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EMA/HMPC/176303/2022  
Committee on Herbal Medicinal Products (HMPC)

## Addendum to Assessment report on *Tilia cordata* Miller, *Tilia platyphyllos* Scop., *Tilia x vulgaris* Heyne, flos

Rapporteur(s)	I Chinou
Peer-reviewer(s)	M Příhodová/M Heroutová

HMPC decision on review of monograph <i>Tilia cordata</i> Miller, <i>Tilia platyphyllos</i> Scop., <i>Tilia x vulgaris</i> Heyne, flos adopted on 22 May 2012	13 January 2021
Call for scientific data (start and end date)	From 01 April 2021 to 30 June 2021
Discussion in Committee on Herbal Medicinal Products (HMPC)	March 2022 May 2022 September 2022 November 2022
Adoption by Committee on Herbal Medicinal Products (HMPC)	23 November 2022

### Review of new data

#### Periodic review (from 2014 to 2022)

#### Sources checked for new information:

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

Scientific/Medical/Toxicological databases

Scopus, PubMed, MEDLINE, HEAL-Link. Libraries: National and Kapodistrian University of Athens (NKUA), Laboratory of Pharmacognosy and Chemistry of Natural Products of NKUA. 2014-February 2022. Keywords: *Tilia cordata* Miller, *Tilia platyphyllos* Scop., *Tilia x vulgaris* Heyne, Lime tree



- Pharmacovigilance databases
  - data from EudraVigilance
  - from other sources (e.g. data from VigiBase, national databases)
- Other

Regulatory practice

- Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)
- New market overview (including pharmacovigilance actions taken in member states)
- PSUSA
- Feedback from experiences with the monograph during MRP/DCP procedures
- Ph. Eur. monograph
- Other

Consistency (e.g. scientific decisions taken by HMPC)

- Public statements or other decisions taken by HMPC
- Consistency with other monographs within the therapeutic area
- Other

**Availability of new information that could trigger a revision of the monograph**

<i>Scientific data</i>	Yes	No
New non-clinical safety data that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical safety data that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New data introducing a possibility of a new list entry	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical data regarding the paediatric population or the use during pregnancy and lactation that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical studies introducing a possibility for new WEU indication/preparation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other scientific data that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Regulatory practice</i>	Yes	No
New herbal substances/preparations with 30/15 years of TU	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New herbal substances/preparations with 10 years of WEU	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New recommendations from a finalised PSUSA	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Feedback from experiences with the monograph during MRP/DCP procedures that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New/Updated Ph. Eur. monograph that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Other regulatory practices that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Consistency</i>	Yes	No
New or revised public statements or other HMPC decisions that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Relevant inconsistencies with other monographs within the therapeutic area that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other relevant inconsistencies that could trigger a revision of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>

### Summary of new references

During the review, 244 new references not yet available during the first/previous assessment were identified.

No references were provided by Interested Parties during the Call for data.

In total, 24 references were filtered to be closer to the studied package but only four references were considered to be relevant for the assessment.

#### *Clinical safety data*

Mostly through VigiLyze, several cases have been reported in concomitant intake of *Tilia* with several other herbal and/or chemical medicines. The causality between exposure to *Tilia* had no proven causal relation with the appeared side effects and potential adverse reactions reported were not confirmed.

#### *Assessor's comment:*

*The searched data do not trigger a revision of the monograph.*

### Assessment of new data

#### **New scientific data that could trigger a revision of the monograph**

Not applicable.

#### **New regulatory practice that could trigger a revision of the monograph**

Three other countries with slight differences in the indications' terminology and posology, all covered by the existing MO and supporting documents, have been referred and evaluated.

No new indication and/or posology for new products on the EU market have been referred.

#### **Inconsistency that could trigger a revision of the monograph**

Not applicable.

#### **Other issues that could trigger a revision of the monograph**

Not applicable.

#### **New information not considered to trigger a revision at present but that could be relevant for the next review**

#### *Quality data*

Two references focused on quality/chemistry referred also to novel metabolites piperidine and dihydropyrrole alkaloids from lime flower (*Tiliae flos*) (Symma *et al.*, 2021i, 2021ii).

### Non-clinical data

The novel metabolites piperidine and dihydropyrrole alkaloids from lime flower infusion (*Tiliae flos*) have exerted spasmodic activity on murine tracheal smooth muscle (Symma *et al.*, 2021i, 2021ii). Moreover, the *Tilia* extracts have antioxidant effect (Yayalaci *et al.*, 2014) as well as antimicrobial properties (Mehrbood *et al.*, 2021).

### Assessor's comment:

*The recent data on chemical composition of the referred infusion in the existing monograph offer scientific information not previously reported.*

## References

### Quality

Symma N, Hake A, Düfer M, Hensel A. Neuartige Piperidin- und Dihydropyrrol-Alkaloide aus Lindenblüten (*Tiliae flos*) mit spasmogener Wirkung auf die Trachealmuskulatur der Maus. *Zeitschrift für Phytotherapie* 2021i, 42(05):225–232

Symma N, Bütergerds M, Sendker J, Petereit F, Hake A, Düfer M, *et al.* Novel Piperidine and 3,4-dihydro-2H-pyrrole Alkaloids from *Tilia platyphyllos* and *Tilia cordata* Flowers. *Planta Medica* 2021ii, 87(09):686-700, in press, doi 10.1055/a-1340-0099

### Non-clinical

Mehrbood P, Safari H, Mollai Z, Fotouhi F, Mirfakhraei Y, Entezari H., *et al.* Potential antiviral effects of some native Iranian medicinal plants extracts and fractions against influenza A virus. *BMC Complementary Medicine and Therapies* 2021, 21(1):1-12

Yayalaci Y, Celik I, Bati B. Hepatoprotective and antioxidant activity of linden (*Tilia platyphyllos* L.) infusion against ethanol-induced oxidative stress in rats. *The Journal of Membrane Biology* 2014, 247:181–188

## Rapporteur's proposal on revision

- Revision needed, i.e. new data/findings of relevance for the content of the monograph
- Revision likely to have an impact on the corresponding list entry (if applicable)
- No revision needed, i.e. no new data/findings of relevance for the content of the monograph

## HMPC decision on revision

- Revision needed, i.e. new data/findings of relevance for the content of the monograph
- No revision needed, i.e. no new data/findings of relevance for the content of the monograph