12 May 2023
EMA/HMPC/883967/2022
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Vaccinium myrtillus* L., fructus recens and *Vaccinium myrtillus* L., fructus siccus

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HMPC decision on review of monographs *Vaccinium myrtillus* L., fructus recens and *Vaccinium myrtillus* L., fructus siccus adopted on 29 September 2015	26 January 2022
Call for scientific data (start and end date)	From 15 March 2022 to 14 June 2022
Discussion in Committee on Herbal Medicinal Products (HMPC)	March 2023 May 2023
Adoption by Committee on Herbal Medicinal Products (HMPC)	12 May 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: PubMed was searched on 2022-05-16; period covered: September 2013 - May 2022
- ☒ 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, 353 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 none could trigger revision of the 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

Non-clinical safety data

NTP performed genotoxicity tests on Salmonella typhimurium using a bilberry fruit extract (no further details). The extract was mutagenic in S. typhimurium strain TA98 when is tested with or without metabolic activation and was not mutagenic on strain TA100 (NTP, 2018).

NTP evaluated *in vivo* the effect of the same extract in the micronucleus test in B6C3F1 mice.

No increases in the frequencies of micronucleated erythrocytes were seen in peripheral blood of male B6C3F1/N mice in the 24-h study (NTP, 2018).

Assessor's comment:

The used extract is not completely characterised to be compared with the corresponding herbal preparation described in the EU herbal monographs on bilberry. Hence, this new data alone does not trigger a revision of the monograph.

Clinical efficacy data

There are some clinical trials conducted on bilberry extracts that investigated a possible beneficial effect on the ciliary muscle of the eye (Kosehira *et al.*, 2020) or may have clinically relevant beneficial effects following acute myocardial infarction (Arevstrom, 2019).

Assessor's comment:

No revision is considered required because medicinal products corresponding to the indications described in the above-mentioned clinical studies are not reported from the EU market. Therefore, the well-established use criteria are not considered fulfilled. Furthermore, the used extract is not completely characterised to be compared with the corresponding herbal preparation described in the EU herbal monographs on bilberry.

Clinical safety data

EudraVigilance was searched by the Pharmacovigilance Department of NAMDMR for adverse reactions on 15 June 2022, using the keywords "bilberry" and "*Vaccinum myrtillus*"; cases related with concomitant administration with other drugs were excluded.

One ICSR was found for the reference period, related with an off-label use of bilberry decoction (adverse reactions list: diarrhoea, abdominal and stomach pain). The causality between exposure to

bilberry and adverse reactions reported is considered "possible" in the descriptive part of ICSR. The ICSR mentioned that digestive problems and abdominal pain persisted after the drug was withdrawn.

Assessor's comment:

This limited data does not trigger a revision of the monograph.

New regulatory practice that could trigger a revision of the monograph

New herbal substances/preparations with 30/15 years of TU or 10 years of WEU

Not aplicable.

Updated Ph. Eur. monographs

Both monographs (*Vaccinum myrtillus* dried 07/2021:1588 and *Vaccinum myrtillus* recens 01/2019:1602) were updated in Ph.Eur edition 10. For the dried bilberry, the content in tannins was reduced from 1.0% to 0.8%, expressed as pyrogallol.

Assessor's comment:

No revision is considered required. Reference to the updated pharmacopoeia monographs should be adapted in the HMPC monograph and supporting documents when there is a need to revise the monograph.

Inconsistency that could trigger a revision of the monograph

Not aplicable.

Other issues that could trigger a revision of the monograph

Not aplicable.

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

Not aplicable.

References

Arevström L, Bergh C, Landberg R, Wu H, Rodriguez-Mateos A, Waldenborg M, *et al.* Freeze-dried bilberry (*Vaccinium myrtillus*) dietary supplement improves walking distance and lipids after myocardial infarction: an open-label randomized clinical trial. *Nutrition Research* 2019, Feb;62:13-22. doi: 10.1016/j.nutres.2018.11.008

European Pharmacopoeia 10th ed. Myrtilli fructus, recens. Council of Europe. 01/2019:1602

European Pharmacopoeia 10th ed. Myrtilli fructus, sicus. Council of Europe. 7/2021: 1588

Kosehira, M, Machida, N, Kitaichi, N. A 12-Week-Long Intake of Bilberry Extract (*Vaccinium myrtillus* L.) Improved Objective Findings of Ciliary Muscle Contraction of the Eye: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Comparison Trial. *Nutrients* 2020, *12(3)*, 600. doi: https://doi.org/10.3390/nu12030600

NTP. Bilberry fruit extract (84082-34-8). Chemical Effects in Biological Systems (CEBS). Research Triangle Park, NC (USA): National Toxicology Program (NTP). Accessed 2022-10-14. doi: https://doi.org/10.22427/NTP-DATA-DTXSID9030836

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