22 May 2012
EMA/HMPC/346780/2011
Committee on Herbal Medicinal Products (HMPC)

# Assessment report on *Tilia tomentosa* Moench, flos

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

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) | *Tilia tomentosa* Moench, flos |
| Herbal preparation(s) | N/A |
| Pharmaceutical form(s) | N/A |
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# 1. Introduction

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

- Herbal substance(s)

Lime tree (Linden, fam. Tiliaceae) is a tall deciduous tree native throughout Europe as far north as 65$^{o}$ in latitude, which can grow to heights approaching to 30 metre. 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. Leaves of *Tilia tomentosa* are covered with white tomentum especially on underneath in contrary to the hairless ones of *Tilia cordata/T. platyphyllos*. The 5-petalated, yellow white flowers are collected in full bloom, dried and preserved under low-moisture conditions (Blumenthal *et al.* 1998).

Tiliae tomentosae flos (silver lime flower) consists of the whole dried inflorescence of *Tilia tomentosa* Moench, gathered during the flowering season (Blumenthal *et al.* 1998; PDR for Herbal Medicines 2007).

Common names: silver linden, common silver lime, basswood, Linden tree.

**Synonym(s)**

*Tilia tomentosa* Moench = *Tilia argentea* Desfontaines

Chemical constituents according to existing references (Blumenthal *et al.* 1998; PDR for herbal Medicines 2007; Duke *et al.* 1985; Review of Natural Products 2005):

- **Acids** - caffeic acid, chlorogenic acid and *p*-coumaric acid
- **Amino acids**
- **Carbohydrates** - mucilage polysaccharides (3%)
- **Flavonoids** - kaempferol, quercetin, myricetin and their glycosides (mainly Kaempferol-3-O-β-D-(6″-E-p-coumaroyl)-glucopyranoside – tiliroside, hyperoside) (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; Toker *et al.* 1999)
- **Other constituents** - saponin (unspecified), tannin (condensed) and tocopherol (phytosterol)

The fragrant components of the flowers degrade rapidly under conditions of high moisture (Blaschek 2010; PDR for Herbal Medicines 2007; Review of Natural Products 2005).

*Tilia tomentosa* = *Tilia argentea* is referred to as a common adulteration of *Tilia cordata* which is detected via macroscopic/microscopic tests (Blumenthal *et al.* 2000; Ph. Eur. 2011).

- Herbal preparation(s)

No herbal preparations are available.

- 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.

No information on combination products is available.

This assessment report refers only to Tiliae tomentosae flos.

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

### Regulatory status overview

| Member State | Regulatory Status | | | | Comments |
|---|---|---|---|---|---|
| Austria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Belgium | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Bulgaria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Cyprus | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Czech Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | One herbal tea, since 2000 |
| Denmark | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Estonia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Finland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| France | ☐ MA | ☒ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Germany | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☒ Other Specify: | No prod. on the market |
| Greece | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Hungary | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Iceland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Not known |
| Ireland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Not known |
| Italy | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Not known |
| Latvia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Not known |
| Liechtenstein | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Not known |
| Lithuania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Luxemburg | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Not known |
| Malta | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Not known |
| The Netherlands | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Norway | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Poland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Portugal | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Romania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Not known |
| Slovak Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Slovenia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Spain | ☐ MA | ☒ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| Sweden | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |
| United Kingdom | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No prod. on the market |

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 tomentosa* Moench, Tiliae tomentosae flos, *Tilia argentea* Desfontaines, 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 flowers of the lime trees 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; Duke *et al.* 1985; Review of Natural Products 2005).

The effectiveness of the herbal substances and preparations thereof is not documented and this is the reason why silver lime flower is stated as unapproved in the collection of the German Commission E Monographs with reference to its use for catarrhs of the respiratory tract, as an antispasmodic, expectorant, diaphoretic and a diuretic (Blumenthal *et al.* 1998). On the other hand in the German Commission E monograph, there are no objections to its use as a corrigent for aroma and flavour (Blumenthal *et al.* 1998; PDR for Herbal Medicines 2007). The official name of the German Commission E monograph is 'Linden flower, Silver'.

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

According to the overview of the European market, no products containing silver lime flowers are available in the Member States of the European Union (EU). In the literature, only two references discussing the activities of Tiliae tomentosae flos (Blumenthal *et al.* 1998; PDR for Herbal Medicines 2007) have been found. However, none of them fulfil the following criteria:
- the data on the traditional use are sufficient
- a period of medicinal use of at least 30 years is demonstrated

as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product.

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

No data available.

# 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***

**Hepatoprotective activity**

The methanolic extract from the flowers of *Tilia argentea* (= syn. *Tilia tomentosa*, silver lime tree) was found to show a hepatoprotective effect against D-galactosamine (D-GalN)/lipopolysaccharide (LPS)-induced liver injury in mice. By bioassay-guide separation using *in vitro* D-GalN-induced damage to hepatocytes, five flavonol glycosides were isolated as the hepatoprotective constituents of the methanolic extract. Tiliroside, the principal flavonol glycoside which is also among the major constituents of *Tilia cordata*, strongly inhibited serum GPT and GOT elevations at doses of 25 - 100 mg/kg (p.o.) in D-GalN/LPS-treated mice. By comparing the inhibitory effects of tiliroside with those of its components alone, the kaempferol 3-O-β-D-glucopyranoside moiety was found to be essential for the activity, and its effect was suggested to depend on the inhibition of tumour necrosis factor-α (TNF-α) production, decreased sensitivity of hepatocytes to TNF-α, and on the protection of hepatocytes against D-GalN (Matsuda *et al*. 2002).

**Sedative and anxiolytic effects**

*Tilia* species are traditional medicinal plants widely used as sedatives and tranquilizers (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 µM) for this receptor, and did not produce sedative or anxiolytic effects in mice. On the other hand, a complex fraction, containing as 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) in, at least, one species of *Tilia* that may explain its ethnopharmacological use as an anxiolytic (Viola *et al.* 1994).

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

No data on silver 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**

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

**Carcinogenicity studies**

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

**Reproductive and developmental toxicity studies**

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

The safety of silver lime flower during pregnancy and lactation has not been established.

### *3.4. Overall conclusions on non-clinical data*

Silver lime flower has officially been recognised as adulterations of Tiliae flos in the European Pharmacopoeia 2011.

# 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)

There is a lack of clinical research, assessing the effects of silver lime flower; further investigation is needed.

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

None reported.

### *4.3. Overall conclusions on clinical pharmacology and efficacy*

There is a lack of clinical research, assessing the effects of silver lime flower; further investigation is needed.

No positive monograph on Tiliae tomentosae flos was approved by the Commission E as the effectiveness for the claimed applications of the herbal substance and preparations thereof is not

documented (Blumenthal *et al.* 1998*)*. On the other hand, the Commission E did no object to the use of silver lime flower as a corrigent for aroma and flavour.

The published data referring to the indications and preparations are limited, and could not support the traditional use of Tiliae tomentosae flos and preparations thereof.

# 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 silver lime flower and further investigation of these aspects is necessary.

## *5.2. Patient exposure*

No data available.

## *5.3. Adverse events and serious adverse events and deaths*

It has been advised in literature that silver lime flower should be avoided by individuals with an existing cardiac disorder as excessive use may result in cardiac toxicity (Duke *et al.* 1985).

## *5.4. Laboratory findings*

No data available.

## *5.5. Safety in special populations and situations*

**Special patient population**

Not applicable (the use of silver lime flower is not supported).

**Use in pregnancy and lactation**

Not applicable (the use of silver lime flower is not supported).

**Overdose**

No cases of overdose have been reported 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.

## *5.6. Overall conclusions on clinical safety*

There are hardly any data documenting the clinical safety of Tiliae tomentosae flos; in any case, the use is not supported.

# 6. Overall conclusions

After seeking information on the products containing *Tilia tomentosa* Moench, flos and preparations thereof marketed in the EU, it appears that there are no products (single-ingredient and/or combination) available.

A comprehensive literature search was conducted and available data, including responses to a request for information on products on the market in the EU, were assessed vis-à-vis the requirements laid down in Directive 2001/83/EC and its Annex I, in particular Article 1, Article 10a and Chapter 2a.

The HMPC/MLWP concluded that the following requirements for the establishment of a Community herbal monograph on traditional and well-established herbal medicinal products containing *Tilia tomentosa* Moench, flos are not fulfilled:

- the requirement laid down in Article 10a of Directive 2001/83/EC that the active substance has a recognised efficacy and an acceptable level of safety and that the period of well-established medicinal use has elapsed
- the requirement laid down in Article 16a(1)(d) of Directive 2001/83/EC that "the period of traditional use as laid down on Article 16c(1)(c) has elapsed".

Based on the above-mentioned information, the HMPC is of the opinion that no Community herbal monograph on *Tilia tomentosa* Moench, flos can be established.

# Annex

## *List of references*