EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Arctostaphylos uva-ursi* (L.) Spreng., folium

Rapporteur(s)	W. Dymowski
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HMPC decision on review of monograph *Arctostaphylos uva-ursi* (L.) Spreng., folium adopted on 30 January 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)	July 2024 September 2024 November 2024 January 2025 March 2025
Adoption by HMPC	19 March 2025

Review of new data

Periodic review (from 2016 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 for terms "Arctostaphylos uva-ursi + toxic" and Uva ursi + toxic" in years 2016 – 2024. Google Scholar was searched for "Bearberry + leaf", "Uva ursi", in years 2016 – 2024.

☒ Pharmacovigilance databases

☒ data from EudraVigilance

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

☒ Other: Lactmed update 2021 (no impact)

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 28 new references were identified. Out of them 14 references were considered to be relevant for the monograph and 5 references that could trigger revision of the monograph.

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

Assessment of new data

During the review period a new traditional herbal medicinal product was registered via decentralised procedure in 2016-2017, which has already been included in the monograph.

Results of clinical trials in the uncomplicated urinary tract infections in woman were published in the review period what need the assessment and may potentially trigger the revision of the monograph.

New scientific data that could trigger a revision of the monograph

Data from Europe indicate 20 new adverse events, 12 on mono-component products and 8 for herbal combined products. Nausea, vomiting, stomach-ache were reported and these possible adverse drug reactions are already included in the monograph. The safety profile of *Arctostaphylos uva-ursi* (L.) Spreng., folium has not been changed.

New regulatory practice that could trigger a revision of the monograph

There were no new registered or authorised herbal preparations which were not included in the current EU herbal monograph.

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

The results of two new clinical trials are available, cited below among the references. The aim of first work was to test the hypothesis whether the use of uva ursi extract or ibuprofen are able to reduce the need of the use of any antibiotic when they are administered in the 2 to 4 days of the symptoms' onset for uncomplicated UTIs in woman.

The project ATAFUTI was based on a factorial group scheme trial, controlled, multicentre, double blinded, with similar fibre product as a placebo (with the same pharmaceutical form and colour). Protocol was published (Trill *et al*., 2017) and was based on the concept that the use of anti-inflammatory ibuprofen, administered during the first 2-4 days of the symptoms' onset can delay or substitute the need of use of antibiotics. The results of the trial are available from (Moore *et al.,* 2019). In the trial there were included 382 women of age 18-70, with symptoms of uncomplicated lower urinary tract infection (UTI) (dysuria, urgency or frequency of urination). There were 4 treating

groups: Uva-ursi extract and ibuprofen n=102), placebo Uva-ursi and ibuprofen (n=86), Uva-ursi extract and placebo ibuprofen (n=97), ibuprofen placebo and Uva-ursi placebo (97). Uva-ursi extract, containing 20% of arbutin in daily doses of 3600mg, divided in three single dose capsules, taken orally. Ibuprofen taken in daily dose 1200 mg. The patients were asked for filling the diaries about seven point severity symptoms (0=no problem to 6=as bad as it could be) with a records on the primary symptoms from day 2, 3 and 4. Secondary symptoms as unwell, symptom severity, duration of moderately bad or worse symptom and mean global severity score and as exploratory analysis were regarded microbiological confirmation of urinary tract infection. Of the 382 patients 369 completed the study but only 286 diaries were received from patients. In terms of symptom severity after 2-4 days, the authors found no evidence of differences between the use of Uva-ursi extract versus placebo. Although odds ratio suggested reduction in antibiotic use for Uva-ursi and ibuprofen group but the confidence interval for Uva-ursi was wide and the results did not reach statistical significance.

In the second double-blind, randomised, controlled, comparative trial (REGATTA) it was tested whether the use of Uva ursi extract, administered during the first 5 days of urinary infections may delay or limit the use of fosfomycin (Afshar *et al*., 2018). The herbal preparation failed in the "non-inferiority" scheme comparison with the use of only fosfomycin (Gayor *et al*., 2021).

References

Afshar K, Fleischmann N, Schmiemann G, Bleidorn J, Wegschneider K, Moore M, Gagyor I. Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi (REGATTA) – a double-blind, randomised, controlled comparative effectiveness trial. BMC Complementary and Alternative Medicine 2018, 18: 203

EU Clinical trial results: Alternative Treatments of Adult female Urinary Tract Infection: a double blind, placebo controlled, factorial randomised trial of Uva ursi and open pragmatic trial of ibuprofen. *EU Clinical Trials Register* 2018. EudraCT number: 2013-003327-11

Gagyor I, Hummers E, Schmiemann G, Friede T, Pfeiffer S, Afshar K, Bleidorn J. Herbal treatment with uva ursi extract versus fosfomycin in women with uncomplicated urinary tract infection in primary care: a randomized controlled trial. *Clinical Microbiology and Infection* 2021, 27: 1441-1447

Moore M, Trill J, Simpson C, Webley F, Radford M, Stanton L, Maishman T, Galanopoulou A, Flower A, Eyles C, Willcox M, Hay AD, van der Verf E, Gibbons S, Lewith G, Little P, Griffiths G. Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomised trial. *Clinical Microbiology and Infection* 2019, 25: 973-980

Trill J, Simpson C, Webley F, Radford M, Stanton L, Maishman T, Galanopoulou A, Flower A, Eyles C, Wollcox M, Hay A, Griffiths G, Little P, Lewith G, Moore M. Uva-ursi extract and ibuprofen as alternative treatments of adult female urinary tract infection (ATAFUTI): study protocol for a randomised controlled trial. *Trials* 2017, 18:421

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