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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Olea europaea* L., folium

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HMPC decision on review of monograph *Olea europaea* L., folium adopted on 31 January 2017	31 January 2024
Call for scientific data (start and end date)	From 15 February 2024 to 15 May 2024
Discussion in Committee on Herbal Medicinal Products (HMPC)	September 2024 November 2024 January 2025
Adoption by HMPC	22 January 2025

Review of new data

Periodic review (from 2018 to 2024)

Sources checked for new information:

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

☒ Scientific/Medical/Toxicological databases

PubMed/ was searched on July and September 2024; period covered: 2018 until september 2024, Search terms: *Olea europaea* folium, olive leaf efficacy and/or safety

☒ Pharmacovigilance databases

☒ data from EudraVigilance

☐ from other sources (e.g. data from VigiBase, national databases)

☐ Other

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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, 238 new references, further filtered to 129 most relevant, not yet available during the first/previous assessment were identified. None out of these new references considered to be relevant for the monograph and/or could trigger a revision of the monograph.

The search in pharmacovigilance databases revealed no serious case report.

Moreover, no new indications, herbal preparations and dosages were identified, towards the existing therapeutic indication in the currently adopted EU herbal monograph.

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

Assessment of new data

New scientific data that could trigger a revision of the monograph

None applicable.

New regulatory practice that could trigger a revision of the monograph

Not reported.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other that could trigger a revision of the monograph

Not applicable.

There are no new products in the market containing *Olea europaea,* folium which could trigger a revision of the EU herbal monograph.

No new publications regarding Ames test or animal reproductive and developmental toxicity studies are available.

Several among new references referred to chemical studies mostly on polyphenols and secoiridoid oleuropein and its derivative hydroxytyrosol (3,4-dihydroxyphenylethanol) as well as their bioavailability and metabolism (Gerbasi & Pojero 2024, Acar-Tek & Ağagündüz, 2020). Moreover, other publications are further reviewing known properties through pre-clinical studies such as antioxidant, anti-infective and cytotoxic ones, of *O. europea* leaf extracts (Rufino-Palomares *et al.,* 2023, Acar-Tek & Ağagündüz, 2020).

Some of them referred to new clinical studies such as psoriasis management (Alkhatib *et al.,* 2023), wound healing activity (Torrecillas-Buena *et al.,* 2023) and the formulation of a drug for the treatment of allergic conjunctivitis based on *Olea europaea* leaf aqueous extract (Zhao & Li 2023).

Several new data referred to clinical pharmacological activities (influence to lipidemia, prediabetes, blood pressure and general cardiac function).

In a review article, literature in the PubMed, ScienceDirect, Google Scholar, Cochrane Library, SciELO, and MEDLINE databases with key words "Olea europaea", "olive leaf", "olive leaf extracts", "phenolic compounds", "oleuropein", "hydroxyl-tyrosol", "health", "glycemia", "diabetes", "hypolipidemic effects", "cardiovascular effects", "safety", and "toxicology" was searched. A number of studies reported that olive leaf has potentially positive effects on the parameters related to diabetes and cardiovascular diseases by various mechanisms. Besides, studies suggested that olive leaf is generally safe. Although current results obtained until today seem promising, the studies in

this subject are usually on cell culture and animal trials. Moreover, mostly the extract forms of olive leaves are used in the studies. The conclusion of the article suggested that more randomized controlled human clinical trials with extensive toxicity studies are needed to evaluate potential health effects and safety (Acar-Tek & Ağagündüz, 2020) In another comparable systematic review and meta-analysis, observed that olive leaf consumption significantly reduced the levels of systolic and diastolic blood pressure, cholesterol, triglycerides, and LDL-c (Fatahian *et al.,* 2022)

In a randomized, double-blind, placebo-controlled study, 77 healthy adult overweight/obese subjects with total cholesterol levels of 5.0–8.0 mmol/L' (5.9 ± 0.7 mmol/L') were randomly assigned to receive 500 mg of olive leaf extract (OLE) (n = 39) or placebo (n = 38) for 8 weeks. The test product that was used was an extract prepared from olive leaves using a 100% water-based extraction method, standardized for its oleuropein content (16.7%), providing 83.5 mg oleuropein per day. In total, 74 subjects completed the study protocol. Blood lipid profiles were not significantly affected by 8 weeks OLE supplementation in overweight/obese subjects with mildly elevated cholesterol levels (Stevens *et al.,* 2021).

Olive leaf tea (5g/Lt) showed positive results for lipid metabolism in adults (57 subjects) for 12 weeks, with prediabetes: in a randomized controlled trial, although the effect of the tested tea on abdominal obesity and glucose metabolism remained unclear, it has been found to have lipid-lowering effects (Araki *et al.,* 2019)

Recent publications referred to potential antiviral protection of *O. europea* leaf extracts, against SARS- COVID 19 (Ahmadpour *et al.,* 2023, Kocyigit *et al.,* 2022) while in a review article 28 most relevant, existing studies of olive leaf polyphenols against SARS-CoV-2 in silico, *in vitro*, and *in vivo* were discussed. These bioactive substances are concluded that may alter many signaling pathways and display a wide range of actions—including anti-inflammatory, antipyretic, immunomodulatory, and antithrombotic capabilities (Bonneti *et al.,* 2023)

Adverse event(s) or other safety data: A search was performed in EudraVigilance data base.
The search revealed three case reports. The first two referred individually to symptoms of headache as adverse event (AE) (one case in Germany and one in Australia) related to the use of *Olea europaea* L., folium as supplementation in parallel use with a lot of co-medications (three medicines/ supplements in total in the first case, 12 in the second one) The third case reported from the USA referred to hepatitis and there is a huge list of 80 different co-supplementation used for bodybuilding (among which one was also Olea leaf)

Assessor's comment:
There is no reported side effect that can directly be linked to the use of Olea europaea L., *folium.*

No revision is considered required because there are no new products in the market and no new scientific data related to non-clinical and clinical safety or clinical efficacy which could trigger a revision.

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

None applicable.

References

a) References relevant for the assessment

Acar-Tek, N; Ağagündüz, D. Olive Leaf (*Olea europaea* L. folium): Potential Effects on Glycemia and

Lipidemia *Ann Nutr Metabol* 2020, 76 (1) 10 – 15.

Ahmadpour, E; Toulabi, T; Yadegarinia, D; Yarahmadi, S Mohammadi, R; Keyvanfar, A. Efficacy of olive leaves extract on the outcomes of hospitalized covid-19 patients: A randomized, triple-blinded clinical trial *Explore* 2023*,* 19(4), 536-5431 DOI 10.1016/j.explore.2022.10.020

Alkhatib, B; Alhilo, S; Alhilo, I Psoriasis Management Using Herbal Supplementation: A Retrospective Clinical Case Study *Alt Ther Health Med* 2023, 29(4), 270 – 273.

Araki, R; Fujie, K; Yuine, N; Watabe, Y; Nakata, Y; Suzuki, H; Isoda, H; Hashimoto, K. Olive leaf tea is beneficial for lipid metabolism in adults with prediabetes: an exploratory randomized controlled trial *Nutr Res* 2019 67, 60 – 66 DOI 10.1016/j.nutres.2019.05.003

Bonetti G; Donato K; Medori MC; Cecchin S; Marceddu G; Gadler M; Guerri G; Cristofoli F; Connelly ST; Gaffuri F.; Tartaglia GM; Nodari S The Role of Olive Tree Polyphenols in the Prevention of COVID-19: A Scoping Review, part 1 Clin ter 2023, 174(6), 142-148 DOI 10.7417/CT.2023.2480

Fatahian, A; Yousefi, S S; Azadbakht, M; Moosazadeh, M, Fakhri, M The effect of olive leaf use on blood pressure; A systematic review and meta-analysis *J Ren Inj Prev* 2022, 11(32022) Art no. e31933 DOI 10.34172/jrip.2022.31933

Gervasi, F; Pojero, F Use of Oleuropein and Hydroxytyrosol for Cancer Prevention and Treatment: Considerations about How Bioavailability and Metabolism Impact Their Adoption in Clinical Routine *Biomedicines 2024,* 12(3) Art no 502. DOI 10.3390/biomedicines12030502

Kocyigit, A; Guler, E M; Irban, A; Kiran, B; Atayoglu, A T Assessment of Association Between the Potential Immunomodulatory Activity and Drinking Olive Leaf Tea in the Coronavirus Disease-2019 Pandemic: An Observational Study *J Integr Compl Med* 2022, 28(12), 940-9471 DOI 10.1089/jicm.2022.0554

Rufino-Palomares EE, Pérez-Jiménez A, García-Salguero L, Mokhtari K, Reyes-Zurita FJ, Peragón-Sánchez J, Lupiáñez JA. Nutraceutical Role of Polyphenols and Triterpenes Present in the Extracts of Fruits and Leaves of *Olea europaea* as Antioxidants, Anti-Infectives and Anticancer Agents on Healthy Growth. *Molecules*. 2022; 27(7):2341. https://doi.org/10.3390/molecules27072341

Stevens, Y; Winkens, B; Jonkers, D; Masclee, A The effect of olive leaf extract on cardiovascular health markers: a randomized placebo-controlled clinical trial *Eur J Nutr 2021,* 60(4), 2111–2120 DOI 10.1007/s00394-020-02397-9

Torrecillas-Baena, B; Camacho-Cardenosa, M; Carmona-Luque, MD; Dorado, G; Berenguer-Pérez, M; Quesada-Gómez, J M; Gálvez-Moreno, M Á; Casado-Díaz, A Comparative Study of the Efficacy of EHO-85, a Hydrogel Containing Olive Tree (*Olea europaea*) Leaf Extract, in Skin Wound Healing *Int J Mol Sci* 2023*,* 24(17) Art no 13328 *DOI 10.3390/ijms241713328*

Zhao, S; Li, Q; Formulation of a drug for the treatment of allergic conjunctivitis: Copper nanoparticles containing Olea europaea leaf aqueous extract *Inorg Chem Commun* 2023, 153 Art no 110867 DOI 10.1016/j.inoche.2023.110867

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

☐ 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