



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2012
EMA/HMPC/337067/2011
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Tilia cordata* Miller, *Tilia platyphyllos* Scop., *Tilia x vulgaris* Heyne or their mixtures, 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)	<i>Tilia cordata</i> Miller, <i>Tilia platyphyllos</i> Scop., <i>Tilia x vulgaris</i> Heyne or their mixtures, flos
Herbal preparation(s)	a) Comminuted herbal substance b) Liquid extract (DER 1: 1), extraction solvent ethanol 25% V/V c) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% V/V
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

Tilia flos (lime flower) consists of the whole dried inflorescence of *Tilia cordata* Miller, of *Tilia platyphyllos* Scop., of *Tilia x vulgaris* Heyne or a mixture of these (European Pharmacopoeia 2008).

Lime tree (Linden) is a tall deciduous tree native throughout Europe as far north as 65° in latitude, which can grow to heights approaching to 30 metres. It is found in the wild and purposely planted in gardens. It is also cultivated in Europe and North America while the material of commerce originates mainly from Balkan countries such as Bulgaria, Romania, former Yugoslavia, Turkey and in part from China. Lime tree bark is smooth and grey and its leaves are heart-shaped. The 5-petalated, yellow white flowers are collected in full bloom, dried and preserved under low-moisture conditions (Blumenthal *et al.* 1998).

All the above-referred species are preferred because the tannin and mucilage content in their flowers produce more favourable teas and extracts (Blumenthal *et al.* 1998).

Tilia has a faint aromatic odour and a faint sweet and mucilaginous taste (European Pharmacopoeia 2008).

Lime flower's inflorescence is yellowish-green. The main axis of the inflorescence bears a linguiform bract, membranous, yellowish-green, practically glabrous, the central vein of which is joined for up to about half of its length with the peduncle. The inflorescence usually consists of 2 - 7 flowers, occasionally up to 16. The sepals are detached easily from the perianth; they are up to 6 mm long, their abaxial surface is usually glabrous, their adaxial surface and their borders are strongly pubescent. The 5 spatule, thin petals are yellowish-white, up to 8 mm long. They show fine venation and their borders only are sometimes covered with isolated trichomes. The numerous stamens are free and usually constitute 5 groups. The superior ovary has a pistil with a somewhat 5-lobate stigma. (European Pharmacopoeia 2008)

Lime flower comprises of the dried inflorescence of *Tilia cordata* Miller, of *Tilia platyphyllos* Scop., of *Tilia x vulgaris* Heyne (fam. *Tiliaceae*), or a mixture of these and is used in herbal medicine. (VIth Hungarian Pharmacopoeia 1970; British Herbal Pharmacopoeia (BHP) 1976; Bradley 1992; Blaschek *et al.* 2010; PDR for Herbal Medicines 2007).

Common names: European Lime, basswood, Linden tree.

Synonym(s)

Tilia cordata Miller = *Tilia officinarum* Crantz, *Tilia officinarum* Crantz subsp. *officinarum* pro parte, *Tilia ulmifolia* Scop., *Tilia parvifolia* Ehrh. ex Hoffm., Small-leaved Lime

Tilia platyphyllos Scop. = *Tilia officinarum* Crantz, *Tilia officinarum* Crantz subsp. *officinarum* pro parte, Large-leaved Lime

Tilia x vulgaris Heyne, a hybrid of the above = *Tilia x europaea* auct. non L.

Chemical constituents according to existing references (BHP 1976; Bradley 1992; Barnes *et al.* 2007; Duke 1985; Review of Natural Products 2005; WHO 2010):

- **Acids** - Caffeic acid, chlorogenic acid and *p*-coumaric acid

- **Amino acids** - Alanine, cysteine, cystine, isoleucine, leucine, phenylalanine and serine
- **Carbohydrates** - Mucilage polysaccharides (3%). Five fractions identified yielding arabinose, galactose, rhamnose, with lesser amounts of glucose, mannose, and xylose; galacturonic and glucuronic acids (Kram & Franz 1985; Yakovlev 1985)
- **Flavonoids** - Kaempferol, quercetin, myricetin and their glycosides (mainly Kaempferol-3-O- β -D-(6''-E-p-coumaroyl)-glucopyranoside – tilliroside) (Nowak 2003)
- **Volatile oil** - (0.02% to 0.1%) Many components including alkanes, phenolic alcohols and esters, and terpenes including citral, citronellal, citronellol, eugenol, limonene, nerol, α -pinene and terpineol (monoterpenes), and farnesol (sesquiterpene) (Fitsiou *et al.* 2007; Rădulescu & Oprea 2008; Ahmadi & Mirza 1999; WHO 2010)
- **Other constituents** - Saponin (unspecified), tannin (condensed) and tocopherol (phytosterol).

The ratio of tannins to mucilage appears to be important in determining the flavour of teas prepared from lime flowers. Those teas with a high (2% or greater) tannin level and low mucilage content produce the more flavourful teas. Flowers from *Tilia cordata* and *Tilia platyphyllos* contain relatively more tannin than mucilage (Blumenthal *et al.* 2000). More than 2 dozen additional minor compounds have been identified in the wood, flowers and fruits of lime. The fragrant components of the flowers degrade rapidly under conditions of high moisture (Blaschek *et al.* 2010; PDR for Herbal Medicines 2007; Review of Natural Products 2005).

The herbal substance should contain not less than 15% water-soluble extractive (BHP 1976), while the Pharmacopoeia of Hungary (VIth Hungarian Pharmacopoeia 1970) requires not less than 18% water-soluble extractive.

Macroscopic and microscopic tests are used for detecting common adulterations with other species (mainly *Tilia tomentosa* = *Tilia argentea*). According to the European Pharmacopoeia (2008), a maximum of 2% of foreign matter can be determined on 30 g. There are no inflorescences with a bract bearing at the abaxial face stellate, five to eight-rayed trichomes and flowers having an apparent double corolla by transformation of five stamens into petal-like staminoids and having a pistil which is not lobular nor indented. Hexamerous flowers occur only occasionally (*Tilia americana* L., *Tilia tomentosa* Moench).

- Herbal preparation(s)
 - a) Comminuted herbal substance
 - b) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V
 - c) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% V/V
- 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.

There are several combinations registered in the European Union (EU):

- herbal tea containing Plantaginifolium(25%), Althaeae radix (20%), Cynosbati fructus sine semine (20%), Liquiritiae radix (15%), Serpylli herba (15%), **Tiliae flos (5%)** (Czech Republic)

- herbal tea containing Foeniculi dulcis fructus (15%), Sambuci nigrae flos (25%), **Tiliae flos (25%)**, Plantaginis folium (20%), Liquiritiae radix (15%) (Czech Republic)
- herbal tea containing Tiliae flos & Salicis cortex (Germany)
- herbal tea containing Tiliae flos, Thymi herba & Anisi fructus, Thymi herba, Foeniculi amari fructus, Lichen islandicus (Germany)
- herbal tea containing Tiliae flos, Farfarae folium and Melissa folium (Poland) (Muszyński 1954)

This assessment report refers only to Tiliae flos.

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

Member State	Regulatory Status (products, indications)
Austria	<p>TU Herbal tea, since 1994</p> <p>Posology For oral use in adults and adolescents over 12 years 1 - 2 times daily a cup of fresh prepared infusion (2-4 g herbal substance) Indication The traditional indication is: for the relief of early symptoms of common cold</p>
Bulgaria	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Cyprus	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Czech Republic	<p>TU Herbal tea, since 2000</p> <p><i>Posology:</i> 1. for oral use Adults: 1.5 g/250 ml of boiling water 2 - 3 times daily Adolescents/children 4 - 12 years of age: 1.5 g/250 ml of boiling water 2 times daily Children 1 - years of age: 1.5 g/250 ml boiling water once daily</p> <p><i>Indication:</i> Traditionally used as an adjuvant for treatment of catarrhs of upper respiratory tract and cold associated with dry, irritating cough <i>Contraindication:</i> Hypersensitivity to the herbal substance/ Special warning: If dyspnoea, fever or purulent sputum occurs, a doctor should be consulted immediately.</p> <p><i>Other information on relevant combination products:</i> 1. Herbal tea containing Plantaginis folium(25%), Althaeae radix (20%), Cynosbati fructus sine semine (20%), Liquiritiae radix (15%), Serpylli herba (15%), Tiliae flos (5%) – on the market since 1995 – for oral use, adjuvant for treatment of catarrhs of upper respiratory tract associated with dry cough 2. Herbal tea containing Foeniculi dulcis fructus (15%), Sambuci nigrae flos (25%), Tiliae flos (25%), Plantaginis folium (20%), Liquiritiae radix (15%) – on the market since 1997 – for oral use – indications: for treatment of common cold associated with elevated temperature; inflammations of oral cavity and upper respiratory tract; diaphoretic effect</p>
Denmark	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Estonia	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Finland	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market

France	Only in combination
Germany	<p>WEU 9 Herbal teas since 1976 <i>Posology:</i> for oral use in adults and adolescents over 12 years 1 - 2 times daily a cup of fresh prepared infusion (2 - 4 g herbal substance) or 1 - 2 cups very hot as "sweat infusion" before going to bed.</p> <p><i>Indications:</i> Used as a diaphoretic in feverish colds 2 authorised combination products 1. herbal tea containing <i>Tiliae flos</i> & <i>Salicis cortex</i> 2. herbal tea containing <i>Tiliae flos</i>, <i>Thymi herba</i> & <i>Anisi fructus</i>, <i>Thymi herba</i>, <i>Foeniculi amari fructus</i>, <i>Lichen islandicus</i> single active ingredient: 9 herbal teas combination products: 11 herbal teas</p>
Greece	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Hungary	<p>TU Can be found in registered products only in combinations, but it can be bought as herbal substance in pharmacies and used according to the literature Herbal tea (Augustin <i>et al.</i> 1948)</p> <p><i>Posology:</i> (VIth Hungarian Pharmacopoeia 1967; English version 1970) For oral use as an infusion Usual single dose 0.5-1 g Usual daily dose 2.5-5 g</p> <p><i>Indication:</i> to promote sweating in the case of common cold, chronic coughing and catarrh</p>
Lithuania	<p>TU Herbal tea, since 1995</p> <p><i>Posology:</i> Children older than 2 years, adolescents and adults Single dose 1.5-2 g of comminuted herbal substance for infusion. Daily dose 4-6 g of comminuted herbal substance for infusion</p> <p><i>Indication:</i> Traditional herbal medicinal product used as expectorant in dry cough associated with cold and to promote perspiration in case of fever</p>

Netherlands	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Norway	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Poland	Herbal tea, since 1991 <i>Posology:</i> for oral use in adults and adolescents over 12 years <i>Indication:</i> Mild antipyretic and diaphoretic agent in common cold and in cough Hypersensitivity reactions (i.e. urticaria)
Portugal	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Slovakia	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Slovenia	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
Spain	Only combination products containing <i>Tiliae flos</i> are registered
Sweden	No authorised herbal medicinal products containing <i>Tilia flos</i> as a single drug preparation are on the market
United Kingdom	Only combination products containing <i>Tilia flos</i> are registered

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Herbal tea as the only active ingredient since 1994
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Multi-component herbal teas since 1962
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	One herbal tea, since 2000
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered

Member State	Regulatory Status				Comments
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
France	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only in combination products
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Herbal tea since 1976
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only in combinations
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Herbal tea since 1995
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Herbal tea since 1991
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combination products are registered <i>Tilia</i> flos can be freely sold as food
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combination products containing <i>Tilia</i> flos are registered

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.

1.3. Search and assessment methodology

Search terms: *Tilia cordata* Miller, *Tilia platyphyllos* Scop., *Tilia x vulgaris* Heyne, flowers, Tiliae flos. *Tilia* sp., tiliroside,

Databases: Pubmed, Medline, HealLink, scopus.

Libraries: University of Athens, Laboratory of Pharmacognosy and Chemistry of Natural Products of the University of Athens.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Since the middle ages, the lime flowers have been used as a diaphoretic to promote perspiration. In addition, the flowers have been used traditionally as tranquiliser and to treat headaches, indigestion and diarrhoea. Infusions of the flowers make a pleasant-tasting tea. Traditionally lime flowers were added to baths to quell hysteria and steeped as a tea to relieve anxiety-related indigestion, heart palpitation and vomiting (Blumenthal *et al.* 1998; 2000). Several sources report the lore that lime flowers were once believed to be so effective in treating epilepsy that one could be cured simply by sitting beneath the tree. Sugar is obtained from the sap of the tree and the seed oil resembles olive oil. In Greek mythology, "Philyra", a nymph, was transformed into a lime tree after begging the gods not to leave her among the mortals (Barnes *et al.* 2007; Duke *et al.* 1985; Review of Natural Products 2005; BHP 1976).

The lime flowers are referred in the VIth Hungarian Pharmacopoeia (1967; English version 1970) with the following posology: usual single dose: 0.5 - 1 g and usual daily dose: 2.5 - 5 g. In the Hungarian book by Augustin *et al.* 1948, it is mentioned that the lime flowers are used in the form of infusion for promoting sweating in the case of common cold, chronic coughing and catarrh and they are even used for preparing candies to relieve cough.

Tiliae flos can be found also in the first edition of the Czechoslovak Pharmacopoeia (Československý lékopis) published in 1947, as well as in the current version of Czech Pharmacopoeia (Český lékopis 2009, suppl. 2010).

Moreover the monograph of Tiliae flos has been defined in details in the Polish Pharmacopoeia of 1970 (Farmakopea Polska 1970), while, also in Poland, Inflorescentia Tiliae (Ożarowski *et al.* 1978) has been known to stimulate secretory and excretory functions - diuretic, gastric fluid, bile flow, transpiration and skin perspiration. It was for oral use as an infusion, as a supportive mean in fever states with sore throat and bronchitis. These infusions have been used also in nervousness, states of nervous tension and even in hysteria or hypochondria.

In Germany, lime flower is approved in the Commission E monographs (Blumenthal *et al.* 1998), and the tea form is official in the German Standard Licence monographs, and it was also official in the pharmacopoeia of the former German Democratic Republic (Blumenthal *et al.* 1998). It is used as a component of common cold and antitussive preparations and also as an urological and sedative drug.

In German paediatric medicine, it is used as a diaphoretic component of an influenza tea for children comprised of lime flower, willow bark, meadowsweet flower, chamomile flower and bitter orange peel. It is also a primary component of "Schweisstreibender Tee" (diaphoretic tea) composed of lime flower, peppermint leaf, meadowsweet flower and bitter orange. In Switzerland, a comparable diaphoretic tea is known, composed of lime flower, elder flower, mint leaves and jaborandi leaf (Blumenthal *et al.* 1998). There is a strong experience available, particularly in the German market, on the use of lime flower preparations, especially the herbal tea, in children of almost all age groups (Peter 1963; Kooperation Phytopharmaka 2002; Bühring *et al.* 2008; Schilcher 1992; Schilcher & Dorsch 2006).

Medicinal Use

The Commission E approved lime flower for colds and cold-related coughs (Blumenthal *et al.* 1998; 2000). Lime flower is stated to possess sedative, antispasmodic, diaphoretic, hypotensive, emollient, diuretic and mild astringent properties. Traditionally it has been used for migraine, hysteria, arteriosclerotic hypertension, feverish colds, and specifically for raised arterial pressure associated with arteriosclerosis and nervous tension (Barnes *et al.* 2007).

Bradley (1992) indicates its use for upper respiratory catarrh, common colds, irritable coughs, hypertension and restlessness.

The German Standard Licence indicates lime flowers infusion for alleviation of cough irritation due to catarrh of the respiratory tract and for feverish colds for which a sweat treatment is desired.

Tilia cordata has been used in other sedative effects therapies include relief of sinus headache and migraines, insomnia, stress and panic disorders. It has been used also to treat nervous palpitations and has been also reported to lower high blood pressure caused by stress and nervous tension (Blumenthal *et al.* 1998).

Food Use

Lime flower is listed by the Council of Europe as a natural source of food flavouring (category N2). This category indicates that lime flower can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product. Previously, lime flower has been listed as GRAS (Generally Recognised As Safe) (Barnes *et al.* 2007).

Conclusion

For *Tilia* flos a period of at least 30 years of medicinal use as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is easily fulfilled. The evidence on traditional medicinal use is confirmed by a large number of publications providing consistent information.

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

According to the overview of the European market, the herbal preparation (a) fulfils the criteria for at least 30 years of medicinal use in the EU, while the herbal preparations (b) and (c) were found in literature references, and the period of their use is longer than 30 years (BHP 1976).

From information on the use in Germany since 1976, in Hungary since 1948 (Augustin *et al.* 1948), in Czechoslovakia/Czech Republic since 1947:

a) Comminuted herbal substance for herbal tea preparation

From the literature (BHP 1976; Augustin *et al.* 1948; Bradley 1992; Blumenthal *et al.* 1998; Barnes *et al.* 2007; PDR 2007):

b) Liquid extract (DER 1 : 1) extraction solvent ethanol 25% (V/V)

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

Indications approved in the Member states:

Herbal medicinal product used as a diaphoretic in feverish colds (Germany, Poland).

Traditionally is used as an adjuvant for treatment of catarrhs of the upper respiratory tract and cold associated with dry, irritating cough (Czech Republic).

The traditional indication is: for the relief of early symptoms of common cold (Austria).

Traditionally used to promote sweating in the case of common cold, chronic coughing and catarrh and to relieve coughing (Hungary).

Traditional herbal medicinal product used as expectorant in dry cough associated with cold and to promote perspiration in case of fever (Lithuania).

Traditional herbal medicinal product used in states of nervous tension (Poland) (Ożarowski *et al.* 1978).

The following indications are proposed for the Community herbal monograph:

1. Traditional herbal medicinal product used for the relief of symptoms of common cold.
2. Traditional herbal medicinal product for the relief of mild symptoms of mental stress.

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

The following posologies have been recorded for lime flower:

- a) Comminuted herbal substance

Single dose: 1.5 g, daily dose 3 - 6 g (Český lékopis 2009, supp. 2010)

1.5 g in 150 ml of boiled water 2 - 4 times daily (Blumenthal *et al.* 1998)

single dose: 0.5 - 1 g, usual daily dose: 2.5 - 5 g (Hungarian Pharmacopoeia 1970)

- b) Liquid extract (1 : 1 in 25% alcohol) 2 - 4 ml daily (BHP 1976)

- c) Tincture (1 : 5 in 45% alcohol) 1 - 2 ml daily (BHP 1976)

Based on literature data and information from the Member States, the following posology and duration of use are proposed for the Community herbal monograph:

Posology

Adolescents, adults and elderly

Indication 1) and indication 2)

- a) Comminuted herbal substance

Herbal tea: 1.5 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion 2 – 4 times daily

Daily dose: 3 – 6 g

- b) Liquid extract.

Single dose: 2 ml, 1 - 2 times daily

Daily dose: 2 - 4 ml

- c) Tincture

Single dose: 1 ml, 1 - 2 times daily

Daily dose: 1 - 2 ml

Children between 4 and 12 years of age

Indication 1)

a) Comminuted herbal substance

Herbal tea: 1 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion
2 – 4 times daily

Daily dose: 2 - 4 g

Duration of use

Indication 1)

The therapy should start at first signs of common cold. If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indication 2)

If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

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 and animal studies

Differential cell growth effects on lymphocytes

The antiproliferative action of aqueous, dichloromethane and ethanol extracts obtained from *Tilia cordata* Miller, flowers on tumoral (BW 5147 lymphoma) and normal lymphocytes was described. All extracts showed a selective action on tumoral cells, inducing apoptosis. In the case of normal T cells these extracts suppressed mitogen-induced proliferation without affecting viability, suggesting a suppressive but not cytotoxic effect. These effects were clearly concentration-dependent. A coumarin (scopoletin), the main component in the dichloromethane extract presented antiproliferative action on BW 5147 cells, suggesting that it may be at least partly responsible for the activity displayed by this extract (Barreiro *et al.* 2006).

Anxiolytic and sedative activity

The aqueous extract of *Tilia cordata* flowers showed *in vitro* stimulatory effects on lymphocyte proliferation (maximum stimulatory concentration: 20 µg/ml). This effect was mimicked by Ro 5-4864, an agonist of the peripheral benzodiazepine receptor, and by Pk 11195, an agonist/antagonist of the same receptor. These results suggest that *Tilia* extract could exert its stimulatory effect by acting as an agonist of the peripheral benzodiazepine receptor (Anesini *et al.* 1999).

Lime flower's sedative effects have been reported as significant upon inhalation of *Tilia* sp. oil in mice (Blumenthal *et al.* 1998).

Antispasmodic – spasmogenic activity

In vitro, lime's seeds water extracts of *Tilia platyphyllos* Scop., *Tilia x vulgaris* Heyne or their mixtures, flos antispasmodic activity followed by a spasmogenic effect on rat duodenum (Lanza & Steinmetz 1986).

The activity of selected constituents of lime flower (flavonoids and phenolic acids) was inhibited by atropine and papaverine, and reinforced by acetylcholine. The diaphoretic and antispasmodic properties claimed for lime flower have been attributed to p-coumaric acid and the flavonoids (Lanza & Steinmetz 1986; Al-Essa *et al.* 2007).

The effects of the ethanol extract of *Tilia cordata* Miller were studied *in vitro* using intestinal smooth muscle cells of guinea pigs dispersed by collagenase. The extract induced a dose-dependent contraction of the dispersed smooth muscle cells. The obtained data indicated a direct effect of the *Tilia cordata* extract on the intestinal smooth muscle cells. In addition, the contractions induced by the extract were inhibited by atropine. These observations indicate an involvement of some active constituents, with cholinergic properties, found in the alcohol extract to induce contraction of the intestinal smooth muscle cells *via* activation of the muscarinic receptors (Al-Essa *et al.* 2007).

Antimicrobial and antifungal activity

Forty-one plant extracts, known in therapy for other properties, have been tested against nine fungal species. Lime flower (*Tilia cordata*) has been documented to possess a range of antifungal activity (Guerin & Reveillere 1984).

Pancreatic lipase inhibition

Lipids are important components in human nutrition; however, their increased intake contributes to the development of obesity and can lead to multiple long-term complications. Pancreatic lipase (triacylglycerol acylhydrolase, EC 3.1.1.3) is a key enzyme for the absorption of dietary triglycerides. Interference with fat hydrolysis of ingested lipids, therefore inhibition of lipases, decreases fat absorption. Extracts from 106 species of medicinal plants, vegetables and fruits were screened for potential lipase inhibitory activity. p-Nitrophenylpalmitate and 5-bromo-4-chloro-3-indoxylpalmitate were used as substrates in an *in vitro* test with crude porcine pancreatic lipase. Large-leaved lime (*Tilia platyphyllos*) extracts were the most active. Additionally, the activity of selected extracts with removed polyphenols was measured. The authors concluded that extracts of large-leaved lime are a promising source for developing functional foods or isolating active compounds (Slanc *et al.* 2009).

Bioactivities of secondary metabolites from lime flower

Diaphoretic activity

The diaphoretic activity of the flowers of lime is suggested to be caused by quercetin, kaempferol and p-coumaric acid. Where "sweat cures" would be an advantage, lime tree has been used mainly for feverish colds and infections. It has been also used to reduce nasal congestion and relieve throat irritation and cough upon inhalation of *Tilia* sp. oil in mice (Blumenthal *et al.* 1998, 2000).

Hepatoprotective activity

Kaempferol-3-O- β -D-(6''-E-p-coumaroyl)-glucopyranoside (tiliroside) has been isolated from many natural plants sources. This compound showed very interesting pharmacological activities, e.g., cytotoxic for human leukaemic cell lines and anti-complement activity. However, there is a lack of data concerning the presence of this compound in medical plants. In this work, a reproducible and quick method was elaborated for the separation and determination of tiliroside in methanolic extracts of selected plants among which *Tilia* species. The content of tiliroside for various plant materials was compared (Nowak 2003).

Antidiabetic activity

A recent study on traditionally used medicinal plants, herbs and spices in Latin America included *Tilia platyphyllos* flowers. These were investigated to determine their phenolic profiles, antioxidant activity and *in vitro* inhibitory potential against key enzymes relevant for hyperglycaemia and hypertension. Lime flowers inhibited strongly both the α -glucosidase (exhibited the highest inhibition against α -glucosidase (~100%) at 2.5 mg of dried sample and its inhibitory activity was high even at lower dose i.e. 75%, at 0.5 mg of dried sample) and α -amylase enzymes (significant inhibition of porcine pancreatic α -amylase at the highest evaluated dose (71%) at 25 mg of dried sample); lime flowers were supposed to have potential for hyperglycaemia and hypertension prevention associated with type 2 diabetes (Ranilla *et al.* 2010).

Diuretic, sedative and antispasmodic effects

Tilia species are traditional medicinal plants widely used as sedatives and tranquilisers (Zhang 2004). For this purpose, the infusion of their inflorescences is used to prepare a tea.

In the study by Viola *et al.*, extracts of inflorescences from *Tilia tomentosa* Moench, one of the species found in the market, were purified using a benzodiazepine (BZD) binding assay to detect BZD receptor ligands in the different fractions. One of the ligands was identified as kaempferol, but it had low affinity ($K(i) = 93 \mu\text{M}$) for this receptor, and did not produce sedative or anxiolytic effects in mice. On the other hand, a complex fraction, containing yet unidentified constituents, but probably of a flavonoid nature, when administered intraperitoneally in mice, had a clear anxiolytic effect in both the elevated plus-maze and hole board tests, two well-validated pharmacological tests to measure anxiolytic and sedative compounds. This active fraction had no effect on total and ambulatory locomotor activity. In conclusion, these results demonstrate the occurrence of active principle(s) like kaempferolin, at least in *Tilia tomentosa* while this can be found also in other *Tilia* species that may explain its ethnopharmacological use as an anxiolytic (Viola *et al.* 1994).

In addition, a number of actions have been associated with volatile oils including diuretic, sedative and antispasmodic effects in mice, which may also account for some of the reputed uses of lime flower (*Tilia cordata*) (Taddei *et al.* 1988; Barnes *et al.* 2007). Volatile oils are not thought to possess any true diuretic activity, but to act as a result of certain terpenoid components having an irritant action on the kidneys during renal excretion.

All these observations of such bioactivities help to account for some of the existing medical effects.

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

No data on lime flower extracts have been found or reported.

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

Single-dose and repeated-dose toxicity studies

No data have been found.

Genotoxicity studies

Among six herbal infusions used worldwide (*Matricaria chamomilla*, *Tilia cordata*, *Mentha piperita*, *Mentha pulegium*, *Uncaria tomentosa* and *Valeriana officinalis*) were assayed for anti-genotoxicity

using the Somatic Mutation And Recombination Test (SMART) in *Drosophila melanogaster*. All these infusions are traditionally used for various medical purposes. Hydrogen peroxide was used as an oxidative genotoxicant to test the anti-genotoxic potency of the medicinal infusions. None of these infusions showed a significant genotoxicity, quite the reverse they were able to behave as desmutagens, detoxifying the mutagen hydrogen peroxide. The phenolic content of such herbal infusions is argued to be the possible scavenger of reactive oxygen radicals produced by the hydrogen peroxide (Romero-Jiménez *et al.* 2005).

No adequate genotoxicity studies carried out on lime flower in the scientific literature.

Carcinogenicity studies

No carcinogenicity studies carried out on lime flower in the scientific literature.

Reproductive and developmental toxicity studies

No reproductive and developmental toxicity studies carried out on lime flower are reported in the scientific literature.

The safety of lime flower during pregnancy and lactation has not been established. In accordance with general medical practice, the herbal medicinal products (herbal teas, other finished products) should not be used during pregnancy and lactation without medical advice.

3.4. Overall conclusions on non-clinical data

Lime flower has officially been recognised since 1947 in the first edition of the Czechoslovak Pharmacopoeia (Československý lékopis) till the current version of Czech Pharmacopoeia (Český lékopis 2009, suppl. 2010). Also it has been proposed since 1948 (Augustin *et al.* 1948) and then introduced in the VIth edition of the Hungarian Pharmacopoeia in 1970 as an herbal remedy traditionally used in for the relief of symptoms in common cold (diaphoretic in feverish cold). Lime flower is in the Polish Pharmacopoeia (Farmakopea Polska 1970). Also according to Ożarowski *et al.* (1978), Inflorescentia Tiliae has been known in Poland to stimulate secretory and excretory functions (diuretic, gastric fluid, bile flow, transpiration, skin perspiration), as supportive treatment in fever states with sore throat and bronchitis, and in states of nervous tension. It has been also referred in the BHP (1976).

Based on the above-mentioned data, it is evident that Tiliae flos has been used as a traditional remedy for a long time and without safety problems for much more than 30 years.

The published data referring to the indications and preparations is limited, but on the basis of existing data the pharmacological activities (BHP 1976; Madaus 1979; Bradley 1992) support the traditional use of *Tilia cordata*, *Tilia platyphyllos* and *Tilia x vulgaris* and preparations thereof in the proposed indications:

1. Traditional herbal medicinal product for the relief of symptoms of common cold
2. Traditional herbal medicinal product used to relieve mild symptoms of mental stress

The efficacy of traditional herbal medicinal products is only plausible but not proven by clinical data.

Although no adequate toxicity data are available, lime flower and lime flower preparations can be regarded as safe based on the fact that lime flower is listed by the Council of Europe as a natural source of food flavouring (category N2). Lime flower is listed as Generally Recognised as Safe (GRAS) by the FDA.

Nevertheless, the lack of genotoxicity, carcinogenicity as well as reproductive and developmental toxicity studies does not allow the establishment of a Community list entry.

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

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Antidiabetic activity

A cross-sectional study was conducted by interviewing 310 diabetic patients visiting two medical centres in Jordan, Jordan University of Science & Technology Medical Centre and Sarih Medical Centre, between December 2003 and August 2004. It was found that 31% of interviewed patients have used herbal products (96 patients). The results revealed that the most commonly used herbs by diabetic patients in Jordan were *Trigonella foenumgraecum* (22.9%), *Lupinus albus* (14.6%), *Allium sativum* (11.5%), *Allium cepa* (5.2%), *Nigella sativa* (7.3%), *Zea mays* (6.3%), *Urtica dioica* (8.3%), *Eucalyptus globulus* (9.4%), *Olea europea* (3.1%), *Cumminum cyminum* (9.4%), *Coriandrum sativum* (10.4%), *Salvia officinalis* (3.1%) and ***Tilia cordata*** (1%). The side effects for all the assayed herbs were reported by 36.5% of the patients and included headache, nausea, dizziness, itching, palpitation and sweating. Among the patients, 72.9% used the herbs as adjunctive therapy along with their antidiabetic drugs and 80.2% of the patients informed their physicians about their use. A 79.2% of the sample confirmed their intention to re-use these herbs as 86.5% of them were satisfied with their diabetes control. Therefore, it is essential to increase the level of awareness among diabetic patients and health care providers regarding the efficacy and toxicity of these medicinal herbs (Otoom *et al.* 2006).

Diaphoretic activity

The diaphoretic action of *Tiliae flos* was investigated in an open controlled clinical trial in patients with uncomplicated catarrhal disease. Fifteen patients with catarrhal disease inhaled water vapour from a preparation made with two sachets of *Tiliae flos* in 500 ml of water. Inhalation was maintained for 10 minutes at 40–50 °C. A control group of 15 patients inhaled vapour from coloured water. Fifteen minutes after inhalation, all patients experienced a certain subjective relief with further improvement of their condition in the group that had inhaled the preparation of *Tiliae flos*. In the control group,

improvement was observed only for the first 120 minutes, and after addition of other symptomatic treatment. It was suggested that the inhalation of a preparation of *Tiliae flos* had a kind of diaphoretic effect. As there was no statistical analysis of the data, an objective assessment of this investigation is not possible (WHO 2010).

There is a lack of clinical research, except the above-referred references by Otoom *et al.* 2006, WHO 2010, assessing the effects of lime flower and rigorous randomised controlled clinical trials are required.

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

None reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

Due to the lack of the data, no conclusion can be drawn.

5. Clinical Safety/Pharmacovigilance

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

There is a lack of clinical and non-clinical safety and toxicity data for lime flower and further investigation of these aspects is needed.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

Observations of suspected allergy to lime flower pollen (*Tilia cordata*) have been published several times and aeroallergen sensitisation due to *Tilia cordata* is believed to be among the most common (Loureiro *et al.* 2005; Krakowiak *et al.* 2004; Mur *et al.* 2001).

A case-report of occupational allergy in a 55-year old woman has appeared in the scientific literature. The woman, a non-smoker, who was working as a cosmetician, had experienced recurrent itching and erythematous papulovesicular lesions on the backs of her hands for around 18 months, and had had a history of sneezing, nasal obstruction and watery eyes for some years when she came into contact with depilatory wax or flowers of *Tilia cordata*. Clinical examination, as well as routine laboratory parameters, remained normal. Total immunoglobulin E was 13 084 IU/ml and skin-prick tests showed positive reactions to common environmental allergens – grass and tree pollens, and to flowers. Specific immunoglobulin E antibodies for grass and tree pollens were negative. The results of patch tests with *Tilia* flowers with a standard series and a series of plant allergens were positive. A bronchial challenge test was performed in an inhalation chamber for 30 minutes. In the first stage, the patient was challenged with placebo (potato flour); during the second stage (after 7 days), with depilatory wax that had been thermally activated, and after 14 days with dried flowers. Following such exposures, clinical symptoms of rhinoconjunctivitis appeared, and were observed for 48 hours after the challenges. In addition, increases in eosinophil and basophil proportions in nasal lavage and tear fluids were observed during the late phase of allergic reaction. A diagnosis of occupational allergy was made based on the positive results of the allergy tests, analysis of the clinical status and medical history, and the positive results of specific challenges (WHO 2010; Krakowiak *et al.* 2004).

Over a 5-year period, 1790 paediatric outpatients were observed for suspected allergic symptoms and 371 children were given a skin prick test to check for responses to aeroallergens. Aeroallergen sensitisation due to *Tilia cordata* was observed in 11.4% of the paediatric patients examined (Loureiro *et al.* 2005).

It has been advised that lime flower should be avoided by individuals with an existing cardiac disorder (Duke 1985), as excessive use may result in cardiac toxicity; however, the scientific basis for this statement, if any, is not known (Barnes *et al.* 2007).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Special patient population

Available evidence and experience on the use of lime flower preparations, especially the herbal tea, in children of different age groups can be found in several textbooks e.g. Kooperation Phytopharmaka 2002 or Bühring *et al.* 2008, where the preparation of a herbal tea from lime flower as well as of two combination teas for the specific paediatric use is described. Similar recommendations for combination teas are given by Schilcher (1992) and Schilcher & Dorsch (2006), e.g. a “species diaphoreticae” with reference to a clinical study of Traisman and Hardy who treated various groups of children suffering from respiratory infections with different medications and non-medicinal measures. Good results have been obtained, using lime flower tea without any other medication.

The use for the relief of symptoms of common cold in children under 4 years of age has not been established due to lack of adequate data.

The use for the relief of mild symptoms of mental stress in children under 12 years of age has not been established due to lack of adequate data.

Fertility, pregnancy and lactation

No data are available. In the absence of sufficient data and in accordance with general medical practice, it is recommended not to use herbal medicinal products containing lime flower during pregnancy and lactation.

No fertility data available.

Overdose

No cases of overdose have been recovered in the scientific literature.

Drug abuse

No information retrieved from the literature search.

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

No data retrieved from the literature search.

Potential for interactions

None reported.

5.6. Overall conclusions on clinical safety

Tiliae flos is intended for use in adolescents, adults and elderly. Tiliae flos can also be used for the relief of symptoms of common cold in children between 4 and 12 years of age, however the use in children under 4 years of age for this indication has not been established due to lack of adequate data.

In the absence of sufficient data and in accordance with general medical practice, it is recommended not to use herbal medicinal products containing Tiliae flos (lime flower) during pregnancy and lactation.

Some cases of allergic reactions have been reported, however the frequency is not known.

No other adverse effects have been reported, showing sufficient safety for the proposed traditional use of Tiliae flos preparations.

The establishment of a Community list entry is not possible, as there are no available data on genotoxicity, carcinogenicity, reproductive and developmental toxicity of lime flower extracts.

6. Overall conclusions

The positive effects of lime flower on the relief of symptoms of common cold as well as its activity to relieve the symptoms of mild nervous tension have been recognised empirically. The traditional use is recognised as plausible, based on the existing *in vitro* and *in vivo* pharmacological data. There is a lack of controlled clinical studies with preparations containing lime flower.

In conclusion, Tiliae flos and its preparations can be regarded as traditional herbal medicinal products in the following indications:

- Traditional herbal medicinal product used for the relief of symptoms of common cold
- Traditional herbal medicinal product for the relief of mild symptoms of mental stress.

Based on information from the Member States and on literature data, Tiliae flos can be recommended for use in adolescents, adults and elderly and can be recommended for use in children between 4 and 12 years of age for the relief of symptoms of common cold.

In the absence of sufficient data and in accordance with general medical practice, it is recommended not to use herbal medicinal products containing lime flowers during pregnancy and lactation.

Safety data reported above support a safe use at the recommended posology in the proposed traditional uses, for traditional herbal medicinal products containing Tiliae flos preparations.

As there are no data available on the genotoxicity, carcinogenicity, reproductive and developmental toxicity of lime flowers and preparations thereof, the establishment of a Community list entry is not possible due to safety concerns.

Annex

List of references