EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Melaleuca alternifolia* (Maiden and Betche) Cheel; *Melaleuca linariifolia* Smith; *Melaleuca dissitiflora* F. Mueller and/or other species of *Melaleuca*, aetheroleum

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HMPC decision on review of monograph *Melaleuca alternifolia* (Maiden and Betche) Cheel; *Melaleuca linariifolia* Smith; *Melaleuca dissitiflora* F. Mueller and/or other species of *Melaleuca,* aetheroleum adopted on 24 November 2014	26 January 2022
Call for scientific data (start and end date)	From 15 March 2022 to 14 June 2022
Discussion in Committee on Herbal Medicinal Products (HMPC)	September 2022 March 2023 May 2023 July 2023
Adoption by Committee on Herbal Medicinal Products (HMPC)	19 July 2023

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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

PubMed/ Search period was set from 2014 until September 2022. Search terms: 'Melaleuca alternifolia' or 'tea tree oil' plus 'efficacy' or 'safety' (52 and 27 references were found, respectively)

☒ 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

Scientific data	Yes	No
New non-clinical safety data that could trigger a revision of the monograph	☐	☒
New clinical safety data that could trigger a revision of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation that could trigger a revision of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data that could trigger a revision of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒

New recommendations from a finalised PSUSA	☐	☒
Feedback from experiences with the monograph during MRP/DCP procedures that could trigger a revision of the monograph	☐	☒
New/Updated Ph. Eur. monograph that could trigger a revision of the monograph	☐	☒
Other regulatory practices that could trigger a revision of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions that could trigger a revision of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that could trigger a revision of the monograph	☐	☒
Other relevant inconsistencies that could trigger a revision of the monograph	☐	☒

Summary of new references

During the review 52 new references not yet available during the first/previous assessment were identified. The search in pharmacovigilance databases revealed 3 cases. From regulatory praxis, no new indications, herbal preparations and dosages were identified.

During the Call of data period, the Australian Tea Tree Industry Association (ATTIA Ltd) sent a submission asking for consideration to not including "…*Melaleuca dissitiflora* F. Mueller and/or other species of *Melaleuca,* aetheroleum…" in any revision to the monograph on *Melaleucae* aetheroleum (EMA/HMPC/120033/2022) to ensure alignment with an anticipated revision to the European Pharmacopoeia Monograph on tea tree oil.

Assessment of new data

New scientific data that could trigger a revision of the monograph

Fifty two new references regarding tea tree oil efficacy were retrieved. Most of them were related to the antifungal and anti-acne properties of the oil which are already included and reflected in the current AR and MO.

During the review 27 new references regarding tea tree oil safety were identified. Some new studies on the effect of tea tree oil on developmental and reproductive toxicity, effects on spermatozoa and mucosal toxicity were found.

The developmental and reproductive toxicity study was conducted with female Hannover Wistar rats in accordance with OECD TG414 (European Chemicals Agency, 2021). Animals were fed by gavage with Tea tree oil doses of 0, 20, 100 and 250 mg/kg bw/day during the days 5 to 19 of gestation (27 rats per group). The results showed:

a) Severe maternal toxicity in dams of 100 and 250mg/kg bw/day: food consumption and weight gain reductions of 20% and 45%, respectively.

b) Seven of the high dose dams died between days 8 an 11 of gestation (no mortality in other groups).

c) Bilateral enlarged adrenals in all high-dose dams that died during the study and in 6/20 survivors.

d) Dose-related decrease in mean foetal weights in mid and high-dose groups.

e) Increase in the number of late-embryonic deaths and post-implantation loss leading to an overall higher total intrauterine mortality in the high-dose group.

f) No statistically significant difference compared to controls in the number of visceral malformations in the foetuses, but statistically significant higher number of visceral variations for the 250 mg group.

g) Statistically significant higher incidences of skeletal malformations unrelated to intrauterine growth retardation in the 250 mg group and a statistically significant increase in the number of skeletal variations secondary to maternal toxicity in the 100 and 250 mg groups.

h) NOAEL for maternal toxicity and for developmental toxicity: 20 mg/kg bw/day of tea tree oil.

Assessor's comment:

This study assessed the developmental and reproductive toxicity of tea tree oil when administered orally to female rats during gestation, providing a NOAEL value for both maternal toxicity and developmental toxicity of 20 mg/kg bw/day. By using allometric factors in line with the "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" (EMEA/CHMP/SWP/28367/07 Rev. 1), a human equivalent exposure of 3.22 mg/kg can be calculated when using a factor derived from the "Guideline for Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (FDA, 2005). The current recommended posology for oromucosal use of tea tree oil is 0.17 to 0.33 ml of essential oil to be mixed in 100 ml of water, several times daily; this volume corresponds to approx. 150-300 mg of the essential oil daily. For the moment it is concluded that the study does not trigger a revision of the monograph, nor the list entry for the following reasons:

- *The use of tea tree oil during pregnancy and lactation is not recommended (monograph section 4.6. Fertility, pregnancy and lactation).*

- *Although the information about oromucosal absorption is not known, it is expected that when used as a gargle, the exposure is lower than from oral use.*

This information could be relevant for the next review when more data is available, e.g. for inclusion of further information in the assessment report and, if necessary, monograph section 5.3.

In order to test the effects on spermatozoa, an *in vitro* study was carried on with porcine spermatozoa samples treated with 0.2-2 mg/ml of tea tree oil during 3h. It was observed a concentration-dependent decrease in motility from 0.4 mg/ml, which was statistically significant at concentrations ≥ 0.8 mg/ml. The viability was statistically significant decreased with ≥ 1 mg/ml of tea tree oil. The spermatozoa acrosome reaction was statistically significant increased at concentrations ≥ 1.4 mg/ml.

Assessor's comment:

Although some toxic effects can be deduced from this study, it was in vitro study and results cannot be extrapolated to in vivo administration and so, it is not relevant for the current EU herbal monograph.

The study conducted by Bertocchi *et al.* (2020) tried to assess the mucosal toxicity of tea tree essential oil on novel porcine uterus models. Tea tree oil at 0.2 – 500 mg/ml was examined in porcine uterine mucosa (n = 8) using an Evans Blue permeability assay; the highest concentration of tea tree oil was used as a positive control. Tea tree oil induced a dose-dependent increase in the amount of dye absorbed, and the increase was statistically significant at concentrations of 40 and

500 mg/ml. No damage was observed with 0.2, 0.4, or 20 mg/ml tea tree oil; at 40 mg/ml, moderate damage was induced to the uterine mucosa, with a multifocal detachment of the epithelium. The same researchers also performed an *ex vivo* study, filling the uterine horns from 8 female sows with 0.2 or 0.4 mg/ml tea tree oil, and incubating the horns for 1 h. After incubation, each uterine horn was emptied, washed with Dulbecco's PBS, and 3 cm x 3 cm section was examined. At these test concentrations, tea tree oil did not alter the structure of swine uterine mucosa.

Assessor's comment:

The results of these studies do not show signs of toxicity and thus, do not trigger a revision of the current EU herbal monograph.

Adverse event(s) or other safety data: A search was performed in EVDAS (EudraVigilance) database. Key words were: spontaneous, other, not available to sender (unknown), report from studies, suspect interacting, in EEA.

The search revealed 3 cases, including the case reports. One of them was related to a patient receiving 8 different drugs, so the observed adverse effects could not be directly related to the use of tea tree oil. The two other cases described the use of tea tree oil alone and led to facial swelling, rash, pruritus, asthma and dermatitis. They disappeared after withdrawal and the casual relationship was assessed as possible.

Several individual case reports have also been published regarding the same adverse events (contact or systematized contact dermatitis) in adults and children. In many occasions, the adverse events were due to misuse of the preparations.

The described adverse events are already included in the current AR and MO on *Melaleuca* spp, atheroleum.

New regulatory practice that could trigger a revision of the monograph

Not applicable.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other

Not applicable.

In summary, there are no new products in the EU market containing *Melaleuca alternifolia* (Maiden and Betch) Cheel, *Melaleuca linariifolia* Smith, *Melaleuca dissitiflora* F. Mueller and/or other species of *Melaleuca*, aetheroleum*,* as the single active substance different from those included in the current EU herbal monograph. The adverse events retrieved from the pharmacovigilance database and published case reports are included in the current EU *herbal monograph*.

The possibility of revise the monograph in order to not include other species of Melaleuca different form *Melaleuca alternifolia* cannot trigger a revision, as the European Pharmacopoeia Monograph has not been revised at this moment and the description of the aetheroleum includes *Melaleuca alternifolia* (Maiden and Betch) Cheel, *Melaleuca linariifolia* Smith, *Melaleuca dissitiflora* F. Mueller and/or other species of *Melaleuca*.

Regarding toxicological studies, although new data have been published in relation to developmental and reproductive toxicity (including effects on spermatozoa) and uterine mucosal toxicity, they do

not show any signs of toxicity or safety concerns for the route of administration and indications included in the current EU herbal monograph.

References

Bertocchi M, Rigillo A, Elmi A, et al. Preliminary assessment of the mucosal toxicity of tea tree (*Melaleuca alternifolia*) and rosemary (Rosmarinus officinalis) essential oils on novel porcine uterus models. *International Journal of Molecular Science* 2020, 21(9):E3350

Guideline for Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (FDA, 2005) Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers | FDA

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal (EMEA/CHMP/SWP/28367 Rev 01 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf)

Elmi A, Venrella D, Varone F, et al. In vitro effects of tea tree oil (*Melaleuca alternifolia* essential oil) and its principal component terpinen-4-ol on swine spermatozoa. *Molecules*. 2019;24(6):E1071

European Chemicals Agency (ECHA). *Melaleuca alternifolia*, ext (tea tree oil; CAS No. 85085-48-9) https://echa.europa.eu/en/registration-dossier/-/registered-dossier/20921. Last Updated 1/21/2021. Accessed 03/02/2023

Expert Panel for Cosmetic Ingredient Safety. Safety assessment of *Melaleuca alternifolia* (Tea Tree)-derived ingredients as used in cosmetics. Cosmetic Ingredient Review. Public Report. 2021 https://www.cir-safety.org/sites/default/files/melalt092021FR.pdf

Zhang SY, Robertson D. A study of tea tree oil ototoxicity. *Audiology & neuro-otology*. 2000;5(2):64-68

Rapporteur's proposal 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

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