19 July 2023
EMA/HMPC/104943/2023
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Capsicum annuum* L. var. *minimum* (Miller) Heiser, fructus

Rapporteur(s)	R Länger
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HMPC decision on review of monograph *Capsicum annuum* L. var. *minimum* (Miller) Heiser, fructus adopted on 05 May 2015	26 January 2022
Call for scientific data (start and end date)	From 15 February 2022 to 14 May 2022
Discussion in Committee on Herbal Medicinal Products (HMPC)	Mar 2023 May 2023 Jul 2023
Adoption by Committee on Herbal Medicinal Products (HMPC)	19 July 2023

Review of new data

Periodic review (from 2015 to 2022)

Sources checked for new information:

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

☒ Scientific/Medical/Toxicological databases
Scopus, 2014-12.12.2022
Search term 'Capsicum': 8071 hits
Limitation to subject area 'medicine': 652 hits remaining
Manual check of relevance of abstracts: 0 hits remaining

☒ Pharmacovigilance databases

☒ data from EudraVigilance

☒ from other sources (VigiBase)

☐ 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 653 new references not yet available during the first/previous assessment were identified. Out of these new references 3 references were considered to be relevant for the monograph and 3 references that could trigger revision of the monograph. New references regarding isolated or chemically snthesied capsaicin were only taken into account for the possible uptake of new indications.

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

New references

Yong YL *et al.* (2017)
The authors summarised the efficacy of topically applied pure capsaicin for the treatment of postherpetic neuralgia. It is concluded that capsicin is considered as promising treatment option in this indication.

Assessor's comment: The meta-analysis deals with isolated capsaicin. The investigated indication is so far not authorised for herbal medicinal products in the EU. As therefore an important aspect for well-established use is not fulfilled the outcome of this meta-analysis is considered not relevant for the EU herbal monograph.

Paterno ER *et al*. (2019)
The clinical efficacy of a traditional herbal preparation made from siling labuyo fruits (special variety of capsicum frutescens) was compared with 1% diclofenac in 47 patients with osteoarthritis of the knee. The authors conclude on a modest therapeutic effect of the capsicum liniment.

Assessor's comment: In this study a traditional herbal preparation of the Philippines was investigated. No details regarding starting material, extraction solvent and capsaicin content are published. Therefore this publication is considered not relevant for monograph. Moreover, the investigated indication is so far not authorised for herbal medicinal products in the EU.

Musharraf & Yaqub (2017)
Three hundred patients with diabetic neuropathy were enrolled in this clinical trial in order to compare the efficacy of topically applied pure turpentine oil and a capsicum-cream standardised to a content of 0.075% capsaicin. The patients took additionally one oral drug for painful diabetic neuropathy and received their treatment of diabetes mellitus. The authors conclude that after 3 months of treatment turpentine oil was considered as effective as the capsicum cream.

Assessor's comment: As a placebo group is missing the magnitude of the effect cannot be estimated. Moreover, the patients continued to take one oral drug for the pain treatment. As the concentration of capsaicinoids in the product is higher compared to authorised medicinal products the publication is considered not relevant for the EU herbal monograph.

Data from pharmacovigilance

Eudravigilance contains 11 reports of adverse events causally related to the administration of capsicum-containing herbal medicinal products. The reported adverse events are already contained in section 4.8 of the EU herbal monograph.

All adverse events mentioned in the EU herbal monograph can be attributed to the following MedDRA system organ class: skin and subcutaneous tissue disorders.

New regulatory practice that could trigger a revision of the monograph

The market overview submitted from DE and BG indicates that products with an indication not contained in the adopted version of the EU herbal monograph are on the market for the relief of minor foot pain/lower leg pain associated with diabetic chronic polyneuropathy. Treatment applicable only within the framework of a holistic therapeutic concept. The treatment does not improve the nerve damage itself.

Both products contain the herbal preparation a) of the current version of the EU herbal monograph. The cream is standardised to a content of 0.053% of capsaicinoids.

The clinical trials regarding this indication which are already contained in the published assessment report were performed with isolated capsaicin, the creams used in those studies which included a relevant number of patients were standardised to a content of 0.075% capsaicin.

Only one publication could be retrieved where a capsicum extract has been clinically investigated in this indication (Musharraf & Yaqub 2017). The cream, which has been tested in parallel with turpentine oil, was standardised to a content of 0.075% capsaicin. No details regarding the herbal preparation are published. The authors conclude that turpentine oil is as effective as the capsicum cream after 3 months of treatment. However, as no placebo group was part of the study design no conclusion on the magnitude of the clinical effect can be drawn.

Assessor's conclusion: No published clinical trial assessing the clinical efficacy of a herbal preparation standardised to a final content of 0.053% capsaicin could be found for this indication. From clinical trials it is known that the clinical effect is dose dependent (e.g. Kulkantrakorn et al. 2012). Therefore the required data to include this indication for concentrations which are not part of clinical trials are not publicly available. Consequently no change of the section 4.1 of the EU herbal monograph is considered possible. As already indicated in the footnote #3 of the EU herbal monograph and in chapter 2.1 of the assessment report applicants are advised to contact national agencies in order to address the need for equivalence data and the possibility of bridging clinical data.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other issues that could trigger a revision of the monograph

Not applicable.

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

Not applicable.

References

Kulkantrakorn K, Lorsuwansiri C, Meesawatsom P. 0.025% capsaicin gel for the treatment of painful diabetic neuropathy: a randomized, double-blind, crossover, plabeo-controlled trial. *Pain practice* 2012, 13(6):497-503

Musharraf & Yaqub 2017: Comparison of topical capsaicin and topical turpentine oil for treatment of painful diabetic neuropathy. *Journal of Ayub Medical College Abbottabad* 2017, 29(3):384-387

Paterno ER, Pangilinan CA, Arollado EC, Rosario RMB. A preliminary study on the safety, efficacy and acceptability of the community preparation of siling labuyo (capsicum frutescens) liniment in the management of knee osteoarthritis in a six-week, active-controlled community-based clinical trial. *Acta Medica Philippina* 2019, 53 (4):327-334

Yong YL , Tan LT-H, Ming LC, Chan K-G, Lee L-H, Goh B-H, *et al*. The effectiveness and safety of topical capsaicin in postherpetic neuralgia: A systematic review and meta-analysis. *Frontiers in Pharmacology* 2017, 7:538

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