24 July 2024
EMA/HMPC/32686/2024
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Pistacia lentiscus* L., resina (Mastic)

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HMPC decision on review of monograph *Pistacia lentiscus* L., resina (Mastic) adopted on 2 February 2016	25 January 2023
Call for scientific data (start and end date)	From 30 April 2023 to 31 July 2023
Discussion in Committee on Herbal Medicinal Products (HMPC)	November 2023 January 2024 March 2024 May 2024 July 2024
Adoption by Committee on Herbal Medicinal Products (HMPC)	24 July 2024

Review of new data

Periodic review (from 2019 to 2024)

Sources checked for new information:

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

☒ Scientific/Medical/Toxicological databases

Scientific data of the period 2013 -2023 was reviewed using Google Scholar browsing machine and sources available in library of (Medline Complete, PubMed, Reaxys, SciFinder, Scopus, The

Cochrane Library, ScienceDirect). Search terms: "*Pistacia lentiscus* L.", "mastic", "*Pistacia lentiscus* var Chia", "mastic gum"

☒ Pharmacovigilance databases

☒ data from EudraVigilance

☒ from other sources (e.g. data from VigiBase; National sources, (access Nov 2023)

☐ 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 (PubMed, Google Scholar + other mentioned databases available) 41 references (2019 - 2024), using as search terms "*Pistacia lentiscus* L.", "mastic", "*Pistacia lentiscus* var Chia", "mastic gum", have been collected among which, there were several articles on chemistry of new metabolites (natural products) (Liu *et al.* 2020; Ann et al 2022; Yu *et al.* 2022).

Moreover, one clinical study on essential oil of *P. lentiscus* resin was found. The mastic gum's essential oil from Chios has been investigated on individuals with abdominal obesity and metabolic abnormalities, i.e., dyslipidemia, hypertension, insulin resistance. Eligible patients (N = 94) were randomly assigned to either the intervention group, receiving capsules containing 200 mg daily for three months adjunct to current treatment for metabolic disorder(s), or the control group. No adverse effects were reported. An anti-obesity effect, probably attributed to modulation of inflammatory and antioxidant processes, is suggested (Gioxari *et al.* 2023).

Assessor's comment: This trial does not comply with the existing EU herbal monograph as it is referred to the essential oil of the mastic resin only.

Furthermore, one publication on DNA Botanical analysis of *P. lentiscus* (Kyriakidi *et al*. 2022) was retrieved. Several references on *In vitro* and *in vivo* preclinical data (Kashimoto *et al.* 2021; Kim *et al.* 2021; Milia *et al*. 2023) were available, including one study designed to evaluate the sub-acute toxicity of gum mastic powder (GMP) and gum mastic tears (GMT) in rats when administered by oral feeding at the dose of 0.2857 g/kg for a duration of 14 days. The results according to the authors indicated that both GMP and GMT could be used safely (towards their proposal as cardio-protective and in gout treatment) (Sadaf *et al.* 2023).

A patch testing was carried out on 18 patients who were allergic to a special branded CE products (used as liquid adhesive) containing a mixture of compounds among which mastic resin. Most of these had a history of postoperative dermatitis including ingredients of a branded CE product, compound tincture of benzoin, and fragrance-related ingredients and botanicals. Among a branded CE product-allergic patients, 13 (72%) of 18 were allergic to gum mastic, whereas seven (44%) of 16 were allergic to gum storax. There was frequent co-reactivity with various fragrance-related materials, including Majantol, Styrax benzoin, Myroxylon balsamum, *Myroxylon pereirae*, propolis, and others (Shaw 2021).

None of the references could trigger revision of the monograph.

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

In Eudravigilance no case report has been found.

In Vigibase there were two reported cases in the United Kingdom and Canada since 2009 and 2016 respectively, both referred in women (of 45-65 years old the one, not specified age the other) showing dyspnoea and hypoaesthesia the one and visual impairment with vomiting the other. In both cases, the adverse rections appeared in parallel intake with a mixture of other co-reported active ingredients such as: betaine, potassium, citric acid, Foeniculum vulgaris, Thymus vulgaris, Eucalyptus globulus, Lavandula angustifolia, Melissa officinalis, Mentha x piperitae, Syzygium aromaticum, Pinus sylvestris, Citrus limon, Polysorbate 20. Thus, these adverse events cannot be taken into consideration, and they do not give any special safety signal.

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

There are no new herbal substances/preparations with 30/15 years of TU or 10 years of WEU.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other issues that could trigger a revision of the monograph

References available in the assessment report may point to a wider possible strength compared to that included in the monograph, but they refer to preparations where mastic was dissolved in organic solvents, which are nowadays not permitted in the medicinal use due to their toxicity. At the time this review report is written there are no data to support the inclusion of wider strength in the monograph, although this should be reconsidered with the next systematic revision of the monograph in case new data become available.

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

Not applicable.

References

References that could be relevant for the next review

An X, Wang J, Yu X, Wu H, Liu W. Two new polypodane-type bicyclic triterpenoids from mastic. *Open Chemistry* 20(1), 267 - 2711 2022

Gioxari Ar, Amerikanou C, Valsamidou E, Kleftaki S-A, Tzavara C, *et al*. Chios mastiha essential oil exhibits antihypertensive, hypolipidemic and anti-obesity effects in metabolically unhealthy adults - a randomized controlled trial. *Pharm Res* 19, 2023 Art n 106821

Kim D-I, Cho Y-B, Lim Y, Hong S-H, Hahm B, Lee S-M, *et al*. Chios mastic gum inhibits influenza a virus replication and viral pathogenicity. *J Gen Virology* 102(38), 2021 Art n 001550

Kishimoto R, Kato N, Koike M, Iwashita N, Takagi Y, Fukuyama T. Topical treatment with mastic (resin from *Pistacia lentiscus*) elicits anti-inflammatory and anti-pruritic responses by modulating keratinocyte activation in a mouse model of allergic dermatitis. *Phytomedicine* 91, 2021 Art n 153679

Kyriakidi P, Kostas S, Zeka-Paschou C, Piliou K, Mylona A, Vasileiadis A, *et al*. Contribution to the molecular taxonomy of mastic tree morphotypes on Chios Island. *J Biol Res* 29 2022 Art n 2

Liu W, Gao J, Li M, Aisa há, Yuan T, Tirucallane triterpenoids from the mastic (*Pistacia lentiscus*) and their anti-inflammatory and cytotoxic activities. *Phytochemistry* 182, 2021 Art n 112596

Milia EP, Sardellitti L, Eick S. Antimicrobial efficiency of *Pistacia lentiscus* L. Derivates against oral biofilm-associated diseases — a narrative review. *Microorganisms* 11(6) 2023

Sadaf F, Siddiqui S, Khan SJ. Safety profile of *Pistacia lentiscus* powder and tears in rat. *Pakistan Journal of Pharmaceutical Sciences* 36(3), 783 – 787, 2023 (abstract only)

Shaw DW. Contact dermatitis from gum mastic (*Pistacia lentiscus*) and gum storax (Liquidambar styraciflua) in mastisol-allergic patients. *Dermatitis* 32, 6, 430-4361 2021 (abstract only)

Yu Y-H, Feng Y-P, Liu W, Yuan T. Diverse triterpenoids from mastic produced by *Pistacia lentiscus* and their anti-inflammatory activities. *Chem Biodiv* 19(3) 2022 Art n e202101012

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