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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Eucalyptus globulus* Labill., folium

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HMPC decision on review of monograph *Eucalyptus globulus* Labill., folium adopted on 15 January 2013	13 January 2021
Call for scientific data (start and end date)	From 01 March 2021 to 31 May 2021
Adoption by Committee on Herbal Medicinal Products (HMPC)	26 January 2022

Review of new data on *Eucalyptus globulus* Labill., folium

Periodic review (from 2013 to 2021)

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

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)

The Eudravigilance database was searched on 23 July 2021 using the key words: "*Eucalyptus* leaf", "*Eucalyptus* extract", "*Eucalyptus globulus*", and "*Eucalyptus* tincture"

☒ Scientific/Medical/Toxicological databases

Base; Embase; Pubmed; Biomedical Reference Collection; DynaMed (09 August 2021; 25 October 2021); key words "*Eucalyptus*", and "*Eucalyptus* leaves".

☐ Other

Regulatory practice

☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)

☒ New market overview (including pharmacovigilance actions taken in member states)

☐ Referral

☒ Ph.Eur. monograph

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☐ 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 (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change 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 likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change 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	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒

Summary and conclusions on the review

During the review, 822 new references not yet available during the first/previous assessment were identified.

1,155 references were found by Interested Parties during the Call for data, 19 were regarded as relevant.

Six references were considered to be relevant for the assessment.

No references justify a revision of the monograph.

No revision is considered required because there are no new data or findings that are relevant for the content of the monograph.

Market overview

Active substance	Indication	Pharmaceutical form, Strength (where relevant) Posology, Duration of use	Regulatory status (date, Member state)
Eucalypti folium tinctura (1:5); extraction solvent: ethanol 70% (V/V)	Herbal medicinal product indicated in addition to therapy for acute or chronic inflammation of the upper respiratory tract	1 ml of solution contains 1 ml of Eucalyptus leaf tincture. Adolescents, adults and elderly: SD (oral): 15 to 30 drops Max DD (oral): 3 times daily To rinse the neck, dilute the Eucalyptus leaf tincture by mixing 10 to 15 drops in a glass of warm water. For inhalation of steam, 15 to 20 drops are poured into a glass of boiling water. Breath the vapours through your mouth and nose for 10 minutes.	1998; LV; National registration procedure

Assessor's comment:

While the preparation is covered by the existing monograph neither the posology nor the method of administration ("rinsing the neck") is covered. Requirements of traditional use (at least 30 years of medicinal use including at least 15 years within the European Union) are not fulfilled yet.

Scientific data

Non-clinical and clinical safety:

Quílez *et al*. (2012) investigated the interactions of milled *Eucalyptus globulus* leaves when administrated with benzodiazepine (diazepam). At doses of 6 mg/kg and 3.25 mg/kg inhibited the effects of diazepam in mice. The clinical relevant of the data in mice are unclear. Thus, the presented data give not evidence that interactions should be listed in the monograph.

Herb-induced liver injury in the Berlin case-control surveillance study has been described by Douros *et al*. (2016). Among others, *Eucalyptus globulus* induced hepatotoxicity has been investigated and despite the data implicating a hepatotoxic potential for the main compound 1.8-cineole involving central venous congestion, granular degeneration, vacuolar degeneration and hepatic necrosis, there are no cases of liver damage in association with the use of *Eucalyptus globulus*.

Gardiner *et al*. (2013) searched the literature for case reports on adverse effects in paediatric population caused by medicinal herbs. A large part of the reported cases were a result of unintended ingestion. Twelve reported cases of *Eucalyptus* caused adverse effects were found, but not described in detail. New unknown adverse effects were not detected.

Sugimoto *et al*. (2020) conducted a 4-weeks pilot study on 6 adult Japanese men. No adverse effects have been observed after an administration of 2,592 mg/day of a *Eucalyptus* leave extract. The used dry extract has been prepared with ethanol 33% (V/V) at 65°C and subsequently evaporation in vacuo. It is not clear whether the essential oil has been reduced by this preparation method. Cineole has been analysed as less than 0.1%. Thus, the relevance for the use of other extracts remains unclear.

Essential oil (as constituent of the *Eucalyptus* leaves):

Galan *et al*. (2020) reviewed in 2020 the pre-clinical and clinical data on effects of *Eucalyptus* oil and eucalyptol (1.8 cineole, the main constituents of *Eucalyptus* oil). The data suggests that cineole has anti-inflammatory, expectorant, bronchodilator and analgesic effects. The authors concluded that these effects might be of therapeutic utility in respirators disorders. Interaction have been described in animal studies as well as in studies on volunteers, but from the authors view, further studies are required to assess the clinical relevance. Regarding data on safety and toxicology, the described effects are in accordance with the already reported effects in the HMPC-AR. In a repeated dose study, there were signs on a reproductive toxicity 100, 500 and 1000 mg/kg bw/day for 50 days in rats. Nevertheless, the use in pregnancy and lactation is already not recommended in the HMPC documents.

Assessor's comment:

New pre-clinical data on toxicological effects or adverse effects that would lead to a revision of the HMPC monograph have not been detected. Thus, there is no need to add new information on safety in the HMPC monograph.

Clinical efficacy:

In a review by Chandorkar *et al*. (2021) several clinical studies with Eucalyptus oil (combinations) or 1.8-Cineol (published 1997-2013) are mentioned.

Assessor's comment:

None of the studies mentioned by Chandorkar et al. (2021) will add new information to the monograph on Eucalyptus globulus leaves. Thus, this publication will not trigger a revision of the monograph.

Eudravigilance data:

Updated data on pharmacovigilance described only a few cases (9) of adverse effects. One serious case of drug induced liver injury has been reported and published (Douros *et al*., 2016), but data which allow detailed evaluation are missing. Thus, the effect has only been classified by the authors as "possible".

Furthermore, only cases describing known adverse effects of *Eucalyptus* oil such as seizures, diarrhoea, and eczema are reported. Since no data on the used posology are available and all cases have been reported with co-medications, an evaluation on the relevance is not possible.

Assessor's comment:

The reported adverse effects have already been regarded and thus, no need for a corresponding revision of the HMPC monograph on Eucalyptus leaves.

References

a) References relevant for the assessment:

Chandorkar N, Tambe S, Amin P, Madankar C. A systematic and comprehensive review on current understanding of the pharmacological actions, molecular mechanisms, and clinical implications of the genus *Eucalyptus*. *Phytomedicine Plus* 2021, 1(4):100089, in press, doi 10.1016/j.phyplu.2021.100089

Douros A, Bronder E, Andersohn F, Klimpel A, Kreutz R, Garbe E, *et al*. Herb-Induced Liver Injury in the Berlin Case-Control Surveillance Study. *Int J Mol Sci.* 2016, 17(1):114, in press, doi 10.3390/ijms17010114

Galan DM, Ezeudu NE, Garcia J, Geronimo CA, Berry NB, Malcolm BJ. Eucalyptol (1,8-cineole): an underutilized ally in respiratory disorders? *Journal of Essential Oil Research* 2020, 32(2):103-110, in press, doi 10.1080/10412905.2020.1716867

Gardiner P, Adams D, Filippelli AC, Nasser H, Saper R, White L, *et al*. A systematic review of the reporting of adverse events associated with medical herb use among children. *Glob Adv Health Med.* 2013, 2(2):46-55, in press, doi 10.7453/gahmj.2012.071

Quílez AM, Saenz MT, García MD. Uncaria tomentosa (Willd. ex. Roem. & Schult.) DC. and *Eucalyptus globulus* Labill. interactions when administered with diazepam. *Phytother Res* 2012; 26(3):458-461, in press, doi 10.1002/ptr.3593

Sugimoto K, Nakagawa K, Fujiwara S, Sakano K, Ebihara S. Safety Assessment of *Eucalyptus* Leaf Extract Oral Consumption for 4 Weeks in Human Subjects: A Pilot Study. *Japanese Journal of Complementary and Alternative Medicine* 2020, 17:24-31, in press, doi 10.1625/jcam.17.24

b) References that justify the need for the revision of the monograph:

None.

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

The HMPC agreed not to revise the monograph, assessment report and list of references on *Eucalyptus globulus* Labill., folium by consensus.