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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Aloysia citrodora* Paláu (syn. *Aloysia triphylla* (L'Hér.) Kuntze; *Verbena triphylla* L'Hér.; *Lippia citriodora* Kunth), folium

Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Aloysia citrodora</i> Paláu (syn. <i>Aloysia triphylla</i> (L'Hér.) Kuntze; <i>Verbena triphylla</i> L'Hér.; <i>Lippia citriodora</i> Kunth), folium
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use Herbal preparation in solid or liquid dosage forms for oral use
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Aloysia citrodora* Paláu (syn. *Aloysia triphylla* (L'Hér.) Kuntze; *Verbena triphylla* L'Hér.; *Lippia citriodora* Kunth), folium. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.



Table of contents

1. Introduction	4
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof .	4
1.2. Search and assessment methodology.....	5
2. Data on medicinal use	5
2.1. Information about products on the market.....	5
2.1.1. Information about products on the market in the EU/EEA Member States	5
2.1.2. Information on products on the market outside the EU/EEA.....	6
2.2. Information on documented medicinal use and historical data from literature.....	7
2.3. Overall conclusions on medicinal use.....	8
3. Non-Clinical Data	9
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	9
3.1.1. Primary pharmacodynamics	9
3.1.2. Secondary pharmacodynamics	13
3.1.3. Safety pharmacology	14
3.1.4. Pharmacodynamic interactions	14
3.1.5. Conclusions	14
3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	14
3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof	14
3.3.1. Single dose toxicity.....	14
3.3.2. Repeat dose toxicity	15
3.3.3. Genotoxicity	15
3.3.4. Carcinogenicity	15
3.3.5. Reproductive and developmental toxicity	15
3.3.6. Local tolerance.....	16
3.3.7. Other special studies.....	16
3.3.8. Conclusions	16
3.4. Overall conclusions on non-clinical data.....	17
4. Clinical Data	17
4.1. Clinical pharmacology	17
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents.....	17
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents.....	17
4.2. Clinical efficacy	17
Only one clinical study testing <i>Aloysia triphylla</i> folium efficacy has been published.	17
4.2.1. Dose response studies.....	17
4.2.2. Clinical studies (case studies and clinical trials).....	17
4.3. Clinical studies in special populations (e.g. elderly and children)	20
4.4. Overall conclusions on clinical pharmacology and efficacy	20
5. Clinical Safety/Pharmacovigilance	20
5.1. Overview of toxicological/safety data from clinical trials in humans.....	20

5.2. Patient exposure	20
5.3. Adverse events, serious adverse events and deaths	20
5.4. Safety in special populations and situations	20
5.4.1. Use in children and adolescents	20
5.4.2. Contraindications.....	21
5.4.3. Special warnings and precautions for use.....	21
5.4.4. Drug interactions and other forms of interaction	21
5.4.5. Fertility, pregnancy and lactation	21
5.4.6. Overdose	21
5.4.7. Effects on ability to drive or operate machinery or impairment of mental ability.....	21
5.4.8. Safety in other special situations	21
5.5. Overall conclusions on clinical safety	21
6. Overall conclusions (benefit-risk assessment).....	21
Annex	22

1. Introduction

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

- Herbal substance(s)

Aloysia citrodora Paláu (syn. *Aloysia triphylla* (L'Hér.) Kuntze; *Verbena triphylla* L'Hér.; *Lippia citriodora* Kunth), folium (Fam. Verbenaceae) has got two different monographs in the following Pharmacopoeias:

- Lemon verbena leaf in the European Pharmacopoeia (01/2012: 1834), with the following definition: Whole or fragmented, dried leaves of *Aloysia citriodora* Paláu (syn. *Aloysia triphylla* (L'Hér.) Kuntze; *Verbena triphylla* L'Hér.; *Lippia citriodora* Kunth).

Content:

- *Acteoside* (C₂₉H₃₆O₁₅; M_r 625): minimum 2.5 per cent expressed as ferulic acid (dried drug).
- *Essential oil*: minimum 3.0 mL/kg for the whole drug and minimum 2.0 mL/kg for the fragmented drug (dried drug).
- Verveine odorante in French Pharmacopoeia (Fr.Ph. VIII ed., 1965): dried leaves from *Lippia citriodora* H.B et K.

Lemon verbena is a deciduous plant growing in the USA, warm regions of Asia and Africa and commonly cultivated in the tropics and Europe (Wren, Potter's Pharmacopoeia 1975; Paris and Moyses, 1971; Pascual et al., 2001). It reaches heights of 1 to 3 meters and plants are characterized by fragrant, lemon smelling, narrow leaves with small white flowers borne in terminal panicles (Simon et al., 1984)

The leaves are opposite on the stem, often three or four in a whorl, elongate-lanceolate, attenuated at both ends, about 3-4 in. long, 1^{3/4} in. wide in the middle, with the lateral veins almost at a right angle to the midrib. When rubbed they give a lemon odour and the taste resembles that of the lemon (Wren, 1975).

After grinding, lemon verbena leaf has a characteristic odour reminiscent of lemon.

The leaves are simple with short petioles. They are narrow, lanceolate, and about 4 times longer than they are wide. The entire, slightly undulating margins are curled towards the upper surface. The upper surface is dark green and rough to the touch; the lower surface is paler green and shows a prominent midrib with secondary veins running to the margins (Eur. Ph., 01/2012: 1834).

Synonyms: Lemon verbena

- Herbal preparation(s)

The main constituents of the essential oil from *L. triphylla* leaves are the monoterpenes citral A, citral B, 1,8-cineole, geraniol, linalool and limonene, and the sesquiterpene caryophyllene oxide (Pascual et al., 2001), which content led to the description of 5 different chemotypes: neral (20.0%), geraniol (29.0%), limonene (40.3%), citronellal (21.6%) and β-thujone (73.4%)(Di Leo Lira et al., 2008 – in Jiménez-Ferrer, 2017). A 50% loss in the oil content of the leaves during flowering has been observed (Guenther, 1948). Regarding the phenolic constituents, a wide variety of caffeic acid derivatives have

been identified, including verbascoside (or acteoside) and the flavonoids salvigenin, eupatorin, eupafolin, hispidulin, cirsiolol and some derivatives from luteolin (Pascual et al., 2001).

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

Not applicable

1.2. Search and assessment methodology

Available literature on *Aloysia triphylla* at the electronic databases PubMed, Toxline and The Cochrane Library and the incoming, on the "call for scientific data for use in HMPC assessment work on *Aloysia triphylla* (L'Hérit.) Britt., folium", was used for a literature search. Articles were filtered by using the following terms: *Aloysia triphylla*, *Aloysia citriodora*, *Lippia citriodora*, *Verbena triphylla*, lemon verbena. No restrictions to language were applied. The search was performed three times July 2017, July 2019 and January 2020.

Only articles found to be relevant for assessment are included in the list of references.

Results in PubMed

Search term "*Aloysia triphylla*": 35 references obtained.

Search term "lemon verbena": 54 results.

Results in Toxline

Search term "*Aloysia citriodora*": 3 references (<https://chem.nlm.nih.gov/chemidplus/rn/977047-96-3>) (teratogenic effect of verbascoside)

Search term "lemon verbena": 2 results.

The Cochrane Library (trials)

Search term "*Aloysia citriodora*": 2 references

Search term "lemon verbena": 16 results

Other resources: Books, Book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations (list of references in Annex).

2. Data on medicinal use

2.1. Information about products on the market

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

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
<i>L. citriodora</i> dried leaf	Dyspepsia, gastrointestinal complaints	Comminuted herbal substance 2-3g/cup, 1-3 times daily	One product, at least since 1974, Spain Two MAs 1985, Spain

Active substance	Indication	Pharmaceutical form	Regulatory Status
			One MA 1986, Spain One MA, 1991, Spain
<i>L. citriodora</i> dried leaf	Relaxing effect	Comminuted herbal substance 2-3g/cup	Since 2014, <i>Spain</i>
<i>Verbenae odoratae</i> dried leaf (syn <i>Verbenae citriodora folium</i>)	Soothing properties Nervous tension, nervous digestive disorders	Comminuted herbal substance: One cup (1.0 g herbal substance) up to 5 times daily, before or after meals; As an aid to sleep: 1 to 2 cups (1.0 g to 2.0 g) half an hour before going to bed. Children > 6 years and adults	1979, Switzerland ¹ , MA

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

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

- Agua del Carmen, MA in Spain since 1954.

Fluid extract obtained by hydroethanolic distillation of 24 species, including *Aloysia citriodora* O. (1.43 mg).

Indication: Traditionally used for the treatment of symptoms of stress such as gastrointestinal disorders and nervousness.

Posology: 2 - 3 small spoons (5 ml each) diluted in an infusion (tilia, chamomilla, etc.) or water, 3-4 times daily

On the market since 1957

Several combinations as herbal teas (Species digestivae)

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

Not applicable

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

Not applicable

¹The products authorized in Switzerland are also authorized in Lichtenstein. According to the Q&A published on the EMA website, Norway, Iceland and Liechtenstein have, through the EEA agreement, adopted "the complete Union acquis on medicinal products and are consequently parties to the Union procedures. Where in this chapter reference is made to Member States of the Union this should be read to include Norway, Iceland and Liechtenstein".

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

The leaves from lemon verbena have been widely commonly used in the form of infusion for the treatment of stomach ache and indigestion (Paris and Moyse, 1971) and as antispasmodic remedy (Bruneton, 1987; Pascual et al., 2001). In the form of a decoction (1 oz to 1 pt.), it has been indicated as febrifuge and sedative (Wren, 1975), antispasmodic, antipyretic, sedative and stomachic (Simon, 1971). It was included in the Pharmacopendium in 1925 because of the existence of a monograph in the Spanish Pharmacopoeia (Soler, 1925).

In Europe, but also in South America and North Africa, it has been used for many years to treat diarrhea, flatulence, insomnia and rheumatism (Bahramsoltani et al., 2018).

Lemon verbena has also been used for the treatment of asthma, cold, fever, flatulence, colic, diarrhoea and indigestion (Newal et al., 1996; Barnes, 2007).

The Handbook of Medicinal Plants (Duke, 2002) describes the indications of lemon verbena for agitation, dyspepsia, insomnia and nervousness, with dosages of 2-5 cups decoction (5-29 g leaf/ liter water/day).

Martindale, the Extra Pharmacopoeia (2014) includes the actions of flowering tops or leaves of *Lippia citriodora* as antispasmodic and sedative and for gastrointestinal disorders and as a tonic.

According to the French Avis aux fabricants (1986), lemon verbena is listed as one of the drugs accepted for infusions with the indication "traditionally used to improve digestion". Also the Belgium legislation includes *Aloysia citriodora* Palau leaves, in the list of plants or preparations from plants accepted for inclusion in the composition of food supplements (Royal degree February 10th, 2017).

According to the Spanish legal framework for Foods (Royal Degree 3176/1983), the leaves from *Lippia citriodora* can be marketed as infusions in the food area.

Table 2: Overview of historical data

Herbal preparation	Documented use / traditional use	Pharmaceutical form	Reference
<i>L. citriodora</i> dried leaves	Stomach ache and indigestion	Comminuted herbal substance	Paris and Moyse, 1971
<i>L. citriodora</i> dried leaves	Dyspepsia Nervousness	Comminuted herbal substance: 1-5g/200ml water, 2-5 times daily Fluid extract (1:1): 0.7-1ml, 2-3 times daily Tincture (1:10): 1.5-2.5ml, 1-3 times daily	Catálogo Gral Consejo General Farm, 2009 Masson, Vademecum de Fitoterapia, 1998
<i>L. citriodora</i> dried leaves	Antispasmodic, stomachic Sedative	No information about the herbal preparation	Simon et al., 1984
<i>L. citriodora</i> leaves	Antispasmodic Digestive	Comminuted herbal substance for infusion: 0.5-2%, several times daily (after meals) Tincture: 20g liquid	Van Hellemont, 1986

Herbal preparation	Documented use / traditional use	Pharmaceutical form	Reference
<i>L. citriodora</i> dried leaves	Stomach ache and indigestion	Comminuted herbal substance	Paris and Moyse, 1971
		extract in 80g 20% alcohol. Take 1 coffee spoon "lors des crampes d'estomac" (= in case of stomach cramps)	
<i>L. citriodora</i> leaves	Antispasmodic Sedative	Decoction: 45ml, several times daily	Newall et al. 1996 Barnes et al. 2007
<i>L. citriodora</i> leaves	Febrifuge Sedative	Decoction: 1 oz to 1 pt tea cup, 3 times daily (equivalent to 5g in 100ml)	Wren, 1975
<i>L. citriodora</i> leaves	Agitation Insomnia, nervousness Dyspepsia	Decoction: 45ml, several times daily (CAN) 2-5 cups decoction (5-29g leaf/l water/day)	Duke, 2002
<i>L. citriodora</i> leaves	Antispasmodic Sedative	No information about the herbal preparation	Martindale 28 th ed., 2014

1 oz = 28.34g

1 pt = 568.25ml

2.3. Overall conclusions on medicinal use

According to the data obtained from the Market overview, there are no single products as medicines in the European member states; in Spain, products under the old registration system (Medicinal plant-PM) can be found in the market as comminuted herbal substance at least since 1974, for digestive complaints. One product in Switzerland is marketed since 1979 and remains in the market in the pharmaceutical form of comminuted herbal substance to treat nervous tension and nervous digestive disorders.

Lemon verbena leaves are listed in the French Cahiers de l'Agence "to improve digestion".

Under the Food area, *Aloysia triphylla* leaves are listed in the Spanish Food legislation "Vegetal species to be used as teas as food" (Royal Decree 3176/1983, November 18th) and also in the Belgium legislation as a vegetal specie to be included in Food Supplements (*Aloysia citriodora* Palau, leaf)(Royal Decree 10 February 2017).

Traditional use from literature supports both indications for dyspepsia and as mild sedative and includes a Posology for comminuted or powdered dry plant, for more than 30 years in the European Union.

Thus, the available sources provide evidence of the period of use, specified strength and specified posology and indications suitable to the legal requirements in the relevant route of administration as shown in Table 3.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
<i>L. citriodora</i> leaves Comminuted herbal substance	Relief of mild symptoms of mental stress and to aid sleep	Decoction: 1 oz to 1 pt tea cup, 3 times daily (equivalent to 5g in 100mL) Infusion: As an aid to sleep: 1 to 2 cups (1.0 g to 2.0 g) half an hour before going to bed. Children > 6 years and adults	Wren, 1975 More than 30 years of medicinal use in the EU
<i>L. citriodora</i> leaves Comminuted herbal substance	Symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence	Infusion 0.5-2%, several times daily (after meals) 1 small spoon (2- 3g) 1-3 times daily	More than 30 years of medicinal use in the EU (Spain, MA 1974) (Van Hellemont, 1986)
<i>L. citriodora</i> leaves Tincture	Dyspepsia Nervousness	Tincture (1:10) 1.5-2.5ml, 1-3 times daily	More than 22 years of medicinal use in the EU (Masson, Vademecum de Fitoterapia, 1998)

3. Non-Clinical Data

Pharmacological studies with *Aloysia triphylla* leaves have focused on the antimicrobial, gastrointestinal and anti-inflammatory effects, but also in the antioxidant activity in different ways, which is not a specific effect for lemon verbena.

Many studies have demonstrated the *in vivo* and *in vitro* pharmacological activity of *Aloysia triphylla* folium. Those studies with relevance for the clinical efficacy are included.

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

3.1.1. Primary pharmacodynamics

Anxiolytic/ sedative effect

In vivo studies

Ragone et al., (2010) shown the sedative effect of the aqueous extract (AEC) of *A. citriodora* in mice through a benzodiazepine-like mechanism on GABA-A receptor. The aqueous extract was prepared from 30 g dried leaves which were boiled in 200 ml distilled water for 20 min and then, lyophilized (obtaining a 15% w/w yield). The lyophilized extract was diluted in distilled water. With this procedure, the essential oil was not included in the lyophilized sample.

Animals were divided in 7 groups which received different treatments by *i.p.* injections: saline solution (negative control), 10 mg/kg diazepam (positive control), 0.15, 1 and 10 mg/kg AEC, 1 mg/kg AEC 5 min after receiving 10 mg/kg diazepam and 1 mg/kg AEC 5 min after receiving 0.5 mg/kg flumazenil. The same protocol was followed for 4 groups of mice administered with 33, 100 and 333 mg/kg of vitexin or saline solution (negative control), for the times of 30, 60, 90 and 120 min.

The exploratory behaviour and the spontaneous locomotion of mice were measured in the open field. Both properties, respectively measured by the number of rearings and crossed lines during 5 min, were dose-dependently decreased by AEC. The AEC from 1 to 10 mg/kg sedative effect was potentiated by diazepam and sensitive to flumazenil, this suggesting a benzodiazepine-like effect of AEC on the GABA-A receptor. Meanwhile, the isolated flavonoid vitexin only increased the spontaneous locomotion at the start of the test and at 100 mg/kg, but not at higher doses or longer periods of testing and did not modify the mice exploration, this indicating that vitexin is not responsible of the sedative effect of *A. triphylla*.

In the same study, normotensive rats receiving 1 to 30 mg AEC/kg showed a transitory hypotension, insensitive to atropine and L-NAME which was not due to cholinergic effect, NO-release or α 1-adrenergic antagonism.

According to the authors, the observed benzodiazepine-like sedation, negative inotropism and antispasmodic effect exerted by the aqueous extract of *A. triphylla* might justify its popular use for abdominal cramps and as coadjuvant for anxiety and angor. These results suggest a benzodiazepine-like effect of AEC on the GABA-A receptor (Ragone et al. 2010).

The anxiolytic effect of fatty acids and terpenes from *Aloysia triphylla* collected in Mexico was studied within male Institute of Cancer Research (ICR) mice (Jiménez-Ferrer et al 2017). Dried stems and leaves were subjected to extractions with ascending polarity solvents and led to n-hexane extract, dichlorometane extract and methanol extract (1kg dried plant per 1L solvent). In the first part of the study, the three extracts (500mg/kg body weight by oral administration) were evaluated in comparison with the negative control group (tween 20); the positive control received 1.0mg/kg diazepam intraperitoneally. The biological effect was assayed by the elevated plus maze (EPM) test.

Then, the most active extract (dichlorometane) was evaluated at 125, 250 and 750mg/kg and subsequently, the extract was fractionated and the fractions assayed to evaluate their activity when administered 30 minutes previous to known sedative drugs on GABA, glutamate and serotonergic systems (baclofen, ketaserine and ketanserine, respectively, as examples).

Results showed an anxiolytic-like effect in mice for all the assayed extracts. Studies with the most active extract and its fractions led to the possibility of lemon verbena modulation of GABA with an over activation of such receptor provoking an effect comparable to that of high dose of baclofen. The most active fraction (F1) mainly comprised fatty acids such as palmitic acid and its activity was blocked when combined with bicuculline methiodide (BICC) or flumazenil. Authors suggested that the sedative action was mediated through the chloride channel in the GABA-A receptors, but not by interaction with the binding site of GABA or benzodiazepines, as only pentylenetetrazole was able to reverse the effect.

The chemical assay of F1 showed the presence of terpenes such as α -amyryn, which had previously demonstrated a decrease in anxiety behavior on animals, this activity being reversed with flumazenil.

Thus, the observed anxiolytic effect of *A. triphylla* could be attributed to the content of fatty acids and terpenes which interact with the GABA system (Jiménez-Ferrer et al., 2017).

In vitro studies

In the study conducted by Ragone et al., (2010), the effect of AEC was evaluated on the dose-response curves (DRC) of phenylephrine in the rat *vas deferens* isolated from male rats (*vas deferens* show α -1 receptors), in order to evaluate whether the hypotensive effect of AEC was due to an antiadrenergic mechanism. AEC was prepared as described above and the lyophilized extract was dissolved in Krebs solution.

Results showed that AEC non-competitively blocked the phenylephrine contraction on *vas deferens*. In isolated rat hearts, AEC and isolated vitexin induced negative inotropism through a non-competitive contractile blockade, which agrees with the antispasmodic effect previously seen in intestine.

Gastrointestinal effects

The gastrointestinal relaxant effects of lemon verbena aqueous extract (AEC) which was prepared by boiling 30g dried leaves in 200mL distilled water for 20min, as the traditional use, were assayed (Ragone et al., 2007). The aqueous extract was lyophilized and diluted as explained above in distilled water and Tyrode solution (Ragone et al., 2010). With this procedure, the essential oil was not included in the final sample.

The drugs used in biological tests were: papaverine hydrochloride, acetylcholine bromide, *N*-(6-aminoethyl)-5-chloro-1-naphtalenesulfonamide, methylene, tetraethylammonium chloride (Sigma) and the flavonoids quercetin, vitexin and isovitexin.

Duodenum (about 2 cm long) were obtained from Sprague–Dawley rats (200–250 g) were subjected to a 24 h fasting with free access to water before experimentation. Then, they were prepared and mounted in organ baths of 20 mL containing Tyrode solution at 37 °C constantly oxygenated with air.

Dose–response curves (DRC) to acetylcholine (Ach) were done for the rats duodenum after a stabilization of 45 min, in the absence and the presence of AEC after 10 min of contact with 0.1, 0.2, 0.6, 1, 2 or 6 mg/mL of lyophilized extract. The same protocol was carried out with the flavonoids vitexin and isovitexin (at 0.3, 1, 3, 10 and 30 g/mL).

For the dose–response curves (DRC) to CaCl₂ assay, AEC (0.1, 0.2, 0.6, 1, 2 or 6 mg/mL final concentration) vitexin and isovitexin (at 20 g/mL); with 30 mol/L W-7 (a calmodulin antagonist) without and with 1mg/mL AEC; with papaverine (5, 15, 30 and 45 mol/L); with AEC (1 mg/mL) plus papaverine (5 and 15 mol/L), were added to the bath.

Results showed that AEC reduced the maximal effect of Ach on a dose-dependent way, this suggesting a non-competitive antagonism over the cholinergic contraction. In order to prove whether AEC interfered with a cellular process between Ca²⁺ influx and the contraction, it was assayed whether AEC blocked the calmodulin-Ca-binding. Curves of Ca²⁺ were done in the absence and presence of either, 1 mg/mL AEC or 30 mol/L W-7 (a Ca-calmodulin-inhibitor) plus 1mg/mL AEC. Results showed that W-7 potentiated the non-competitive inhibition produced by AEC. On the other side, to evaluate whether AEC acts by a mechanism similar to papaverine (one of the most active relaxant of smooth muscle) their effects were compared. Papaverine non-competitively inhibited the Ca²⁺ curve, and completely blocked the response at 30–45 mol/L. The relaxation curve of AEC was non-competitively

blocked by an inhibitor of the guanylate cyclase, methylene blue, this suggesting that the extract increased the GC activity.

The same authors also proved that the relaxant effect of AEC was at least, due to inhibition of the aerobic metabolism on duodenum, as papaverine did. Finally, results of the assays with isolated vitexin and isovitexin showed that the first one produced a non-competitive antagonism on the Ach dose-response curve, while the stereoisomer isovitexin did not significantly inhibit the DRC of Ach.

Authors concluded that the antispasmodic effect of lemon verbena could be explained by a non-competitive inhibition of Ca²⁺ influx, which may be mostly associated to a target shared with papaverine and quercetin. Other mechanism of AEC was the activation of K⁺ -channels, which could be a consequence of increasing cGMP, and drives to hyperpolarization and relaxation. Finally, at low concentrations, AEC inhibited the aerobic metabolism. Vitexin, but not isovitexin, contributed to the antispasmodic effect by a non-competitive inhibition of Ach but not on Ca²⁺ influx, this suggesting that other components are implied in the spasmolytic effect (Ragone et al., 2007).

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
comparable/similar preparations to preparations of the monograph				
Aqueous extract of <i>A. citriodora</i> leaves (AEC)	1 to 10 mg AEC/kg	<i>In vivo</i> Male mice	Ragone et al., 2010	sedative effect
	1 to 30 mg AEC/kg	<i>In vivo</i> Male normotensive rats		transitory hypotension
	AEC	Isolated rat hearts		negative inotropism
Aqueous extract of lemon verbena	boiling 30g dried leaves in 200mL distilled water for 20min, then lyophilised: .1, 0.2, 0.6, 1, 2 or 6 mg/mL	<i>In vitro</i> Rat duodenum	Ragone et al., 2007	gastrointestinal relaxant effects
other preparations				
Fatty acids and terpene fraction from dichloromethane extract from stems and leaves from lemon verbena	15mg/kg bw Oral route (once)	<i>In vitro</i> Male ICR mice	Jiménez-Ferrer et al., 2017	Anxiolytic effect due to interactions on GABAergic and serotonergic transmission

3.1.2. Secondary pharmacodynamics

In vivo studies

A study conducted by El-Hawary et al (2012) in male albino rats showed that oral administration of aqueous and ethanolic extracts (50mg/kg bw) from leaves of lemon balm exerted anti-inflammatory, analgesic, antipyretic and antioxidant activities. For every activity, the extract potency was compared to a positive control (indomethacin, novalgin, paracetamol and glucose damage, respectively).

The antiinflammatory activity could be attributed to the iridoids content, mainly thevitidoside (Simon et al, 1984; in El-Hawary et al, 2012), while the analgesic activity might be due to the phenylethanoid, verbascoside (Nakamura et al., 1997) and the high antioxidant activity might be attributed to its phenolic content (Mothana et al., 2010).

The anti-inflammatory effects and the gastric wound capacity after oral administration of *A. triphylla* hexane extract (ATHE) were studied *in vivo* (Ponce-Monter et al., 2010).

ATHE was obtained from 114g dried leaves macerated in 500mL hexane at room temperature for 24h. Its main component, citral, was quantified by gas chromatography, reaching 32-41% of the total content of the extract.

To test the anti-inflammatory activity, virgin female Wistar rats were used and evaluated by the carrageenan-induced paw edema model; rats orally received one dose of vehicle, ATHE (100-800 mg/kg), citral (100-800 mg/Kg) or indomethacin (30mg/Kg). Animals receiving the highest doses were also evaluated for gastric damage. Also in this experiment, both ATHE and citral showed a significant anti-inflammatory effect in the carrageenan model without the gastric injury provoked by indomethacin (Ponce-Monter et al., 2010).

Also the effect of lemon verbena infusion against mild-moderate dextran sulfate sodium (DSS)-induced colitis in rats has been assayed (Lenoir, 2011). Male Wistar rats drank a daily infusion obtained from 40g of lemon verbena leaves in 1L water and then, diluted ten times, for 22 days. Since the average daily intake was 29.7mL infusion, animals were supposed to ingest 1.97 $\mu\text{mol/day}$ verbascoside, 0.64 $\mu\text{mol/day}$ isoverbascoside, 2.1 $\mu\text{mol/day}$ diosmetin, 0.75 $\mu\text{mol/day}$ luteolin, 0.11 $\mu\text{mol/day}$ apigenin and a total polyphenol amount of 5.57 $\mu\text{mol/day}$. After the experimental period, the colon was taken for histopathological examination, determination of myeloperoxidase (MPO) activity, antioxidant enzymatic activity [superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), catalase (CAT), glutathione and lipid peroxidation.

Results shown that lemon verbena exerted no protective effect on neutrophil infiltration in the colon, but could help to manage oxidative stress by stimulating antioxidant enzymatic activity and reducing lipid peroxidation.

In vitro studies

The spasmolytic effect of *A. triphylla* hexane extract (ATHE) and its main component, citral, were evaluated on the uterine contraction *in vitro* (Ponce-Monter et al., 2010). ATHE was obtained as described above with a 32-41% citral.

For the *in vitro* spasmolytic effect, uterine strips were obtained from virgin female Wistar rats and the contractile responses were recorded for ATHE (3-230 $\mu\text{g/mL}$). Results showed the inhibitory effect on the spontaneous phasic contraction of myometrial smooth muscle in a concentration-dependent manner, this indicating an uterine relaxing activity which is not evoked through the activation of β -adrenoceptor. The same results were obtained for citral, the main component of ATHE (Ponce-Monter et al., 2010).

3.1.3. Safety pharmacology

Aloysia triphylla is listed in the USA as generally recognized as safe for human consumption in the form of alcoholic beverages and herbal teas (Simon et al, 1984; in El-Hawary et al, 2012).

According to data from literature (Duke, 2002) it is included in Class 1 (AHP) "Hazards and/or side effects not known for proper therapeutic dosages".

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Pharmacodynamic studies have been performed with *Aloysia triphylla* folium. The observed sedative effects after *in vivo* tests are related to its affinity for GABA receptors and are in accordance with the traditional use of this specie and with the *in vitro* studies which proved a direct relaxing effect of the aqueous extract of *A. triphylla* on the intestinal smooth muscle. *In vivo* studies showed the lack of effect on heart rate but *in vitro* studies revealed a dose-dependent negative cardiac inotropism, which could contribute to the transitory hypotension, and gives support to the use of *A. triphylla* as a coadjuvant for treating anxiety.

Results also proved that the flavonoid vitexin is not the responsible for such sedative effects, since it did not decrease locomotion. This lack of effect is important when considering that vitexin is a component of sedative and anxiolytic plants from other genus (i.e. *Passiflora*) and implies that the sedative component of *A. triphylla* remains undetermined. There is no information available on the pharmacodynamic interactions of *Aloysia triphylla* folium.

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

No data available.

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

Only a few studies have been published about the toxicity of lemon verbena aqueous extract and isolated compounds from *Aloysia triphylla* in different toxicological studies.

3.3.1. Single dose toxicity

Etemad et al., (2016) assessed the acute, subacute and cell toxicity of the aqueous extract of lemon verbena.

The aqueous extract was obtained by boiling 100g of dried leaf powder in one liter of distilled water for 20 min. Male BALB/c mice (25-30g) were selected for the acute toxicity study, while male Wistar rats (200-250g) were used for the subacute toxicity study.

Acute toxicity. 24 animals received three different doses of the aqueous extract: 1, 2 and 5g/kg of body weight via *i.p.* injection (control group received normal saline) with a volume of 0.25ml/25g bw. After single dose administration, animals were observed for general behavioural changes, signs of toxicity and mortality.

The LD₅₀ value for the aqueous extract of *Lippia citriodora* was calculated as 5g/kg body weight (Etemad et al., 2016).

3.3.2. Repeat dose toxicity

Subacute toxicity. 24 male Wistar rats received four different doses of the aqueous extract: 0, 50, 100 and 200 mg/kg of body weight via i.p. injection (control group received normal saline) with a volume of 0.5ml/25g bw for 21 days. Animals were observed for mortality and clinical signs until the end of the experiment. After sacrifice, blood samples were collected for haematological and biochemical analysis.

No symptoms of toxicity or behavioural changes were recorded during the study; moreover, *L. citriodora* aqueous extract had no effect on the mean body weight, food or water consumption (Etemad et al., 2016).

Hematological and Biochemical parameters. After 21 days of treatment with the aqueous extract of *Lippia citriodora* at different doses, no significant changes were observed in haematological parameters including haemoglobin, haematocrit, platelet count, white blood cell count and red blood cell count vs control group. Similarly, none of the evaluated biochemical parameters (creatinine, amylase, lipase, CPK, LDH, urea, total cholesterol, total protein, albumin, alkaline phosphatase and total bilirubin) of the treated groups displayed significant changes vs control group. For the groups receiving doses of 50 and 100mg/kg, a significant decrease in triglycerides level was observed (Etemad et al., 2016).

Histopathology. After 21 days of treatment with the aqueous extract of *Lippia citriodora* at different doses, vital organs such as the liver, kidney, lung, brain, heart and spleen were examined and indicated no histological changes when compared with control group (Etemad et al., 2016).

3.3.3. Genotoxicity

No data available.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

The study performed by Shirvan *et al.* (2016) aimed to assay the effect of *L. citriodora* aqueous extract on pregnancy outcome in mice. 10 female BALB/c pregnant mice received a single *i.p.* injection of 0.5g/kg body weight AE dissolved in normal saline (the equivalent volume of solvent by the same route was given to the control group), during the organogenesis period. Mortality, morbidity and general appearance, together with maternal body weights were evaluated daily. On the 18th day of pregnancy, the embryos were removed by cesarean and examined for external malformations, and size and body weight were recorded.

All pregnant mice included in the experiment were alive at the moment of cesarian extraction. No significant changes in maternal body weight, behaviour, food or water consumption, mean number of implantation, live or resorbed fetuses were observed. In relation to the fetus, no effect on the mean fetal weight was observed and the total number of defects in treated group compared to control group was higher although no significant.

Results revealed that administration of the AE of *L. citriodora* leaves during the period of organogenesis was not associated with fetal malformations or maternal toxicity. Authors concluded

that a moderate consumption of *A. citriodora* as infusion or tea had no harmful effect on the development of the mouse embryo during pregnancy (Shirvan *et al.*, 2016).

Moreover, the effect of isolated verbascoside (acteoside) on pregnancy outcome in mice was studied by administering 1g/kg/day verbascoside (or the vehicle alone) during organogenesis, intraperitoneally, to BALB/c female mice (Etemad *et al.*, 2015). Maternal body weights were measured during pregnancy and the litters were examined for external malformations and skeletal abnormalities.

Results showed no significant toxicity on the mother or in the development of fetuses (mean number of implantation sites, resorbed fetuses), this demonstrating no risk of verbascoside during organogenesis (Etemad *et al.*, 2015).

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

Etemad *et al.*, (2016) evaluated the *in vitro* cytotoxicity of the aqueous extract of *L. citriodora* leaves (prepared as explained above) in HepG2 cells. Concentrations of 0, 50, 100 and 200 µg/ml of extract were tested on cell culture for 24 and 72 hours. The maximum concentration tested did not reach 50% of cell death, with an overall viability greater than the IC₅₀, this indicating the absence of toxic effects.

Some studies reported the protective effect of lemon verbena against genetic damage induced by cisplatin (Zamorano-Ponce *et al.*, 2004) or acrylamide-induced DNA damage (Zamorano-Ponce *et al.*, 2006). Both studies were performed with a 5% infusion from *Aloysia triphylla* leaves which was given orally (0.5ml to a 20g mouse) during 20 days, twice daily.

The first study showed an inhibition of cisplatin's side effects, with a prevention of cis-DDP-induced genetic damage by acting as a free-radical scavenger, probably due to the polyphenolic composition of the herbal (mainly verbascoside) (Zamorano-Ponce *et al.*, 2004).

The latter study investigated the chemoprotective effect of lemon verbena infusion against the genetic damage induced by acrylamide (AA) by means of the alkaline version of the comet assay technique in mice. Results showed that pre-treatment of the animals with the infusion prior to AA injection significantly reduced the capacity of AA to induce genetic damage. Also in this case the authors suggested an *in vivo* chemoprotective action, probably due to the free-radicals scavenging activity of the infusion (Zamorano-Ponce *et al.*, 2006).

3.3.8. Conclusions

Toxicity data for the aqueous extract of lemon balm leaves indicate a low toxicity and thus, toxicity in humans, when taken at the recommended doses, is not expected. No constituents with safety concerns have been described in *Aloysia triphylla* folium.

Although terpene-rich volatile oils are generally regarded as irritant and may cause kidney irritation during excretion (Duke, 2002), results of the toxicity studies conducted with lemon verbena do not confirm such irritation, probably due to the low content of these kind of components in the drug (according to the Eur. Ph. D, dried plant content in essential oil is 2.0%).

Non-clinical information on the safety, reproductive and developmental toxicity of *Aloysia triphylla* folium is scarce. As there is no information, the use during pregnancy and lactation cannot be recommended. Due to the lack of genotoxicity studies, the list entry cannot be recommended.

Some studies carried out with isolated compounds from lemon balm showed no toxicity or even a protective effect against AA-induced or cisplatin-induced damage.

3.4. Overall conclusions on non-clinical data

The scientific information available on *Aloysia triphylla* folium pharmacological activity is limited to support the proposed indication. Nonetheless, the reported pharmacological activities are in agreement with the traditional uses as sedative and relaxant of the intestinal smooth muscle. This experimental pharmacological evidence is strengthened by a dose- and concentration dependent activity.

For the preclinical experiments water extracts were mostly used. These data are in accordance with the traditional use of the plant, which can be found in the European market for more than 30 years without any safety concern.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of *Aloysia triphylla* refers to some studies conducted with the aqueous extract of the leaves (similar preparation to preparations of the monograph). The safety profile of herbal preparation was assessed in both acute and medium term use (21 days).

Information on reproductive and developmental toxicity is only based upon single dose administration in mice. So the use during pregnancy and lactation cannot be recommended. Due to the lack of genotoxicity studies, the list entry cannot be recommended.

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

No data available.

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

No data available.

4.2. Clinical efficacy

Only one clinical study testing *Aloysia triphylla* folium efficacy has been published.

4.2.1. Dose response studies

No data available

4.2.2. Clinical studies (case studies and clinical trials)

Afrasiabian *et al.* (2019) tested the effect of *Aloysia citriodora* on insomnia patients through a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety (Table 5). Both male and female patients (18 and 72, respectively) over 18 years of age, diagnosed with insomnia on the basis of Diagnostic and Statistical Manual (DSM-5), with a global Pittsburg Sleep Quality index (PSQI) score > 5, were included. The required sample size was calculated to be 33 subjects in each group,

Assessment report on *Aloysia citriodora* Paláu (syn. *Aloysia triphylla* (L'Hér.) Kuntze; *Verbena triphylla* L'Hér.; *Lippia citriodora* Kunth), folium
EMA/HMPC/376761/2019

considering the test power of 80%, the type 1 error of 5%, and the effect size of 40%. At the end, 50 patients were included in each group of the study after considering the possible dropouts. A total number of 90 patients (47 at the intervention group and 43 at the control group) completed the study and were assessed.

Using a random list generated by random allocation software, patients were assigned to the intervention or control group. Patients included in the intervention group received 10ml of syrup prepared from *A. citriodora* leaves (5g leaves boiled in 330 ml water until a final volume of 200 -ml; then, it was filtered and 140g of sugar were added and boiled to reach a volume of 120 ml), one hour before bedtime by oral route during 4 weeks. The placebo group received 10ml of syrup prepared by adding 140 g sugar to 330 ml water and then concentrated to 120 ml by boiling.

Results showed a significant improvement of different components of sleep quality when compared to placebo; insomnia severity also decreased in the intervention group. The greatest effect was related to the improvement of daily function, subjective quality of sleep, reduction of insomnia and improvement of total quality of sleep. The weaker effect was on the delayed onset of sleep. Indeed, an of OR for the PSQI = 10.97 and a 95% CI 9.96 – 11.97 were found, which is indeed highly significant after 2 weeks

According to the authors, the observed effect may be related to the benzodiazepine-like effect of *A. citriodora* extract on the GABA-A receptor (Ragone et al., 2010) which had been previously assessed in mice.

Regarding the undesirable effects among all the patients, eight cases (including six in the intervention group and two in the control group) with mild and transient side effects were observed, namely restlessness, diarrhea, tremor, sleepines and localized itching. Authors assessed and graduated the drug toxicity according to the National Cancer Institute's Common Toxicity Criteria (CTC) Version and found that all reported side effects were of Grade 1 and were not so severe such that they prevent the participants from continuing the treatment.

Nonetheless, the authors considered some limitations for the study: first, the lack of objective measurement of sleep quality and severity of insomnia as an outcome despite the reliability and validity of the PSQI and ISI questionnaires used in the study; second, the failure to follow up the patients to assess their sleep status and possible recurrence of the disease (insomnia) for a longer period of time, especially after discontinuation of the drug; third, the CONSORT guideline for writing report of the trial was followed, instead of the "CONSORT guidelines for medicinal plants"; and fourth, the pharmaceutical formulations were prepared in the form of syrup, which resulted in the reluctance of some patients to participate. Especially, diabetic patients (due to the presence of sugar in the preparation of the syrups) had some concerns about their blood glucose. In addition, sugar has some biological effects and may affect sleep.

Moreover, this preparation is not covered by this AR.

Table 5.

Type (aim) and objective(s) of Study <i>Reference</i>	Study Design and Type of Control Study duration (if available)	Test Product(s): <i>herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment</i>	Number of Subjects <i>(including age, sex, drop out)</i>	Type of subjects <i>(inclusion criteria)</i>	Outcomes <i>(primary and secondary endpoints)</i>	Statistical analysis (e.g. ITT yes/no, CI 95%) <i>Quality score</i>	Comments on Clinical relevance of results
Efficacy and safety of <i>A. citriodora</i> for insomnia patients Afrasiabian et al., 2019	Randomized, double-blind, placebo-controlled clinical trial of efficacy and safety	Syrup ^a (1.66mg/10ml essential oil and 3.22mg/10ml total flavonoids expressed as quercetin) 10ml syrup, one hour before bedtime Oral route 4 weeks	100 patients (18 male, 73 female) Drop out: 3 patients in <i>A. citriodora</i> group (2-reluctance to continue treatment; 1 non-provision of detailed history), 7 patients in placebo group (reluctance to continue treatment) >18 years	Insomnia patients Global Pittsburg Sleep Quality Index (PSQI) > 5	Significant improvement in sleep quality components vs placebo ($p < 0.001$) Significant decrease in insomnia severity ($p < 0.001$) After 2 weeks: Difference in PSQI: Pittsburgh Sleep Quality Index and ISI: Insomnia Severity Index: $P < 0.001$	SPSS 20.0 PSQI score and its four components were assessed over 4 weeks of treatment Generalized estimating equations (GEE) model Results adjusted for gender, age, marital status	Improvement of daily function, subjective quality of sleep, reduction of insomnia, improvement of total quality of sleep. Nonetheless, this assay refers to a specific preparation not covered by this AR and it is not conclusive due to the limited number of patients

^a the syrup was prepared as follows: 5g *A. citriodora* leaves were boiled in 330 ml water until a final volume of 200 cc. Thereafter, it was filtered and 140g of sugar were added and boiled to reach a volume of 120 cc. Placebo was prepared by adding 140 g sugar to 330 cc water and then boiled to 120cc.

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

The existing data do not meet the criteria for "well established medicinal use" in accordance with Directive 2001/83/EC.

The published clinical trial cannot be considered for the preparations covered by this AR, due to several limitations of the study, such as the lack of objective measurement of sleep quality and severity of insomnia, the failure to follow up the patients to assess their sleep status and possible recurrence of the disease (insomnia) for a longer period of time, the fact of not following the CONSORT guidelines for medicinal plants and fourth, and the use of a preparation not covered by this AR in the form of a syrup which could itself exert some biological effects and may affect sleep.

Thus, the plausibility of efficacy of the medicinal product is only based on long-standing use and experience and allows the development of a Community herbal monograph on the traditional use of *Aloysia triphylla* folium.

5. Clinical Safety/Pharmacovigilance

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

No data available.

Data from clinical trials revealed a low severity (Grade 1 according to the National Cancer Institute's Common Toxicity Criteria –CTC): restlessness tremor, sleepiness, localized itching, which were not severe enough to prevent the participants from continuing the treatment (Afrabasian et al., 2019)

Although terpene-rich volatile oils are generally regarded as irritant and may cause kidney irritation during excretion, no adverse effects related to kidney toxicological effects have been reported.

In conclusion, oral administration of *Aloysia triphylla* can be regarded as safe at traditionally used doses with the exception of patients with severe renal disease e.g. renal failure.

5.2. Patient exposure

No data available

5.3. Adverse events, serious adverse events and deaths

No data available

5.4. Safety in special populations and situations

No data available

5.4.1. Use in children and adolescents

No data available

5.4.2. Contraindications

Due to the possible irritation during excretion, patients with renal problems should avoid it.

5.4.3. Special warnings and precautions for use

None reported.

5.4.4. Drug interactions and other forms of interaction

None reported.

5.4.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

5.4.6. Overdose

No data available.

5.4.7. Effects on ability to drive or operate machinery or impairment of mental ability

Based on the indication proposed, products containing *Lippia triphylla* L., *folium*, may cause drowsiness. This risk may increase in combination with alcohol or other sedatives or if excessive doses are taken.

5.4.8. Safety in other special situations

Not applicable.

5.5. Overall conclusions on clinical safety

On the basis of the information on its traditional use, the medicinal product proves not to be harmful in the specified conditions of use.

Based on the data on terpene-rich volatile oils, and considering their irritant effect, the contraindication for patients with renal problems was previously reported (Duke, 2002). Nonetheless, due to an oil content of only 2% in the dried drug and in the view of the available clinical safety data, they are irrelevant to the use of lemon verbena leaf preparations as specified in the HMPC monograph.

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

6. Overall conclusions (benefit-risk assessment)

Well-established use cannot be accepted for *Aloysia triphylla* L., *folium*, due to the lack of data on clinical efficacy, in accordance with Directive 2001/83/EC.

There data in relation to reproductive and developmental safety are scarce, so the use of *Aloysia triphylla* L., *folium* in pregnancy is not recommended. A European Union list entry is not supported due to lack of data on genotoxicity.

Studies related to the toxicity of the aqueous extracts of *Aloysia triphylla* L., *folium* demonstrate a very low toxicity risk after oral intake. Safety of lemon balm has been investigated and because of the long-standing use, no major safety concerns can be derived in relation to the use of *Aloysia triphylla* L., *folium* in the recommended posology and conditions of use.

Thus, medicinal use of *Aloysia triphylla* L., *folium*, fulfils all the requirements for Traditional Use in the European Union (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, plausibility and safety): it is well documented in several handbooks and marketed throughout a period of at least 30 years under Directive 2001/83/EC as comminuted herbal substance for its traditional use as sedative and gastrointestinal relaxant.

Traditional use has shown that *Aloysia triphylla* L., *folium* can be recognized as safe when used in recommended dosages under the conditions specified in the monograph.

In conclusion, a monograph for *Aloysia triphylla* L., *folium*, for oral use is recommended with the following indications:

Indication 1)

THMP product for relief of mild symptoms of mental stress and to aid sleep.

Indication 2)

TMHP for symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence.

Annex

List of references