18 November 2020
EMA/HMPC/475451/2020
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Syzygium aromaticum* (L.) Merill et L. M. Perry, floris aetheroleum

Rapporteur(s)	R Länger
Peer-reviewer	E Svedlund

HMPC decision on review of monograph *Syzygium aromaticum* (L.) Merill et L. M. Perry, floris aetheroleum adopted on September 2011	13 September 2011
Call for scientific data (start and end date)	From 01/02/2020 to 30/04/2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	18 November 2020

Review of new data on *Syzygium aromaticum* (L.) Merill et L. M. Perry, floris aetheroleum

Periodic review (from 2011 to 2020)

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

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

☒ Scientific/Medical/Toxicological databases: Scopus (key words 'Syzygium aromaticum AND essential oil', clove oil), search date 8.7.2020, in total 859 hits, 595 documents published between 2010 and 2020, 5 references considered relevant.

☐ 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

☐ Other

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

☐ Public statements or other decisions taken by HMPC

☐ Consistency with other monographs within the therapeutic area

☐ Other

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 595 new references not yet available during the first/previous assessment were identified.

0 references were provided by Interested Parties during the Call for data.

5 references were considered to be relevant for the assessment.

0 references justify a revision of the monograph.

In a review by El-Saber *et al*., 2020, the phytochemical composition and biological activities of clove extracts along with clove essential oil and the main active compound, eugenol, were examined and implicates new findings from gas chromatography-mass spectroscopy (GC-MS) analysis.

Srinath, 2014, reviewed the uses of selected spices like *Curcuma longa*, *Zingiber officinale*, *Piper nigrum*, *Elettaria cardamomum*, *Cinnamomum verum*, *Syzygium aromaticum*, *Trigonella foenum graecum*, *Myristica fragrans* and their applications in dentistry.

Moon *et al*., 2011 reported that the antibacterial activity of clove oil was higher than b-caryophyllene but was similar to eugenol against all tested oral bacteria. Furthermore, the MIC and MBC were reduced to one half-one sixteenth as a result of the combination of clove oil or eugenol with antibiotics. The synergistic interaction was verified by time kill studies using the clove oil or eugenol with antibiotics. 60 minutes of treatment with MIC of the clove oil or eugenol with ampicillin or gentamicin resulted in an increase in the rate of killing in units of CFU/mL to a greater degree than was observed with alone.

In the study by Shoeibi *et al*., 2009, an AMES test using Salmonella typhimurium TA 100 with and without S9 mix, concentrations 50-2000 µg/ml, showed negative results without S9 mix, but with S9 mix a dose related positive response were identified. The test is not a full test compliant with current guidelines i.e. additional bacterial strains are required.

Shalaby *et al*., 2011, have determined the LD50 (oral administration) of clove oil to 3,597.5 mg/kg BW. At 1/10 of LD50 (every third day for one months) significant changes of white blood cell counts, decrease of haemoglobin concentration, increase of liver enzymes, creatinine and urea concentrations.

Pharmacovigilance database: 14 entries, 4 entries refer to allergic reactions caused by application of clove oil; other entries refer to administration of several drugs where the causality regarding clove oil is not clear. Mucosal irritation and allergic reactions are already mentioned in the monograph.

No revision is considered required because no relevant new references were found and no pharmacovigilance actions were taken.

References

a) References relevant for the assessment:

Shoeibi S, Rahimifard N, Pirouz B *et al*. Mutagenicity of four natural flavors: clove, cinnamon, thyme and *Zataria multiflora* Boiss. *J Med Plants* 2009, 8(Supp. 5): 89-96:

Moon S-E, Kim H-Y, Cha J-D. synergistic effect between close oil and its major compounds and antibiotics against oral bacteria. *Arch Oral Biol* 2011, 56:907-916

Shalaby SEM, El-Din MM, Abo-Donia SA, Mettwally M, Attia ZA. Toxicological affects of essential oils from Eucalyptus *Eucalyptus globule*s and Clove *Eugenia caryophyllus* on albino rats. *Polish J Environ Stud* 2011, 20:429-434

Srinath J. Application of spices in dentistry– A literature review. Int J Drug Dev Res 2014, 6:1-9

El-Saber Batiha G, Alkazami LM, Wasef LG *et al*. *Syzygium aromaticum* L. (Myrtaceae): traditional uses, bioactive chemical constituents, pharmacological and toxicological activities. *Biomolecules* 2020, 10: 202 (16 pages)

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 *Syzygium aromaticum* (L.) Merill et L. M. Perry, floris aetheroleum, by consensus.