15 March 2023
EMA/HMPC/709373/2022
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Helichrysum arenarium* (L.) Moench, flos

Rapporteur(s)	W. Dymowski
Peer-reviewer(s)	H. Kuin

HMPC decision on review of monograph *Helichrysum arenarium* (L.) Moench, flos adopted on 05 April 2016	26 January 2022
Call for scientific data (start and end date)	15 February 2022 to 14 May 2022
Adoption by Committee on Herbal Medicinal Products (HMPC)	15 March 2023

Review of new data on *Helichrysum arenarium* (L.) Moench, flos

Periodic review (from 2015 to 2022)

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

☒ Scientific/Medical/Toxicological databases

BMJ Online, DOAJ, EBSCOhost, J-Stage, JSTOR, Karger, Nature, NEJM, Ovid, ProQuest, Springer Link, Taylor and Francis Online, Thieme Connect, and Wiley Online Library, which were searched in the last decade. PubMed was searched in the period 2014-2022. Google Scholar with the priority of relevance, without limits, was used as a confirmatory tool. Key words: "*Helichrysum* + *arenarium*", "Sandy + everlasting".

☒ Pharmacovigilance databases

☒ data from EudraVigilance

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

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: No monograph for Helichrysi flos is in the European Pharmacopoeia. The monograph for Helichrysi flos (Kwiat kocanek) is included in last national editions of Polish Pharmacopoeia Ed. XI 2017 and XII 2020.

☐ Other: No referrals, no new data supplied by the interested parties

Consistency (e.g. scientific decisions taken by HMPC)

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

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

The library of Warsaw Medical University's search browser Primo with resources: BMJ, Cochrane Library, EBSCOhost, Medline Complete, Oxford University Press, Polska Bibliografia Lekarska, PubMed,

Reaxys, ScienceDirect, SciFinder, Scopus, Springer, Taylor & Francis Online, WebofScience, Wiley Online Library; searched years 2016-2022. Searched terms: "*Helichrysum* + *arenarium*", "sandy + everlasting".

During the review 394 references were identified, out of these 64 were possibly influencing the assessment report in regards to quality, safety and efficacy. Also 23 references were identified to be possibly relevant for the monograph but were not yet available during the first/previous assessment (10 phytochemical, 4 antimicrobial, 4 on protective effects on vessels and antidiabetic, 2 on antioxidative effects). Two publications were on the use effect of the sandy everlasting infusion by subjects with metabolic syndrome. The 11 references which are referred below may influence the future assessment of Helichrysi flos. None of the references could trigger the revision of the monograph.

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

Assessment of new data

Kenig S *et al.* (2022) a parallel two arm observational study towards the effect of drinking 200 ml herbal infusions of *Helichrysum arenarium* (L.) Moench (n=14) or *Helichrysum italicum* (Roth) G. Don (n=13) once daily during 28 days on several health parameters in subjects with metabolic syndrome. Metabolic syndrome was diagnosed when at least 3 out of the 5 following criteria were present: larger waistline, elevated blood pressure, raised triglyceride levels, reduced HDL-cholesterol and raised fasting glycaemia. Patients with type-II diabetes were excluded. Consumption of *Helichrysum arenarium* infusion was correlated with a significant reduction of body weight, BMI, serum glucose levels, improvement in the serum lipid and cholesterol profile. This was explained by the authors as an effect of choleretic activity of the infusion.

Petelin *et al.* (2022) published observational results regarding the regular use of herbal tea infusion (sachets 1g) with *Helichrysum arenarium* or *H. italicum* (part of plant not mentioned, herb or inflorescence) in a group of 30 patients with metabolic syndrome (see above). The infusion was administered once a day for 4 weeks. Patients were randomised between both species of teas. For the patients with metabolic syndrome, when consuming the herbal teas the authors observed: reduction of serum levels of proinflammatory markers; intestinal environement improvement similar to prebiotics and a positive impact on microbial dysbiosis with a trend for Protobacteria reduction.

Assessor's comment:

In both publications similar aspects of the same dietetic observation were presented. The authors did not define the herbal substances observed. The observation was not controlled, not even compared to the pre-observation state. The observed groups were small. The possible symptoms were not presented qualitatively in a form of diagram confirming the observation. There is no reason to influence the monograph for Helichrysi flos.

New scientific data that could trigger a revision of the monograph

Not applicable.

New regulatory practice that could trigger a revision of the monograph

Not applicable.

No new herbal substances/preparations with 30/15 years of TU or 10 years of WEU were reported for the review period in the EU countries.

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

Review articles

Plevljakušić D *et al*. 2018 reviewed data on chemical and biological properties of *Helichrysum arenarium* (L.) Moench, flos.

Antimicrobial activity

Babota M *et al*. 2018 tested the antimicrobial activity of methanol, ethanol and ethanol 70% (V/V) extracts of 1 g of powdered Helichrysi flos. *E. coli* (ATCC 25922) was found susceptible to the methanol and ethanol extracts and *S. aureus* (ATCC 49444) to all extracts, with a minimum inhibitory concentration (MIC) of 7.81 mg/mL and a minimum bactericidal concentrations (MBC) of 15.62 mg/mL (for comparison streptomycin, a well-known antibiotic, has a MIC value for *E. coli* of 0.24 mg/mL and for S. aureus of 0.06 mg/mL). Among tested fungi, *Penicillium fumiculosum* was found susceptible to ethanol and ethanol 70% extracts, with respective MIC/MBC values of 7.81/15.62 mg/mL (for comparison fluconazole, a well-known fungicide, has MIC/BIC values of 0.15/0.3 mg/mL).

Kutluk I *et al*. (2018) tested the activity of water and ethanol extracts of *Helichrysum* sp. flower against Gram negative bacteria (*E. coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*), Gram positive bacteria (*S. aureus*, *E. faecalis*), fungi (*C. albicans*, *C. parapsilosis*) and human viruses HSV-1 (DNA virus), parainfluenza-3 virus (PI-3, RNA virus) by making use of the microdilution method. The authors observed activity of the extract against Gram positive bacteria (e.g. *S. aureus* MIC of 8 mg/mL) and antiviral activity against HSV-1 and PI-3 viruses (at levels of 2-32 and 4-64 mg/mL).

Akin and Saki (2019) tested antimicrobial activity of an ethanol extract of *Helichrysum arenarium* (not specified whether the whole herb or flower and 100 g of herbal substance was first defatted with 500 ml of hexane), dried and extracted with 300 ml of ethanol, dissolved in ethanol and diluted before tests on *E. coli* (ATCC 25922) and *S. aureus* (ATCC 25923). The extract was active only on *S. aureus* strain.

Non-clinical tests

Mao Z *et al*. (2017) tested flavonoids of *H. arenarium* flowers (narirutin, naringin, eriodictyol, luteolin, galuteolin, astragalin, kaempferol) on thoracic aorta rings (a model for atherosclerosis). Morphological changes of the blood vessels, proliferation of the vascular smooth muscle cells (VSMC) and the endothelium cells were observed. The expression of inflammatory biomarker CRP and the activity of JNK2 and p38 were inhibited. Flavonole aglycones had more significant anti-inflammatory effect than their glycosides; flavonoles more than flavanones and flavones.

Morikawa T *et al*. (2017) analysed methanol extract of Helichrysi flos for its inhibition of blood glucose elevation in sucrose loaded mice at 500 mg/kg oral dose. The methanol extract inhibited dipeptyl peptidase-IV (DPP-IV, with IC_{50} = 41.2 µg/mL) but was not active against intestinal α-glucosidase. Other constituents of the extract with DPP-IV inhibitory activity were chalconaringenin-2'-O-β-D-glucopyranoside and aureusidin-6-O-β-D-glucopyranoside (with IC_{50} = 23.1 and 24.3 µg/mL respectively).

Park JY *et al*. (2022) observed that *Helichrysum arenarium* extract (no further details given) and apigenin and galangin (flavonoids from its herb and flower) alleviated keratinocytes damage caused by blue light on skin HaCaT cells model.

Judzentiene A *et al*. (2022) tested possible toxicity for water organisms of essential oil distilled from dried *H. arenarium*, inflorescences and leaves and by its methanol-water extract, with the use of the brine shrimp (Artemia salina) test. The LC_{50} of the essential oil obtained from the inflorescence of H. arenarium was 23.42 µg/mL; LD_{95} 83.82 µg/mL.

Liu H and Lan W (2022) tested the influence of *Helichrysum arenarium flavonoid extract* (6.25, 12.5, 25 µg/mL and control group) on a high-glucose cardiomyocyte injury model and in Sprague Dawley rats.

The *Helichrysum arenarium flavonoid extract* reduced the degree of damage of cells induced by high glucose and decreased the cellular inflammatory response. In the animal experiments the extract reduced the histopathological damage of myocardium in diabetic rats, decreased the inflammatory response in the tissue, and protected the myocardium.

References

Akin M, Saki N. Antimicrobial, DPPH scavenging and tyrosinase inhibitory activities of Thymus vulgaris, Helichrysum arenarium and Rosa damascena Mill. ethanol extracts by using TLC bioautography and chemical screening methods. *Journal of Liquid Chromatography & Related Technologies* 2019; 42(7-8): 204–216 https://doi.org/10.1080/10826076.2019.1591977

Babota M, Mocan A, Vlase L, Crişan O, Ielciu I, Gheldiu A-M, *et al*. Phytochemical Analysis, Antioxidant and Antimicrobial Activities of *Helichrysum arenarium* (L.) Moench. and Antennaria dioica (L.) Gaertn. flowers. *Molecules* 2018, 23, 409; doi:10.3390/ molecules23020409

Judzentiene A, Budiene J, Nedveckyte I, Garjonyte R. Antioxidant and toxic activity of Helichrysum arenarium (L.) Moench and Helichrysum italicum (Roth) G. Don essential oils and extracts. *Molecules* 2022; 27:1311. https://doi.org/10.3390/molecules27041311

Kenig S, Kramberger K, Novak KŠ, Karnjuš I, Bandelj D, Petelin A, *et al*. Helichrysum italicum (Roth) G. Don and Helichrysum arenarium (L.) Moench infusions in reversing the traits of metabolic syndrome: a double-blind randomized comparative trial. *Food & Function,* Open Access Article. Published on 24 June 2022, DOI:10.1039/d2fo00880g

Kutluk I, Aslan M, Orhan IE, Özçelik B. Antibacterial, antifungal and antiviral bioactivities of selected Helichrysum species. *South African Journal of Botany* 2018; Vol. 119:252-257

Liu H, Lan W. Alleviation of myocardial inflammation in diabetic rats by flavonoid extract of Helichrysum arenarium and its effect on damaged myocardial cells induced by high glucose. *Frontiers in Surgery* 2022; Vol. 9, Art. 873010

Mao Z, Gan C, Zhu J, Maa N, Wua L, Wang L, *et al*. Anti-atherosclerotic activities of flavonoids from the flowers of Helichrysum arenarium (L.) Moench through the pathway of anti-inflammation. *Bioorganic & Medicinal Chemistry Letters* 2017; 27:2812–2817

Morikawa T, Ninomiya K, Akaki J, Kakihara N, Kuramoto H, Matsumoto Y, *et al*. Dipeptidyl peptidase-IV inhibitory activity of dimeric dihydrochalcone glycosides from flowers of *H*elichrysum arenarium. *J Nat Med* 2015; 69:494–506

Park JY, Park SH, Oh SW, Kwon K, Yu E, Choi S, *et al.* Yellow chaste weed and its components, apigenin and galangin, affect proliferation and oxidative stress in blue light-irradiated HaCaT cells. *Nutrients* 2022, 14, 1217. https://doi.org/10.3390/nu14061217

Petelin A, Novak KŠ, Hladnik M, Bandelj D, Arbeiter AB, Kramberger K, *et al*. Helichrysum italicum (Roth) G. Don and Helichrysum arenarium (L.) Moench infusion consumption affects the inflammatory status and the composition of human gut microbiota in patients with traits of metabolic syndrome: a randomized comparative study. *Foods* 2022, 11, 3277. https://doi.org/10.3390/foods11203277

Plevljakušić D, Bigović D, Janković T, Jelačić S, Šavikin K. Sandy everlasting (*Helichrysum arenarium* (L.) Moench): Botanical, chemical and biological properties. *Front. Plant Sci.* 9:1123. doi:10.3389/fpls.2018.01123

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

The HMPC agreed not to revise the monograph, assessment report and list of references on *Helichrysum arenarium* (L.) Moench, flos, by consensus.