute oral LD_{50} of lavender oil in rats was found to be >5 g/kg b.w. Other authors reported the oral LD_{50} in male rats as 6.2 ml/kg and in female rats as 5.0 ml/kg; the oral LD_{50} in male rats as 5 ml/kg and in female rats as 3 ml/kg.
Furthermore an oral LD_{100} in male rats as > 7 ml/kg and in female rats as >6 ml/kg was reported. In an earlier study the acute oral LD_{50} of lavender oil was determined as 9 g/kg (Buchbauer *et al*. 1991; Delaveau *et al*. 1989; von Skramlik 1959).

Acute oral LD_{50} values in rodents have been reported as 2.2-3.9 g/kg b.w. for linalool and 5.0-48.8 g/kg for linalyl esters. The dermal LD_{50} of linalool in rabbits exceeded 5 g/kg. No adverse effects were reported from administration of linalool to female mice via a stomach tube at 94, 188 or 375 mg/kg/day for 5 days (Bickers *et al*. 2003).

Subacute toxicity

In a 90-day chronic dermal toxicity study in rats (20 per group), linalool was applied daily at 250, 1000 and 4000 mg/kg b.w.. At 250 mg/kg no changes were observed except decreased activity and transient erythema; at 1000 mg/kg weight gain and activity were reduced; at the highest dose level, 11 animals died (Bickers *et al*. 2003).

In a 90-day study, a 1:1 mixture of linalool and citronellol was added to the diet of rats to provide an intake of about 50 mg/kg/day of each substance. A slight retardation of body weight gain was

observed in the males, but no effects were evident from histopathology, haematology, clinical chemistry or urine analysis at weeks 6 and 12 (Bickers *et al*. 2003).

Investigations on rats showed that the acute toxicity of essential oil of lavender (OL), given p.o. in olive oil, was relatively low, while when given to mice pharmacological tests demonstrated that it had anxiolytic effects and prolonged sleep induced by i.p. pentobarbital Na, though the latter effect was reduced after repeated p.o. administration. Impaired balance, piloerection and hypersalivation sometimes occurred. The authors concluded that, if its chronic toxicity is also low, OL might be used instead of more active anxiolytics or tranquilizers for minor conditions (Delaveau *et al*. 1989).

Undiluted lavender oil was not irritant when applied to the backs of hairless mice or pigs, but was slightly irritant on intact or abraded rabbit skin under occlusion for 24 h (Opdyke 1976).

Undiluted linalool caused slight to severe irritation to guinea pigs and rabbits when applied to open or occluded skin; no irritation was observed at 10% dilution. Undiluted linalyl acetate caused slight to severe irritation in guinea pigs and rabbits; at 5% dilution it was slightly irritating to rabbits (Bickers *et al*. 2003).

Mutagenicity

Linalool and linalyl acetate showed no mutagenic potential in the Ames mutagenicity test, with or without metabolic activation (Eder *et al*. 1980; Eder *et al*. 1982a; Eder *et al*. 1982b; Ishidate *et al*. 1984).

In the mouse lymphoma assay, no effects were seen with linalool in the absence of metabolic activation at concentrations up to 300 µg/ml; weak positive effects were observed in the presence of metabolic activation at doses of 200 µg/ml and above (Bickers *et al*. 2003).

Linalool did not induce chromosomal aberrations when incubated with Chinese hamster fibroblast cells at concentrations up to 0.25 mg/ml (Ishidate *et al.* 1984) nor with Chinese hamster ovary cells at concentrations up to approximately 300 µg/ml (Bickers *et al*. 2003).

No induction of unscheduled DNA synthesis in rat hepatocytes was evident at concentrations of linalool up to 50 µg/ml or linalyl acetate up to 300 µg/ml (Bickers *et al*. 2003).

Evrandi *et al*. (2005) studied the antimutagenic activity of lavender essential oil in the bacterial reverse mutation assay using *Salmonella typhimurium* TA98 and TA100 strains and in *Escherichia coli* WP2 uvrA strain, with and without an extrinsic metabolic activation system, without pre-incubation. Lavender essential oil had no mutagenic activity on the two tested *Salmonella* strains or on *E. coli*, with or without the metabolic activation system. Lavender oil exerted strong antimutagenic activity, reducing mutant colonies in the TA98 strain exposed to the direct mutagen 2-nitrofluorene. Antimutagenicity was concentration-dependent: the maximal concentration (0.80 mg/plate) reduced the number of histidine-independent revertant colonies by 66.4%. Lavender oil (0.80 mg/plate) also showed moderate antimutagenicity against the TA98 strain exposed to the direct mutagen 1-nitropyrene.

Rahimifard *et al.* (2010) investigated the mutagenic and antimutagenic activities of lavender (and cardamom) oil by reverse mutation assay in the same strains of *Salmonella typhimurium* with and without S9 (microsomal mutagenesis assay) for 7 dilutions. For lavender oil, the concentration per plate varied from 0.13 to 0.80 mg/plate. No mutagenicity was seen. On the contrary, there was a antimutagenic effect when 0.4 mg lavender essential oil per plate was applied.

3.4. Overall conclusions on non-clinical data

Most of the experiments were done with Lavandulae aetheroleum, the herbal preparation that is used in clinical conditions. Lavender flowers were used for investigating a diuretic action.
Experimental pharmacological data point to an activity in the central nervous system: anticonvulsive effects, sleep prolongation, locomotor activity, explorative or anticonflict behaviour and anxiety. Well known inflammatory and nociceptive experimental models were used. As far as these interventions are concerned, high doses of lavender oil were used to obtain pharmacological effects. These doses mostly cannot be extrapolated to human conditions. On the other hand, dose-response relationship could be demonstrated in some investigations. The outcomes are mostly positive. This may be due to a publication bias. The effect on enzyme induction by linalool is difficult to translate to metabolic consequences.

The experimental pharmacokinetic data are limited. Most probably, oil constituents are excreted by the urine as glucuronic conjugates.

Toxicity of lavender oil is not a major concern. Some components like linalool and linalyl acetate are not mutagenic. The essential oil did not demonstrate mutagenic activity towards two strains of *Salmonella typhimurium* and one of *Escherichia coli* with and without metabolic activation. The number of strains used for testing and the procedure used are not according to the recent regulatory guidelines. A Community list entry cannot be established for *Lavandula*.

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

Effects on the central nervous system and neuronal activity

Clinical question	Patients	Intervention	Outcome
to what extent lavender oil can influence indicators for mood status	healthy adults (n=20)	subjects were exposed to lavender oil (10% in grape seed oil, 3 drops on a cotton swab held 8 cm from the participant's nose for 3 minutes)	As compared to baseline, beta power in the EEG increased, suggesting increased drowsiness; significantly lower scores were obtained for depressed mood (assessed by the Profile of Mood States: -56% $p<0.01$) and anxiety (assessed by the State Trait Anxiety Inventory: -9%, $p<0.05$); the volunteers reported feeling more relaxed (tense/relaxed and drowsy/alert visual analogue mood scales: + 25.9%, $p<0.001$) and performed mathematical computations faster and more accurately (von

Clinical question	Patients	Intervention	Outcome
			Skramlik 1959). Further data analysis revealed significant EEG shift ($p<0.05$) with greater left frontal EEG activation (associated with extrovert behaviour and less depressed mood) (Sanders *et al*. 2002).
possible influence of a.o. lavender oil on the EEG-pattern	24 healthy women	acute sedative effects of p.o. extracts of *Valeriana officinalis*, *Lavandula angustifolia*, *Passiflora incarnata*, *Kava-kava*, *Melissa officinalis*, *Eschscholzia californica*, *Hypericum perforatum* and *Ginkgo biloba* (all Lichtwer) were compared to those of diazepam using quantitative EEG recordings; studies followed a double-blind, randomised, crossover design	Diazepam, Valerian and *Lavandula* were sedative on a self-rating of tiredness; diazepam increased power in the beta frequency band of the EEG and decreased power in the alpha and sub-alpha bands; Valerian increased power in the delta, theta and alpha1 bands; *Lavandula* had a minimal effect on power; quantitative EEGs are a sensitive means of describing drug-induced CNS activity changes, but do not constitute a good screening method for potential sedatives (Schulz *et al*. 1998).
influence of lavender oil on EEG-patterns	healthy women (n=13)	EEG recordings made during and after inhalation of lavender oil for 90 seconds (diffuser fixed on the chest; no details on concentration given)	Alpha I frequencies (8-10 Hz) in parietal and posterior temporal regions significantly decreased soon after the onset of inhalation ($p<0.01$); this was associated with a comfortable feeling in the subjects (Masago *et al.* 2000).
influence of lavender oil on EEG and behaviour of newborn babies	newborn babies (n=20)	the effects of inhalation of lavender oil (10% V/V in grape seed oil, 3 drops on a cotton swab held 15 cm from the nose for 2 minutes) on the behaviour of 20 newborn babies were evaluated	Infants of depressed mothers showed increased relative left frontal EEG asymmetry from baseline during the odour exposure phase ($p<0.01$); in contrast, infants of non-depressed mothers showed no change in frontal EEG-asymmetry from baseline during the odour exposure phase; among the behaviours recorded

Clinical question	Patients	Intervention	Outcome
			(negative affect, head turns, lip licking, and nose wrinkling), the only differences were that infants of depressed mothers showed increased head turning during exposure to the odour ($p<0.05$) (Fernandez *et al*. 2004).
influence of lavender oil on mood and positive behaviour towards future events	healthy women (n=40)	randomised single-blind study, the effect of a lavender oil bath (3 ml/bath) on psychological well-being was evaluated; participants, randomly assigned to use either grape seed oil or 20% lavender oil in grape seed oil in their bath for 14 days, assessed their well-being with the Mood Adjective Checklist of the University of Wales Institute of Science and Technology; in a further study a similar design and assessment by the Macleod and Byrne Future Events procedure was done	"Positive" effects of bathing - irrespective of whether or not lavender oil was added to the bath - were evident with respect to energetic arousal, tense arousal and hedonic tone, while anger-frustration was selectively reduced by lavender oil; in the further study using the Macleod and Byrne Future Events procedure, no effect was observed on the rate of positive responses to possible future events but negative responses were reduced after lavender oil baths (Morris 2002).
influence of lavender oil on cognitive functions	healthy volunteers (n=144)	participants assigned to one of three independent groups and subsequently performed the Cognitive Drug Research computerized cognitive assessment battery in a cubicle containing the odour of lavender oil or rosemary oil (from 4 drops on a diffuser pad, placed under a bench in the testing cubicles) or no odour (as a control); visual analogue mood questionnaires were completed prior to exposure to the odour and after completion of the test battery	Compared to controls, lavender odour caused significant impairment in performance of working memory ($p<0.05$) and impaired reaction times for both memory and attention based tasks (working memory subfactor, speed of memory factor, speed of attention factor, alertness and contentedness) (Moss *et al*. 2003).
influence of lavender oil on arousal and mental stress	healthy volunteers (n=42)	the effect of lavender oil (from a diffuser on the floor of the experimental room for 20 minutes) was assessed by a Japanese version of Cox and	Analysis suggested that lavender odour was associated with reduced mental stress and increased arousal rate ($p<0.01$) (Motomura *et al*. 2001).

Clinical question	Patients	Intervention	Outcome
		Mackay's stress/arousal adjective checklist in three groups of healthy volunteers; stress was induced by waiting in a soundproofed small room for 20 minutes. One group of 14 was placed in the room without exposure to the oil, a group of 15 was exposed to lavender oil, and a group of 13 did not have to wait in the soundproofed room	
influence of lavender oil on pain sensation	healthy volunteers (13 men and 13 women)	effects of inhalation of lavender oil (5 drops on cotton gauze placed 30 cm below the nose for 10 minutes), rosemary oil or water (as a control) on sensory and affective responses to experimentally-induced pain were studied in 13 men and 13 women in a randomised cross-over design; pre- and post-treatment scores were documented for quantitative sensory ratings of contact heat pain (thermode placed on the forearm), pressure pain (pressure algometer applied to the trapezius and masseter) and ischaemic pain (submaximal effort tourniquet procedure: elevating the arm above heart level for 30 seconds, occlusion of circulation with a standard blood pressure cuff, hand-grip exercises with lowered arm); subjective ratings of treatment-related changes in pain intensity and pain unpleasantness were obtained for each condition using a visual analogue scale	Quantitative pain sensitivity ratings were unchanged in both groups; retrospectively, however, subjective ratings of both perceived pain intensity and perceived pain unpleasantness were significantly less after treatment with lavender ($p<0.01$) (Gedney *et al*. 2004).
influence of lavender on sustained attention	healthy volunteers (n=7; aged 20-24 years)	exposure to volatile oil vapours, an odour delivery system passed air at a standard rate through sample bottles and presented, in randomised order, dispersions of lavender oil (0.29 mg/l of air),	During 30-minute vigilance tasks, involving selection responses in relation to numbers changing every second on a computer screen, the gradual increase in reaction time was

Clinical question	Patients	Intervention	Outcome
		eucalyptus oil (4.8 mg/l of air) and a no-odour control to a point exactly 10 cm below the nose	found to be significantly lower with lavender oil odour than with the control ($p<0.001$); results suggested that the odour of lavender oil helped to maintain sustained attention during the long-term task (Shimizu *et al*. 2008).
influence of lavender on EEG activity, alertness and mood	healthy volunteers (n=40; mean age 31 years)	aromatherapy given to subjects seated in a special massage chair; lavender or rosemary oil (3 drops) diluted with a 10% concentration in grape seed oil were placed on a dental swab and presented in a 100 ml plastic vial which the subjects held about 3 inches from their nose for a period of 3 minutes	State Anxiety scores decreased in both groups ($p<0.05$); only the lavender group had a significantly better mood on the POMS (= Profile Of Mood States) ($p< 0.01$); both groups felt more relaxed ($p< 0.001$); accuracy scores improved significantly ($p< 0.05$); frontal alpha power increased after lavender, suggesting increased drowsiness (Diego *et al*. 1998).
influence of lavender oil on neuropsychic activity	healthy medical students (n=48; 22-23 years), subdivided in groups of 16 subjects, receiving lavender, rose or geranium oil	inhalation of lavender oil (50 ml of a 1% solution nebulized in a room of 176 m^3); assessment of neuropsychic activity by the Pauli-test (assessing concentration, working efficiency, reaction and attention)	Lavender oil stimulated neuropsychic activity, but results are difficult to interpret by differentiation of parameters (Tašev *et al*. 1969).
influence of lavender oil on reaction time	healthy volunteers (n=10)	computer-based reaction-time tests (parts of the Munich Attention Test) were performed while inhaling air or lavender oil vapour in 6 daily sessions	Increases in reaction time were observed on days 4 and 6 when the subjects performed the tests while inhaling lavender oil vapour (Buchbauer *et al*. 1993b).

Cardiovascular system

Clinical question	Patients	Intervention	Outcome
examination	healthy young	continuous electrocardiographic	Increases in the

Clinical question	Patients	Intervention	Outcome
whether the power spectral analysis of heart rate variability (HRV) could detect changes in autonomic tone following a treatment with Lavandula essential oil	women (n=10; 23+/- 3 years)	(ECG) monitoring before and after (10, 20, 30 minutes) a stimulus with lavender oil; lavender oil was topically administered by a commercially available plaster for aroma therapy (Lavender girl®); no information given on the dose; HRV was expressed by three indices: low (0.04-0.15 Hz) and high (0.15-0.40 Hz) frequency components (nLF and nHF respectively) as well as LF/HF ratio	parasympathetic tone were observed after the lavender oil seen as increases in the HF component and decreases in the LF/HF; additional measurement with positron emission tomography (PET) demonstrated the regional metabolic activation in the orbitofrontal, posterior cingulate gyrus, brainstem, thalamus and cerebellum, as well as the reductions in the pre/post-central gyrus and frontal eye field. These results suggested that lavender aromatic treatment induced not only relaxation but also increased arousal level in these subjects (Duan *et al*. 2007).
influence of lavender oil on blood flow and nerve activity when taken as a footbath	healthy young women (n=10; 19-21 years)	randomised cross-over study; subjects took a hot footbath for 10 minutes with and without lavender oil (2 ml to 4 liters of water; 0.05%); effects on the autonomic nervous system were recorded on an electrocardiogram and by finger tip blood flow and respiratory rate; autonomic function was evaluated using spectral analysis of heart rate variability	Significant increase in finger tip blood flow (34.8 to 40.1 ml/min/100 g; no change without lavender oil) was recorded; parasympathetic nerve activity increased significantly ($p<0.05$) during both types of footbath; with lavender oil, delayed changes in the balance of autonomic activity were observed, suggesting relaxation; no changes observed in heart or respiratory rates (Saeki 2000).
influence of lavender oil on cardiovascular parameters after exercise	healthy volunteers (n=20)	after performing moderate physical exercise for 2 minutes, subjects rested for 10 minutes; during this time they were randomly exposed to an atmosphere with or without lavender oil (10 drops in water, nebulized)	Compared to the controls, the volunteers exposed to lavender oil had lower diastolic (-6.1 mmHg) and systolic blood pressure (-15.1 mmHg), and lower arterial pressure (-8.5 mmHg) and heart rate (-15 beats/minute), although the differences were not statistically significant (Romine *et al*. 1999).

Antioxidative activity

Clinical question	Patients	Intervention	Outcome
influence of the smelling of lavender and rosemary essential oil on the total salivary FRSA (Free Radical Scavenging Activity)	22 healthy volunteers	After sniffing aroma for 5 minutes, and each subject's saliva was collected immediately. FRSA was measured using 1.1-diphenyl-2-picrylhydrazyl.	Various physiologically active substances in saliva such as cortisol, secretory IgA, and α-amylase activity were found to be correlated with aroma-induced FRSA. FRSA values were increased by stimulation with low concentrations (1000 times dilution) of lavender or by high concentrations (10 times dilution) of rosemary. In contrast, both lavender and rosemary stimulations decreased cortisol levels; significant inverse correlation was observed between the FRSA values and the cortisol levels with each concentration of rosemary stimulation; no significant changes were noted in sIgA or α-amylase. These findings clarify that lavender and rosemary enhance FRSA and decrease the stress hormone, cortisol, which protects the body from oxidative stress; the body possesses various antioxidative systems (FRSA) for preventing oxidative stress, and saliva contains such activity (Atsumi & Tonosaki 2007).

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

Patient	Intervention	Outcome
male volunteer	massage oil containing 2% of lavender oil (approximately 25% linalool and 30% linalyl acetate) was gently massaged on to the abdomen for 10 minutes	Trace amounts of both linalool and linalyl acetate were detected in the blood within 5 minutes of finishing the massage, and peak plasma concentrations of 121 ng/ml for linalool and 100 ng/ml for linalyl acetate were reached after 19 minutes; most of the linalool and linalyl acetate disappeared from the blood

Patient	Intervention	Outcome
		within 90 minutes, both having a biological half-life of approximately 14 minutes (Jäger *et al*. 1992).

4.2. Clinical Efficacy

4.2.1. Dose response studies

Not applicable.

4.2.2. Clinical studies (case studies and clinical trials)

Anxiety

Purpose	Patients	Intervention	Outcome
to evaluate possible anxiolytic effects of lavender oil	healthy volunteers (n=97; 57 women, 39 men; aged between 18 and 74 years); participants refrained from alcohol, tea and coffee 24 h prior to the study	orally administered lavender capsules (placebo, 100, 200 µl) were tested in a randomised between-subjects double-blind study; film clips were used to elicit anxiety; measures included anxiety, State Trait Anxiety Inventory (STAI), mood, positive and negative affect scale (PANAS), heart rate (HR), galvanic skin response (GSR), and heart rate variation (HRV); following baseline measurements, capsules were administered; participants viewed a neutral film clip, then an anxiety-provoking and light-hearted recovery film clip	For the 200 µl lavender dose during the neutral film clip there was a trend towards reduced state anxiety, GSR and HR and increased HRV; in the anxiety-eliciting film, lavender was mildly beneficial in women but only on HRV measures; in men sympathetic arousal increased during the anxiety film (GSR); HRV significantly increased at 200 µl during all three film clips in females, suggesting decreased anxiety. These findings suggest that lavender has anxiolytic effects in humans under conditions of low anxiety, but these effects may not extend to conditions of high anxiety (Bradley *et al*. 2009).
to investigate the effect of lavender oil in general anxiety disorder (GAD)	patients (n=77; 18 to 65 years) with primary diagnosis of GAD according to the DSM-IV criteria and outpatient treatment by	double-blind, randomised, double dummy, controlled clinical study; performed to evaluate the efficacy of Silexan® (80 mg lavender oil), a new oral lavender oil capsule preparation, versus a benzodiazepine; in this study, the efficacy of a 6-week intake of Silexan® compared to lorazepam (0.5 mg) was investigated in adults with GAD; primary target	Results suggest that Silexan® effectively ameliorates generalized anxiety comparable to a common benzodiazepine (lorazepam); mean of the HAM-A-total score (primary parameter) decreased clearly and to a similar extent in both groups (by 11.3±6.7 points (45%) in the Silexan® group and by 11.6±6.6 points (46%) in the

Purpose	Patients	Intervention	Outcome
	a general practitioner were selected; in order to be eligible for study inclusion, all patients were required to have a Hamilton Anxiety (HAM-A) total score of ≥18 and item 1 'anxious mood' ≥2 and item 2 'tension' ≥2; before being included, patients underwent a one-week screening phase to ensure wash-out of any other drugs; patients with a decrease of 25% or more of the HAM-A total score during this phase were to be excluded	variable was the change in the Hamilton Anxiety Rating Scale (HAM-A-total score) as an objective measurement of the severity of anxiety between baseline and week 6	lorazepam group, from 25±4 points at baseline in both groups); during active treatment period, the two HAM-A subscores "somatic anxiety" (HAM-A subscore I) and "psychic anxiety" (HAM-A subscore II) also decreased clearly and to a similar extent in both groups; changes in other subscores measured during the study, such as the SAS (Self-rating Anxiety Scale), PSWQ-PW (Penn State Worry Questionnaire), SF 36 Health survey Questionnaire and Clinical Global Impressions of severity of disorder (CGI item 1, CGI item 2, CGI item 3), and the results of the sleep diary demonstrated comparable positive effects of the two compounds. Safety of Silexan® was demonstrated. Since lavender oil showed no sedative effects in the study and has no potential for drug abuse, Silexan® appears to be an effective and well tolerated alternative to benzodiazepines for amelioration of generalised anxiety, according to the authors (Woelk & Schläfke 2010).
to review the effect of lavender scent on anticipatory anxiety in dental consultations	dental patients in ambulatory practice (n=340)	cluster randomised-controlled trial; patients' anxiety was assessed while waiting for a scheduled dental appointment, either under the odour of lavender or with no odour; current anxiety, assessed by the brief State Trait Anxiety Indicator	Analyses of variance (anovas) showed that although both groups showed similar, moderate levels of generalized dental anxiety (MDAS F=2.17, p>0.05) the lavender group reported significantly lower current anxiety (STAI: F=74.69,

Purpose	Patients	Intervention	Outcome
		(STAI-6), and generalized dental anxiety, assessed by the Modified Dental Anxiety Scale (MDAS) were examined	p<0.001) than the control group; although anxiety about future dental visits seems to be unaffected, lavender scent reduces state anxiety in dental patients (Kritsidima *et al*. 2010).
to investigate the effects of aromatherapy massage on the anxiety and self-esteem	Korean elderly women (n=36)	a quasi-experimental, control group, pretest-posttest design was used: 16 patients in the experimental group and 20 in the control group; aromatherapy massage using lavender, chamomile, rosemary and lemon was given to the experimental group only; each massage session lasted 20 minutes, and was performed 3 times per week for two 3-week periods with an intervening 1-week break	Intervention produced significant differences in the anxiety and self-esteem and no significant differences in blood pressure or pulse rate between the 2 groups; results suggest that aromatherapy massage exerts positive effects on anxiety and self-esteem; more objective, clinical measures should be applied in a future study with a randomised placebo-controlled design (Rho *et al*. 2006).
to evaluate the use of aromatherapy to reduce anxiety prior to a scheduled colonoscopy or esophago-gastro-duodenoscopy	controlled, prospective study done on a convenience sample of 118 patients (mean age 52 years, range 24-57 years, 50% men); no difference between the experimental and control group in enjoyment of scent (p=0.94)	state component of the State Trait Anxiety Inventory (STAI) was used to evaluate patients' anxiety levels pre- and post-aromatherapy; control group was given inert oil (placebo) for inhalation, and the experimental group was given lavender oil for inhalation	STAI state anxiety raw score revealed that patients were at the 99th (women) and 96th (men) percentiles for anxiety; intervention group and control group had similar levels of state anxiety prior to the beginning of the study (p=0.64); no difference in state anxiety levels between pre-and post-placebo inhalation in the control group (p=0.63); no statistical difference in state anxiety levels between pre- and post-lavender inhalation in the experimental group (p=0.47). Although this study did not show aromatherapy to be effective based on statistical analysis, patients did generally report the lavender scent to be pleasant; lavender is an inexpensive and popular technique for relaxation that can be offered to patients as an opportunity to promote preprocedural stress reduction in a hospital setting (Muzzarelli *et*

Purpose	Patients	Intervention	Outcome
			al. 2006).

Depression

Clinical question	Patients	Intervention	Outcome
influence of a lavender flower tincture on depressed patients as compared to imipramine	patients who met the DSM criteria for major depression (based on the structured clinical interview for DSM IV) and had a baseline score of at least 18 on the Hamilton Rating Scale for depression (HAM-D) (n=45)	patients were assigned to the following daily oral treatments for 4 weeks: group A: lavender flower tincture (60 drops/day) + a placebo tablet; group B: imipramine tablet (100 mg/day) + placebo drops; group C: lavender flower tincture (60 drops/day) + 1 imipramine tablet (100 mg/day)	Highly significant improvements in HAM-D scores ($p<0.0001$) were observed in groups A (approximately 19 to 12) and B (approximately 19 to 9), although lavender tincture at this dosage was less effective than imipramine ($p=0.0001$); in group C the combination of lavender tincture and imipramine was more effective than imipramine alone (approximately 19 to 5 versus 19 to 9; $p<0.0001$) (Akhondzadeh *et al*. 2003).

Analgesia

Purpose	Patients	Intervention	Outcome
analgesic efficacy of postoperative lavender oil aromatherapy	patients undergoing breast biopsy surgery (n=50)	25 patients received supplemental oxygen through a face mask with two drops of 2% lavender oil postoperatively; the remainder of the patients received supplemental oxygen through a face mask with no lavender oil, outcome variables included pain scores (a numeric rating scale from 0 to 10) at 5, 30, and 60 minutes postoperatively, narcotic requirements in the postanesthesia care unit (PACU), patient satisfaction with pain control, as well as time to discharge from the PACU	No significant differences in narcotic requirements and recovery room discharge times between the two groups; postoperative lavender oil aromatherapy did not significantly affect pain scores; patients in the lavender group reported a higher satisfaction rate with pain control than patients in the control group ($p=0.0001$) (Kim *et al*. 2006).

Purpose	Patients	Intervention	Outcome
efficacy of acupressure using lavender oil	adults (32 patients enrolled of which 28 completed the study; mean age 51.2 $\pm$ 7.6 years) with sub-acute non-specific neck pain	add-on treatment for pain relief and enhancing physical functional activities; a course of 8-session manual acupressure with lavender oil over a 3-week period; changes from baseline to the end of treatment were assessed on neck pain intensity (by Visual Analogue Scale (VAS)), stiffness level, stress level, neck lateral flexion, forward flexion and extension in cm, and interference with daily activities	8 experts in the musculoskeletal field verified the content validity of the outcome measures (inter-raters reliability=0.98); baseline VAS score of neck pain intensity (primary outcome) for the intervention and control groups were 5.12 and 4.91 out of 10, respectively (p=0.72); one month after the end of treatment, compared to the control group, the manual acupressure group had 23% reduced pain intensity (p=0.02), 23% reduced neck stiffness (p=0.001), 39% reduced stress level (p=0.0001), improved neck flexion (p=0.02), neck lateral flexion (p=0.02), and neck extension (p=0.01); improvements in functional disability level were found in both the manual acupressure group (p=0.001) and control group (p=0.02). Results show that 8 sessions of acupressure with aromatic lavender oil were an effective therapy for short-term neck pain relief (Yip & Tse 2006).

Clinical question	Patients	Intervention	Outcome
effect of lavender oil on low back pain	adult patients with sub-acute or chronic non-specific low back pain (number that completed the study: intervention group=27; control	randomised controlled study; effect on pain relief and enhancement of physical functional activities of acupoint stimulation with electrodes combined with acupressure using lavender oil (in addition to conventional treatment); over a 3-week period, patients had 8 sessions of relaxation acupoint stimulation, each of 35-40 minutes, followed by acupressure	Baseline VAS scores for the intervention and control groups were 6.38 and 5.70 respectively (p=0.24); one week after the end of treatment the intervention group reported 39% greater reduction in pain intensity than the control group (p=0.0001) and had improved walking time (p=0.05) and greater lateral spine flexibility (p=0.01) (Yip & Tse 2004).

Clinical question	Patients	Intervention	Outcome
	group=24)	massage with 3% lavender oil in grape seed oil using light to medium finger pressure on 8 fixed acupoints for 2 minutes each; patients in the control group received conventional treatment only; outcome measures were changes in pain intensity scores (10 cm VAS) and duration from baseline to end of treatment, lateral fingertip-to-ground distance, walking time (to cover 15 meter) and interference with daily activities	
influence of lavender oil on postoperative pain	morbidly obese patients who had undergone surgery for laparoscopic adjustable gastric banding (n=54)	randomised, placebo controlled study; patients were treated, upon arrival at the post-anaesthesia care unit, by application of either lavender oil or non-scented baby oil to the oxygen face mask; the two groups were comparable with regard to patient characteristics, intra-operative drug use and surgical time; postoperative pain was treated with morphine and the level of pain was assessed at 5, 30 and 60 minutes from numerical rating scores (0-10)	Patients in the lavender group required significantly less morphine postoperatively than those in the placebo group: 2.38 mg vs 4.26 mg (p=0.04); significantly more patients in the placebo group (22/27, 82%) than in the lavender group (12/26, 46%) required analgesics for postoperative pain (p=0.007) (Kim *et al*. 2007).
influence of lavender oil on pain perception	patients with vascular wounds requiring frequent painful dressing changes (n=8)	in a pilot study, the effects were assessed of diffusion of 15-20 drops of lavender oil by means of an aroma stream diffuser during the dressing change (in addition to conventional analgesics); pain perception was assessed by 2 measures from the McGill Pain Questionnaire, the Visual Analogue Scale (VAS) and the Present Pain Inventory; a Sleep Questionnaire and the Spielberger State Trait Anxiety Inventory were also used; during 5 dressing changes the patients received, in random order, 2 odor therapies	Lavender oil diffusion did not reduce pain intensity during dressing changes, but at post-dressing change assessments of lavender therapy a significant reduction in pain intensity was evident from VAS scores (p<0.05) (Kane *et al*. 2004).

Clinical question	Patients	Intervention	Outcome
		(lavender or lemon), music therapy of 2 types, or no treatment	

Sleeping disorders

Purpose	Patients	Intervention	Outcome
effect of essential oil of lavender has a sedative effect and that the resultant sleep promotes therapeutic activity	acutely ill elderly people and long-term patients	pilot study was arranged, followed by a more detailed trial with long-term patients	Results show a positive trend towards improvement with lavender (Hudson 1996).
hypnotic effects of lavender oil	12 mid-life women with sleep disturbances (56 years range 50-59 years): mean sleep time 6.5 h	cross-over placebo-controlled study; patients received a dose of 0.86 g (3 drops) lavender oil, jasmine oil or base oil (placebo) on their pillow on 3 separate occasions (for 2 nights in a balanced, placebo-controlled cross-over design)	*L. angustifolia* oil was mild hypnotic and jasmine oil a stimulant; in contrast to jasmine oil, lavender oil significantly increased actual sleep time by a mean of 69 minutes ($p<0.05$); perceived changes in self-rated sedation and residual side-effects did not reveal any significant subjective impairment; in comparison to jasmine oil, ease of getting to sleep and quality of sleep was positively improved with the lavender oil; mean trends indicated that in comparison to jasmine, awakening was also positively improved with lavender oil, whilst jasmine decreased sleep in contrast to the placebo; lavender oil may be of value as a mild hypnotic whilst jasmine, having an opposite effect, may be helpful in counteracting daytime sleepiness (Austin & Alford 1997).
influence of lavender fragrance on sleep and depression in women college	42 women college students who complained of insomnia	patients were studied during a four-week protocol (control treatment week, 60% lavender fragrance treatment week, washout week, 100% lavender fragrance treatment week); single blind repeated measurements	Among sleep variables, length of time taken to fall asleep, severity of insomnia, and self satisfaction with sleep were improved for the 60% ($p<0.001$, $p<0.001$, $p<0.001$) and 100% ($p<0.001$, $p<0.001$, $p<0.001$)

Purpose	Patients	Intervention	Outcome
students		experiment; for the duration of the study, weekly evaluations of sleep, patterns of sleep disturbance, severity of insomnia scale, self satisfaction with sleep, and severity of depression were performed	week while the severity of depression was improved only for the 100% (p=0.002) week. It was concluded that the lavender fragrance had a beneficial effect on insomnia and depression in women college students; repeated studies are needed to confirm effective proportions of lavender oil and carrier oil for insomnia and depression (Lee & Lee 2006).

Malignant diseases

Clinical question	Patients	Intervention	Outcome
lavender oil as useful adjuvant in cancer therapy	study population consisted of 17 still conscious and oriented in-home hospice patients; the abstract categorizes them as 'cancer' patients without further specification; there are no details about age and gender	patients were evaluated for the effects of exposure to a lavender oil atmosphere on levels of pain, anxiety, depression and perceived sense of well-being; on 3 different days, prior to and after a 60-minute session involving no intervention (as a control), exposure to an atmosphere humidified with water (as a control) or to an atmosphere humidified with 3% lavender oil vapour, each patient was evaluated using 11-point verbal analogue scales and vital signs were also measured	Compared to the no-intervention control, small non significant decreases in blood pressure and heart rate, and decreases in pain and anxiety, as well as an improvement in sense of well-being, were observed after both water humidification and lavender oil treatment (Louis & Kowalski 2002).

Cardiovascular effects

Clinical question	Patients	Intervention	Outcome
effects of aromatherapy on blood	patients (n=52) with essential	application of aromatherapy was the inhalation method of blending oils with lavender, ylang-ylang,	Blood pressure, pulse, subjective stress state anxiety and serum cortisol levels among the 3

Clinical question	Patients	Intervention	Outcome
pressure and stress responses of clients with essential hypertension	hypertension at random assigned to an essential oil group, a placebo group and a control group	and bergamot once daily for 4 weeks; to evaluate the effects of aromatherapy, blood pressure and pulse were measured 2 times a week and serum cortisol levels, catecholamine levels, subjective stress and state anxiety were measured before and after treatment in the 3 groups	groups were significantly statistically different; differences of catecholamine among the 3 groups were not significant statistically. The results suggest that the inhalation method using essential oils can be considered an effective nursing intervention that reduces psychological stress responses and serum cortisol levels, as well as the blood pressure of clients with essential hypertension (Hwang 2006).

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

Purpose	Patients	Intervention	Outcome
to study the influence of lavender oil on stress in newborns	five-day-old human infants' responses to heelstick stress (n=83)	infants were assessed with behavioural and physiological indices; subjects were divided randomly into 3 groups: the LAV group, who were presented with artificial odour of lavender during the heelstick; the MILK group, who were presented with artificial odour of milk during the heelstick; and the control group, who were presented with no special odours	The control group showed more adrenocortisol release in saliva than the other groups ($p<0.05$), but there were no differences between the 2 odours (lavender and milk) (Kawakami *et al*. 1997).
to study the mother-infant interactions during bathing and post-bath time sleep behaviors	infants with variable age: 1 week to 4.5 months (mean 2.2 months; n=30; 73 female)	infants were randomly assigned to three groups: 1. lavender oil bath group 2. non-aroma bath oil group 3. lavender bath oil group of mothers who received an advertisement that the aroma-bathoil 'helps calm down babies when they get irritated or helps settle them down before bedtime'; no further specification was given on the preparation and the dose used; a bath was prepared by the research assistant, and the mother placed	Bath behaviour: it seemed like the aromatic treatment lead to more affective mutual interaction between mother and child; sleep behaviour: infants in group 1 were in deep sleep a greater percentage of the time and tended to spend less time crying; cortisol levels: saliva cortisol decreased in mothers and infants of the aroma group 1 (Field *et al*. 2008).

Purpose	Patients	Intervention	Outcome
		the infant in the bathtub with scented or unscented oil; interaction of the mother and the infant during bathing were videotaped as well as the 20 first minutes of sleep of the infant thereafter no details on the preparation used were given	
to study the influence of lavender oil on autistic behaviour in children	twelve children with autism and learning difficulties (2 girls and 10 boys aged between 12 years 2 months to 15 years 7 months) in a residential school	within subjects repeated measures design: 3 nights when the children were given aromatherapy massage with lavender oil were compared with 14 nights when it was not given; the children were checked every 30 minutes throughout the night to determine the time taken for the children to settle to sleep, the number of awakenings and the sleep duration. One boy's data was not analysed owing to lengthy absence	Repeated measures analysis revealed no differences in any of the sleep measures between the nights when the children were given aromatherapy massage and nights when the children were not given aromatherapy massage. Results suggest that the use of aromatherapy massage with lavender oil has no beneficial effect on the sleep patterns of children with autism attending a residential school (Williams 2006).
to examine the effectiveness of an aromatherapy intervention on the reduction of children's distress in a perianesthesia setting	sample included children with and without develop-mental disabilities who underwent (mostly orthopaedic) surgery (n=94: age: 7-17 years); other surgery included phenol or Botox injections, skin surgery, neurosurgery or cranofacial surgery	randomised, controlled, blinded design; subjects in the intervention group received an aromatherapy intervention of lavender and ginger essential oils as a comfort measure; a drop of essential oil was placed on a cotton ball and then taped to the subject’s hospital gown approximately 12 inches from the face; a drop of essential oil was also placed over a pulse point and then covered with a small non-occlusive adhesive dressing; the essential oils were reapplied postoperatively if the subject was in the operating room for longer than 3 h; the control group received a placebo intervention of jojoba oil; distress was measured at 2 times: before induction and in the post anaesthesia care unit (stay of 15 to 75 minutes) using	The mean distress level was lower for the children in the essential oil group, but the effect was not statistically significant (p=.055); parents' responses to survey questions about satisfaction with aromatherapy did not differ between groups, although open-ended comments indicated a more positive opinion of the benefits of the intervention in the aromatherapy group (Nord & Belew 2009).

Purpose	Patients	Intervention	Outcome
		the Faces, Legs, Arms, Cry and Consolability (FLACC) scale; all subjects received standard care, which included pharmacologic treatment for postoperative pain, anxiety, nausea and vomiting	
to investigate the effects of lavender oil for insomnia, on the duration of sleep of psycho-geriatric patients	4 psycho-geriatric patients, 3 of whom were receiving hypnotics or tranquilizers	hours of sleep of the patients were measured for 2 weeks, then measured for another 2 weeks period after medication withdrawal, and then measured for a final 2 weeks, during which lavender oil was diffused into the ward	The amount of time spent asleep was significantly reduced after withdrawal of medication, but that amount of time asleep returned to the same level with lavender oil as that under medication (Hardy *et al*. 1995).
to determine whether smelling lavender oil decreases the frequency of agitated behaviour in patients with dementia	7 agitated nursing home residents with advanced dementia	study design within-subjects ABCBA (A = lavender oil, B = thyme oil, C = unscented grape seed oil): 4 weeks of baseline measurement, 2 weeks for each of the 5 treatment conditions (10-week total intervention time), and 2 weeks of postintervention measurement; oil was placed every 3 h on an absorbent fabric sachet pinned near the collarbone of each participant's shirt; study was performed in a long-term care facility specifically for persons with dementia; agitation was assessed every 2 days using a modified Cohen-Mansfield Agitation Inventory; olfactory functioning was assessed with structured olfactory identification and discrimination tasks and with qualitative behavioural observation during those tasks	Split-middle analyses conducted separately for each patient revealed no treatment effects specific to lavender, no treatment effects nonspecific to pleasant smelling substances, and no treatment effects dependent on order of treatment administration; there were no differences between participants with more and less intact olfactory abilities. This study found no support for the use of a purely olfactory form of aromatherapy to decrease agitation in severely demented patients; cutaneous application of the essential oil may be necessary to achieve the effects reported in previous controlled studies (Snow 2004).

Clinical question	Patients	Intervention	Outcome
influence of lavender oil	patients (mean age 79	placebo-controlled study; during a total of 10 daily treatment	Compared to placebo, 9 patients (60%) showed improvement

Clinical question	Patients	Intervention	Outcome
on agitation in psycho-geriatric patients	± 6.3 years) meeting ICD-10 diagnostic criteria for severe dementia and suffering from agitated behaviour (minimum score of 3 points on the Pittsburgh Agitation Scale, PAS) (n=15)	sessions a stream of 2% lavender oil vapour, alternated every other day with placebo (water) was diffused into the community area of a long-stay psychogeriatric ward for a 2-hour period; for each subject 10 PAS scores were obtained: 5 during treatment and 5 during placebo periods	during exposure to lavender oil, 5 (33%) showed no change and agitated behaviour worsened in 1 patient (7%); group median PAS scores showed that lavender oil therapy produced a modest improvement in agitated behaviour compared to placebo (p=0.016) (Holmes *et al*. 2002).
influence of lavender oil on postnatal discomfort in childbearing mothers	mothers (total n=635) after normal child birth	mothers (total n=635) used 6 drops of pure lavender oil (n=217) or a synthetic lavender oil (n=213) or an inert substance (205) as an additive to their daily bath for 10 days in a randomised single-blind study; analysis of daily VAS scores for perineal discomfort was recorded; a power calculation was made on the level of significance	VAS scores revealed no significant differences between groups; there was a trend between the 3rd and 5th day, those women using lavender oil reporting lower mean scores for perineal discomfort (Dale & Cornwell 1994).
influence of lavender oil on the mood and anxiety in hospital stress	patients admitted to an intensive care unit (n=122); the youngest patient was 2 years old and the oldest 92 years old	patients were randomly allocated to receive either massage, massage with lavender oil (1%) or a period of rest	Patients who received lavender oil massage reported significantly greater improvement in their mood and perceived levels of anxiety (p=0.05); the patients used a 4-point scale to score their level of anxiety, their mood and their ability to cope with the present situation; a pilot study was conducted to test the reliability and the validity of the final assessment tool (Dunn *et al*. 1995).
influence of lavender aroma	28 patients with moderate to severe	patients with BPSD were divided into 2 groups; one was treated with lavender aromatherapy (3x 1	The neuropsychiatric inventory (NPI) significantly improved with lavender as compared to

Clinical question	Patients	Intervention	Outcome
therapy in the treatment of behavioural and psychological symptoms of dementia (BPSD)	dementia (9 men and 19 women; mean 1 standard deviation [SD], 78 +/- 10 years; MMSE 9 +/- 8)	h daily) and another group was not. Lavender treatment consisted of 2 drops of lavender oil on the collar of the hospital underwear of the patients. Duration of treatment: 4 weeks Tiapride HCl (25 mg) was used as needed.	baseline ($P < 0.01$). The Barthel index and the Mini Mental State Evaluation (MMSE) did not change in both groups (Fujii *et al*. 2008).

4.3. Overall conclusions on clinical pharmacology and efficacy

The anxiolytic activity of lavender oil has been studied in different conditions. Patients can be considered as representative for ambulatory practice. The number of patients per study is low, only in some trials a critical mass is obtained. Lavender oil is administered in dosage forms or nebulised as aromatherapy. The former is more reliable as compared to the latter. It will always remain difficult to assess clinical activity when no exact ingested dose can be calculated. Moreover, a significant change towards baseline does not automatically mean that the difference between control and lavender groups differs significantly. When combined treatments are used or co-medication was allowed, the clinical relevance of the results is more safety related.

Abstraction made from these limitations and weaknesses, independently from the form administered, lavender oil seems to positively influence anxiety and stress-related restlessness. However, the peroral use of lavender oil cannot be accepted as well-established use, as the essential factors to be taken into account in order to establish a well-established medicinal use (according to Annex I of Directive 2001/83/EC) are not fulfilled. So only for completeness, this assessment report presents also one of the most recent studies (Woelk & Schläfke, 2010), where patients with general anxiety disorder are included. The study is organised according to good clinical practice. Patients are well characterised, capsules with lavender oil are directly compared with lorazepam, and primary and secondary outcomes are clearly distinguished. Before entering, there was a one-week screening phase. Results were calculated using the full analysis set (Intention to treat or ITT) as well as per protocol (PP). However, the number of patients is low and no power calculation is made. Furthermore, no placebo arm was included. Therefore it is not possible to grant a well-established use for lavender. More studies with the same preparation and positive outcome will be necessary to ponder a well-established use.

Lavender oil has been studied in special populations like newborn children, children with autistic behaviour, psychogeriatric patients and hospitalised patients with positive outcomes. However the study populations are small and might be too diverse.

5. Clinical Safety/Pharmacovigilance

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

In clinical studies involving patients treated orally with a lavender flower tincture (Buchbauer *et al*. 1993b), and patients or healthy volunteers treated with lavender oil either topically (Dale & Cornwell 1994; Yip & Tse 2004; Dunn *et al*. 1995) or by inhalation of the odour (Diego *et al*. 1998; Louis & Kowalski 2002; Kane *et al*. 2004), only a few mild adverse events have been reported.

At a concentration of 16% in petrolatum, lavender oil did not produce any irritation after 48 h in the closed-patch test and produced no sensitization reactions in the maximisation test (Opdyke 1976).

From evaluation of linalool and linalyl acetate for skin irritation in male volunteers, no irritation was observed with 20% linalool or up to 32% linalyl acetate, while mild irritation was observed with 32% linalool. No sensitization reactions were observed in the human maximisation test with linalool at concentrations of 8% or 20% in 50 volunteers, nor with 10% linalyl acetate in 131 volunteers. With linalyl acetate at 12% and 20% no reactions were observed in 25 subjects (Bickers *et al*. 2003).

In very rare cases allergic reactions have been reported due to contact with lavender oil. Coulson & Khan (1999) described two case reports of mild facial 'pillow' dermatitis due to lavender oil allergy. Lavender oil does not seem to be a major sensitizing substance (Hausen & Vieluf 1997). A case of allergic reactions have been reported in young students (20 years). When an aromatherapy student started massaging the feet of a client with a mixture of *Lavandula*, *Origanum* and *Juniperus* oil, her hands started to tingle and became swollen with redness to her arms and throat area. Shortness of breath occurred within 3 minutes of exposure. The symptoms were reversible upon cleaning the skin of lavender oil (Maddocks-Jennings 2004).

Another case of contact dermatitis was reported after rubbing the face with hands that were not cleaned from a massage gel, containing 5% benzylamine and lavender fragrance. Erythema, followed by acute vesicular dermatitis developed (Rademaker 1994).

Three cases of gynecomastia in prepubertal boys were seen after topical application of products that contained lavender and tea tree oils. The boys were between 4 and 10 years old. Exposure was as a 'healing balm' with lavender on the skin, styling gel containing lavender on hair and scalp and the use of lavender-scented soap. Gynecomastia resolved after discontinuing of the therapy. No re-application is mentioned. Nevertheless, causality was accepted between the topical use of the plant species mentioned and the gynecomastia (Henley *et al*. 2007).

5.2. Patient exposure

Lavender flowers and essential oil have been used for centuries. Exact exposure data related to the use of registered preparations have not been retrieved.

5.3. Adverse events and serious adverse events and deaths

There have been reports of contact dermatitis associated with lavender oil in shampoo, and facial dermatitis after application of the oil to pillows for its sedative properties (Sweetman 2009).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.6. Overall conclusions on clinical safety

There is no major concern about human toxicity due to lavender essential oil or lavender flowers. Contact dermatitis may be possible in rare cases.

6. Overall conclusions

Lavender essential oil as well as the dried lavender flowers can be considered as safe. There is no major concern about the quality of the herbal substance and the herbal preparation thereof.

Experimental as well as clinical evidence converge to central nervous effects, more particularly related to anxiety. There are many small- and larger-scale studies available with a patient population representative for ambulatory practice, including children and elderly. Some criticism can be given to the doses and the method of administration. Especially inhalation is difficult to quantify, although the substances will be more directly delivered to the circulation. There are no major concerns on the safety of lavender flowers or essential oil.

Lavender oil and flowers have been used for more than 30 years in the EU. A well-established use cannot be proposed for lavender flowers and oil in the treatment of general anxiety disorders (cf. ICD-10 F 41.1). Although the quality of the studies has increased with time, the number of patients treated with essential oil of lavender in RCTs is too low. No structured clinical research has been done on the cutaneous use of *Lavandula* preparations. The use as bath additive of the oil is considered as traditional.

The regulatory position of lavender flowers was discussed. There is a long-standing use of the flowers, in a very wide range of therapeutic indications. Moreover, no authorised preparations with flowers were reported in the EU countries. However, the effects for the relief of mild symptoms of mental stress and exhaustion and to aid sleep are plausible on the basis of long-standing use and tradition, thus a monograph is established.

As the genotoxicity of lavender flowers and total essential oil was not appropriately tested, a Community list entry cannot be established.

Annex

List of references