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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Achillea millefolium* L., flos

Rapporteur(s)	B Tóth
Peer-reviewer	M Heroutova

HMPC decision on review of monograph *Achillea millefolium* L., flos adopted on 12 July 2011	29 September 2015
Call for scientific data (start and end date)	From15 December 2015 to 15 March 2016
Agreed by Working Party on European Union monographs and list (MLWP)	September 2018
Adoption by Committee on Herbal Medicinal Products (HMPC)	16 January 2019

Review of new data on *Achillea millefolium* L., flos

Periodic review (from 2011 to 2018)

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

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases): EudraVigilance was searched by the Pharmacovigilance Department of OGYÉI for adverse reactions on 11-09-2018, but no reports were found for the reference period.

☒ Scientific/Medical/Toxicological databases PubMed (Using the Mesh term "*Achillea millefolium*" from 2011 to present, Search date: 10 September 2018, 268 hits), Embase (Using the term "*Achillea millefolium*" from 2011 to present, Search date: 10 September 2018, 644 hits), Cochrane Database of Systematic Reviews (Using the term "*Achillea millefolium*" from 2011 to present, Search date: 10 September 2018, 15 hits).

☐ Other

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Regulatory practice

- ☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)
- ☒ New market overview (including pharmacovigilance actions taken in member states)
- ☐ Referral
- ☐ 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 (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change 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 likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change 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	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒

Summary and conclusions on the review

During the review 645 new references not yet available during the first/previous assessment were identified.

No reference was provided by Interested Parties during the Call for data.

Three references were considered to be relevant for the assessment.

No reference justifying a revision of the monograph has been found.

Some clinical studies performed with yarrow flower as a single component have been published since 2011.

A double-blind randomised clinical trial investigated the effect of adding *Achillea millefolium* distillate solution to routinely used mouthwash in the treatment of chemotherapy-induced oral mucositis (OM). To prepare 20 l of the distillate: 10 kg of yarrow plant flower was boiled with 50 l of water in a boiler connected to a condenser placed in cold water. Patients were randomly assigned into control and experimental groups (28 patients/group). Patients in the control group received the routine mouthwash while patients in the experimental group received a mixture of the routine mouthwash and *A. millefolium* distillate (50/50). Patients had to hold 15 ml of the solution for 3 minutes in their mouth gargle the solution and then discard it. The mean severity score of OM was 2.39±0.875 in both groups at start of the study that was changed to 1.07±0.85 and 0.32±0.54 in the intervention group in days 7 and 14 ($p<0.001$). However, the severity of OM was increased to 2.75±0.87 and 2.89±0.956 in the control group respectively ($p<0.001$) (Miranzadeh *et al*., 2015).

A double-blind, placebo-controlled randomized clinical trial evaluated the effectiveness of *A. millefolium* flowers on relief of primary dysmenorrhea in 96 students. The participants drank either three teacups of *A. millefolium* or placebo (starch) in morning, noon and night with each meal (a teabag in 300 mL of hot water per teacup) for 3 days in 2 menstruation cycles. Teabags were prepared with 4 g of *A. millefolium* powder. The mean reduction in pain score in the *A. millefolium* group was significantly greater than that in the placebo group after one ($p=0.001$) and two months of treatment ($p<0.0001$). None of the patients in this trial had any side effects after using *A. millefolium.* The main limitation of the present study was the small sample size of the study groups. In addition, the study was conducted in single adolescents and may not be generalised to females outside that age range (Jenabi and Fereidoony, 2015).

The possible effect of *A. millefolium* on plasma nitric oxide concentration was evaluated in 31 chronic kidney disease patients in a randomised controlled trial. Out of 31 patients, 16 patients received 1.5 g of powdered *A. millefolium* flower in capsules for three days a week for two months, while 15 received placebo for the same period. Plasma nitrite and nitrate concentrations decreased marginally in the intervention group. Adverse reaction of skin rashes was observed in one female subject who was excluded from the study (Vahid *et al*., 2012).

No revision is considered required because medicinal products corresponding to the preparations used in the above mentioned clinical studies are not available on the EU market. In one study (Jenabi and Fereidoony, 2015) the preparation used complies with preparation a) in the current EU herbal monograph, but the posology is significantly higher in comparison with the monograph or with the medicinal products on EU market. Therefore, the well-established use criteria are not fulfilled.

Adverse reaction mentioned in one of the studies is already included in the current monograph.

No other new data that would change of the content of the monograph have been found.

References

References relevant for the assessment:

Jenabi E, Fereidoony B. Effect of *Achillea Millefolium* on Relief of Primary Dysmenorrhea: A Double-Blind Randomized Clinical Trial. *J Pediatr Adolesc Gynecol* 2015, 28:402-404

Miranzadeh S, Adib-Hajbaghery M, Soleymanpoor L, Ehsani M. Effect of adding the herb *Achillea millefolium* on mouthwash on chemotherapy induced oral mucositis in cancer patients: A double-blind randomised controlled trial. *Eur J Oncol Nurs* 2015, 19:207-213

Vahid S, Dashti-Khavidaki S, Ahmadi F, Amini M, Salehi Surmaghi MH. Effect of herbal medicine *Achillea millefolium* on plasma nitrite and nitrate levels in patients with chronic kidney disease: a preliminary study. *Iran J Kidney Dis* 2012, 6:350-354

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

☒ 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

HMPC agreed with Rapporteurs position that no monograph revision is needed because no new data of relevance were detected that would change the content of the monograph.

The HMPC decided by consensus not to revise the monograph, assessment report and list of references on Millefolii flos.