



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Cynara cardunculus* L. (syn. *C. scolymus* L.), *folium*

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HMPC decision on review of monograph <i>Cynara cardunculus</i> L. (syn. <i>C. scolymus</i> L.), <i>folium</i> adopted on 27 March 2018	31 January 2024
Call for scientific data (start and end date)	From 01 April 2024 to 30 June 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: *Cynara cardunculus* L. (syn. *Cynara scolymus* L.), *folium* *Artichoke 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

<i>Scientific data</i>	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	☐	☒
<i>Regulatory practice</i>	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	☐	☒
<i>Consistency</i>	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, 187 new references, further filtered to 56 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 reports, contrary due to new clinical trials where artichoke leaf extracts were used, has been published good tolerance.

Moreover, no new indications, herbal preparations and dosages were identified, towards the existing therapeutic indication in the adopted MO

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

Not 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 *Cynara cardunculus* folium (artichoke leaf) 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 publications referred to chemical studies mostly on phenolic content (caffeoylquinic acid derivatives and flavonoids) proposing a validated ultra-high-performance liquid chromatography-photodiode array detector (UPLC-PDA) method capable of quantifying simultaneously 12 polyphenol compounds (Nguyen *et al.*, 2024). Other publications are further reviewing known properties of artichoke leaf extracts (ALE) through pre-clinical studies such as antioxidant, cholesterol-lowering, liver-protective, anti-inflammatory and antioxidant ones (Celepli *et al.*, 2022).

The hepatoprotective effects of ALE have been studied in comparison with silymarin, towards an acetaminophen-induced liver damage *in vivo* in mice. ALE and/or silymarin are suggested to protect against acetaminophen-induced hepatotoxicity in mice by ameliorating liver enzymes, antioxidant effect, decreasing liver damage and proliferation (Elgarawany *et al.*, 2019). Furthermore, the protective effects of an ethanol extract of artichoke leaves (EEA) compared to Atorvastatin in the kidney of Wistar rats fed a high-fat diet (HFD) showed a renoprotective effect of EEA probably due to its antioxidant kidney effects in HFD- induced obese rats (Ben Salem *et al.*, 2022)

In a recent *in vivo* study, performed to 56 laboratory dyslipidemia induced rats to, the potential drug-herb interaction due to the simultaneous use of ALE with two doses of rosuvastatin has been evaluated. All treatment protocols of rosuvastatin, ALE, or their combination and chlorogenic acid

(CGA) had a hypolipidemic activity that altered all lipid profile parameters. In addition, the pharmacokinetics study showed that coadministration between ALE and a low dose of rosuvastatin decreased rosuvastatin's bioavailability, with decreasing its concentration in the serum blood mainly in male rats. After the separation of the results into males and female rats, the gender factor showed an important role, so further experiments are needed in better determining the results and their accuracy (Al Masalmeh *et al.*, 2023)

Moreover, the use of ALE in several clinical trials has been evaluated so far. The influence of ALE on blood pressure (BP) as an adjunctive to captopril, not previously studied, has been investigated in a clinical trial carried out on 40 patients to determine the effect of ALE (500 mg twice daily for eight weeks) on BP and body mass index (BMI) in hypertensive patients. The results demonstrated that the consumption of ALE could potentially improve BMI and Systolic Blood Pressure in hypertensive patients while more trials are needed to confirm or reject such impact. (Ardalani *et al.*, 2020)

The effects of ALE on the lipid profile of chronic kidney disease (CKD) patients in a randomized, double-blind, placebo-controlled clinical trial, conducted in 38 CKD subjects, demonstrated that consumption of ALE supplementation may improve appetite and lipid profile in CKD patients (Gatmiri *et al.*, 2019).

In another double-blind placebo-controlled randomized clinical trial, 80 patients with Metabolic Syndrome (MetS) using ALE food supplementation (1800 mg as four tablets per day for 12 weeks). ALE decreased serum ox-LDL level in patients with MetS, with no beneficial on other antioxidant indices (Rezazadeh *et al.*, 2018)

A meta-analysis by Kamel & Farag 2022, summarized evidence from recent RCTs that evaluated ALE in nonalcoholic fatty liver disease (NAFLD) patients. Data from five RCTs (333 patients) showed that ALE resulted in a reduction in alanine aminotransferase and aspartate aminotransferase levels compared with the control group and furthermore to a significant reduction in total cholesterol, low-density lipoprotein and triglycerides supporting its potential hepatoprotective agent in NAFLD patients (Kamel & Farag 2022).

Adverse event(s) or other safety data: A search was performed in EudraVigilance data base. The search revealed several case report related to the use of *artichoke*. They were considered as non-serious adverse events (AEs) (diarrhoea, upper abdominal pain and allergic reactions such as rash and erythema) which disappeared after withdrawal the use. In several cases the artichokes's medication was used in co-medication with other drugs (thyroxin, anticancer drugs etc) as well as in and/or , combination Herbal medicinal products (artichoke with Milk thistle, Dandelion, Boldo etc)

Assessor's comment:

*The observed adverse events (AEs) are related to products with artichoke or in which artichoke was not the main component, so is not possible to relate the observed gastric or allergic disturbances only with it. Moreover, all reported AEs are covered by the already existing European Union herbal monograph on *Cynara cardunculus* L. (syn. *Cynara scolymus* L.), folium EMA/HMPC/194014/2017 (Under 4.8 Undesirable effects) where [Slight diarrhoea with abdominal spasm, epigastric complaints like nausea, and heartburn have been reported - Allergic reactions may occur] are referred.*

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 of the EU herbal monograph.

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

Not applicable.

References

a) References relevant for the assessment

- Al Masalmeh, AM; Mallah, E; Mansoor, K; Abu-Qatouseh, L; El-Hajji, FD; Idkaidek, N; Basheti, I; Issa, IH; Al Meslamani, AZ; Aws, S. Pharmacokinetic interaction of rosuvastatin with artichoke (*Cynara scolymus* L.) leaf extract in rats *J Appl Pharm Sci* 2023, 13(6), 179 – 192 DOI 10.7324/JAPS.2023.116608
- Ardalani H; Jandaghi P; Meraji A; Moghadam MH. The Effect of *Cynara scolymus* on Blood Pressure and BMI in Hypertensive Patients: A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial. *Complement Med Res* 2020, 27 (1): 40–46. <https://doi.org/10.1159/000502280>
- Ben Salem, M; Affes, H; Dhouibi, R; Charfi, S; Turki, M; Hammami, S; Ayedi, F; Sahnoun, Z; Zeghal, K M; Ksouda, K. Preventive effect of Artichoke (*Cynara scolymus* L.) in kidney dysfunction against high fat-diet induced obesity in rats *Arch Physiology Biochem* 2022, 128(3), 586–592. DOI 10.1080/13813455.2019.1703755
- Celepli S, Çolak B, Celepli P, Bigat I, Batur HG, Soysal F, Karakurt S, Hücümenoğlu S, Kismet K, Şahin M Artichoke for biochemistry, histology, and gene expression in obstructive jaundice *Rev Assoc Med Bras* 2022;68(5):647-652
- Elgarawany GE, Abdoub AG, Taiec DM, Motawea SM. Hepatoprotective effect of artichoke leaf extracts in comparison with silymarin on acetaminophen-induced hepatotoxicity in mice *J Immun Immunochem* 2020, 41(1), 84–96. DOI 10.1080/15321819.2019.1692029
- Gatmiri SM, Khadem E, Fakhrian T, Kamalinejad M, Hosseini H, Ghorat F, Alamdari A, Naderi N. The effect of artichoke leaf extract supplementation on lipid profile of chronic kidney disease patients; a double-blind, randomized clinical trial *J Ren Injury Prev* 2019, 8(3) 225–229 DOI 10.15171/jrip.2019.42
- Kamel, AM; Farag, MA Therapeutic Potential of Artichoke in the Treatment of Fatty Liver: A Systematic Review and Meta-Analysis *J Med Food* 25(10) 931 – 9421, 2022 DOI 10.1089/jmf.2022.0025 (Abstract only)
- Nguyen, NAT; Le, TM; Nguyen, HT; Pham, KHT; Truong, HPC; Pham, PD; Tran, MH Method Development for Simultaneous Quantification of Polyphenol Compounds in Artichoke (*Cynara scolymus* L.) Leaf Dry Extract by UPLC-PDA *Trop J Natural Prod Res* 2023, 7(9), 3995 - 40023 DOI 10.26538/tjnpr/v7i9.22
- Rezazadeh K, Aliashrafi S, Asghari-Jafarabadi M, Ebrahimi-Mameghani M. Antioxidant response to artichoke leaf extract supplementation in metabolic syndrome: A double-blind placebo-controlled randomized clinical trial *Clin Nutr* 2018, 37(3), 790–796 DOI 10.1016/j.clnu.2017.03.017

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