EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2024
EMA/HMPC/509451/2023
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Silybum marianum* L. Gaertn., fructus

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HMPC decision on review of monograph *Silybum marianum* L. Gaertn., fructus adopted on 05 June 2018	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
Adoption by Committee on Herbal Medicinal Products (HMPC)	31 January 2024

Review of new data

Periodic review (from 2018 to 2023)

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 in October 2023; period covered: January 2018 until October 2023.

Search terms: *Silybum marianum* or milk thistle 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	☐	☒

Other	Yes	No

Summary of new references

During the review, 427 new references not yet available during the first/previous assessment were identified. None out of these new references were considered to be relevant for the monograph or could trigger revision of the monograph. Most of them referred to the chemistry of the herbal substance or included new pre-clinical studies to previously reported properties such as antioxidant, anti-inflammatory or antifibrotic effects (Abenavoli *et al.,* 2018; Soleimani *et al*., 2019). Three metanalysis reviewed the use of milk thistle preparations in drug-induced liver injury or dyslipidemia, among others. Twelve randomized clinical trials included the use of milk thistle preparations for different purposes.

The search in pharmacovigilance databases revealed 233 case reports.

From regulatory praxis no new indications, herbal preparations and dosages were identified.

No references were provided by Interested Parties during the Call for data (30 April 2023 – 31 July 2023).

Assessment of new data

New scientific data that could trigger a revision of the monograph

No new publications regarding Ames test or animal reproductive and developmental toxicity studies that could lead to a list entry are available.

A search was performed in EudraVigilance database. Key words were ''Silybum, Spontaneous, Other, Not available to sender (unknown), Report from Studies, suspect interacting'' in EEA.

The search revealed 233 case reports. Some of them referred to hepatitis or altered liver function after treatment with several drugs or combinations including *Silybum marianum* preparations. Other reports included adverse effects such as gastrointestinal complaints, which are already reflected in the EU herbal monograph.

One case report showed liver injury (liver parameters were elevated with ALT 349 U/L, AST 142 U/L, alkaline phosphatase (AP) 293 U/L, gammaglutamyl transferase (GGT) 696 U/L and TBL 2.7 mg/dl after concomitant use of clindamycin for dental infection (Benesic and Gerbes, 2018). After stopping silymarin and clindamycin, liver enzymes dropped after two weeks. The authors supposed that silymarin might have caused liver injury by interaction with clindamycin and performed an *in vitro* test for drug causality. In the *in vitro* test, clindamycin was tested positive and silibinin was negative, while a synergistic effect of clindamycin and silibinin could be shown.

Assessor's comment:

This case report is related to the simultaneous use of clindamycin and silibinin. Nevertheless, it is not clear what preparation of Silybum marianum was taken; moreover, for the in vitro test, only 10 µM Silibinin was tested. Results of the assessment of causality using an in vitro test showed that silibinin was negative. Thus, it cannot be assumed that this isolated case is due to the use of silibinin and so, it does not trigger a revision of the monograph.

One study among the randomized clinical trials that have been published during the searched period included the evaluation of *Silybum marianum* extracts on liver disease. The study by Navarro *et al*. (2019) was a randomized, double-blind, placebo-controlled phase II multicentre trial to evaluate the safety and explore the efficacy of two doses of a standardized form of silymarin [dry extract from *Silybum narianum* (36 – 44:1), extraction solvent ethyl acetate], higher that customary doses (420

mg or 700 mg three times daily, for 48 weeks) in non-cirrhotic patients with non-alcoholic steatohepatitis (NASH). Results demonstrated that, despite the fact that higher doses of the extract are safe and well tolerated, no improvement in the non-alcoholic fatty liver disease (NAFLD) was seen. Thus, according to the authors, the effect of silymarin in patients with non-alcoholic steatohepatitis remains inconclusive.

The study by Ghiasian *et al*. (2021) about the antioxidative effects of silymarin on the reduction of liver complications of fingolimod in patients with relapsing-remitting multiple sclerosis could not be evaluated since complete information regarding the milk thistle extract which was used, is lacking.

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 issues that could trigger a revision of the monograph

Not applicable.

In conclusion, 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 existing EU herbal monograph.

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

None applicable.

References

References relevant for the assessment

Abenavoli L, Izzo AA, Milić N, Cicala C, Santini A, Capasso R. Milk thistle (*Silybum marianum*): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. *Phytother Res* 2018, 32(11):2202–2213, in press, https://doi.org/10.1002/ptr.6171

Benesic A, Gerbes A. Herbal tea and liver injury – Tea extract or comedication can make a difference. *J Hepatol* 2018, 69(2):547–558

Ghiasian M, Nafisi H, Ranjbar A, Mohammadi Y, Ataei S. Antioxidative effects of silymarin on the reduction of liver complications of fingolimod in patients with relapsing-remitting multiple sclerosis: A clinical trial study. *J Biochem Mol Toxicol* 2021, 35(8):e22800, in press, doi:10.1002/jbt.22800

Navarro VJ, Belle SH, D'Amato M, Adfhal N, Brunt EM, Fried MW et al. Silymarin in NASH and C Hepatitis (SyNCH) Study Group. Silymarin in non-cirrhotics with non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled trial. *PLoS One* 2019, 19;14(9):e0221683, in press, doi:10.1371/journal.pone.0221683

Soleimani V, Delghandi PS, Moallem SA, Karimi G. Safety and toxicity of silymarin, the major constituent of milk thistle extract: An updated review. *Phytother Res* 2019, 33(6):1627–1638, in press, https://doi.org/10.1002/ptr.6361

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