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Committee on Herbal Medicinal Products (HMPC)

## Addendum to Assessment report on *Chamaemelum nobile* (L.) All. (*Anthemis nobilis* L.), flos

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HMPC decision on review of monograph <i>Chamaemelum nobile</i> (L.) All. ( <i>Anthemis nobilis</i> L.), flos adopted on 22 November 2011	22 November 2011
Call for scientific data (start and end date)	From 01/02/2020 to 30/04/2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	18 November 2020

### Review of new data on *Chamaemelum nobile* (L.) All. (*Anthemis nobilis* L.), flos

#### Periodic review (from 2010 to 2020)

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

- Pharmacovigilance data (e.g. data from [EudraVigilance](#), VigiBase, national databases)
- Scientific/Medical/Toxicological databases (Web of Knowledge, PubMed, SciFinder)
- Other

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

Other

**Availability of new information (i.e. likely to lead to a relevant change of the monograph)**

<i>Scientific data</i>	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical safety data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New data introducing a possibility of a new list entry	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical studies introducing a possibility for new WEU indication/preparation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other scientific data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Regulatory practice</i>	Yes	No
New herbal substances/preparations with 30/15 years of TU	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New herbal substances/preparations with 10 years of WEU	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other regulatory practices likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Referrals likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Consistency</i>	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other relevant inconsistencies that require a change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>

## Summary and conclusions on the review

During the review 200 new references not yet available during the first/previous assessment were identified.

0 references were provided by Interested Parties during the Call for data.

38 references were considered to be relevant for the assessment.

0 references justify a revision of the monograph.

No revision is considered required because neither the references published since the previous assessment nor other data (e.g. pharmacovigilance data, data from the market overview) justify the revision of the monograph.

No data were submitted during the call for scientific data period.

According to the feedback of 11 member countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Germany, Hungary, Ireland, Latvia, Slovakia, Sweden), there are no medicinal products on the market containing *Chamaemelum nobile* (L.) All. (*Anthemis nobilis* L.), flos.

The literature search in 3 major scientific databases (PubMed, SciFinder and Web of Knowledge) resulted in 200 references in the period 2010-2020 for the search terms »*anthemis nobilis*« or »*chamaemelum nobile*«. During literature search, no filter was used for the language of publication etc. The original set of references was then analysed for articles containing data that may justify the revision of the assessment report or the monograph. 31 references contained relevant data, the majority of these reported studies on the antibacterial and antifungal effects (Al-Marby *et al.*, 2016; Choi *et al.*, 2010; De Mieri *et al.*, 2017; Ebani *et al.*, 2017; Ghaedi *et al.*, 2015; Kazemian *et al.*, 2018, 2015; Tadrent *et al.*, 2016), chemical composition (Al-Otaibi *et al.*, 2020; Aremu *et al.*, 2018; De Mieri *et al.*, 2017; Farhoudi, 2013; Farhoudi and Lee, 2017; Guimarães *et al.*, 2013; Rustaiyan *et al.*, 2011; Sándor *et al.*, 2018; Zhao *et al.*, 2014) or antioxidant capacity (Choi *et al.*, 2010; Farhoudi, 2013; Farhoudi and Lee, 2017; Sharifzadeh *et al.*, 2016) of Roman chamomile essential oils or extracts. 2 animal experiments were carried out to study central nervous system effects (Dooraghi *et al.*, 2010; Hashikawa-Hobara *et al.*, 2019), whereas one paper reported the effects on smooth muscles (Sándor *et al.*, 2018).

Two papers reported the effects observed in clinical trials (Lopez Jornet & Aznar-Cayuela 2016; Tvarijonaviciute *et al.*, 2018). Lopez *et al.* (2016) carried out a double-blind study, randomized clinical trial involving 60 patients to compare the clinical efficacy of topically applied Roman chamomile gel vs. a placebo in the treatment of oral lichen planus (OLP). A visual analogue scale was used to rate pain, itching and burning sensation, and Thongprasom Index, the Oral Health Impact Profile 14 (OHIP-14) and the Hospital Anxiety-Depression Scale. Patients were evaluated at baseline and after 4 weeks of treatment. Patients treated with chamomile showed significant improvements after 4 weeks for pain ( $p < 0.001$ ), burning sensation ( $P < 0.001$ ), itching ( $P = 0.011$ ), OHIP-14 ( $< 0.001$ ) and Thongprasom index ( $p = 0.001$ ); 92% of patients treated with chamomile showed a partial or total response, while only five subjects (17%) in the placebo group showed any improvement. Although this study supports the efficacy of the Roman chamomile-containing gel in OLP, this trial cannot be used as a proof of efficacy, since the composition of the study product is insufficiently characterized. According to the

article, »the product assayed was 2% *Chamaemelum nobile*, with a gel consistency supplied in 500 ml containers, as was the placebo. Both products consisted of the same excipients and composition – water, hydroxyethyl, sorbitol <0.1%, E - 202 (potassium sorbate) <0.1%, E - 223 (sodium metabisulfite) <0.1%, food colouring <0.1%, Chamomile aroma <0.1% (Ababbo, Murcia, Spain) – except that the experimental gel included 2% chamomile and the placebo did not.” It is not clear whether the study products contained essential oil or extract, no data on extracting solvent, DER are available. The other randomized, double blind clinical trial (Tvarijonaviciute *et al.*, 2018) does not report clinical outcomes as endpoints. The reported endpoint (salivary total antioxidant status) might be related to the clinical picture or the severity of the disease but cannot be considered as basis for therapeutic indications. Overall, the available new data are not sufficient to revise the monograph of *Chamaemelum nobile* (L.) All. (*Anthemis nobilis* L.), flos.

The safety of Roman chamomile was assessed based on the adverse events registered in EUGRAVigilance. Altogether 15 reports contained data related to chamomile use. 9 of these were related to the use of *Matricaria chamomilla*-containing preparations (Kamillosan and Kamillan Supra). 5 reports contained data related to the use of chamomile (not further specified) - based products with concomitant application of other (plant - based or synthetic) preparations. These reports cannot be used to assess the safety of Roman chamomile. There is only one report on an adverse event (rash) related to the use of a chamomile mono-preparation, however, the exact botanical identity of the plant cannot be determined based on the data found in this report. Overall, the data from the EUGRAVigilance database do not raise any substantial concern about the safety of Roman chamomile.

## References

a) References relevant for the assessment:

Al-Marby A, Ejike CECC, Nasim MJ, Awadh-Ali NA, Al-Badani RA, Alghamdi GMA *et al.* Nematicidal and antimicrobial activities of methanol extracts of 17 plants, of importance in ethnopharmacology, obtained from the Arabian Peninsula. *J. Intercult. Ethnopharmacol* 2016, 5: 114–121. Available at: <https://doi.org/10.5455/jice.20160217040157>

Al-Otaibi WA, Alkhatib MH, Wali AN. Protective role of nanoemulsion containing roman chamomile oil against mitomycin C-induced toxicity in Ehrlich ascites carcinoma bearing mice. *Indian J. Biochem. Biophys* 2020, 57: 33–44

Aremu OO, Tata CM, Sewani-Rusike CR, Oyedeji AO, Oyedeji OO, Nkeh-Chungag BN. Phytochemical composition, and analgesic and anti-inflammatory properties of essential oil of *Chamaemelum nobile* (Asteraceae L All) in rodents. *Trop. J. Pharm. Res* 2018, 17: 1939–1945. Available at: <https://doi.org/10.4314/tjpr.v17i10.7>

Choi IY, Song YJ, Lee WH. DPPH Radical Scavenging Effect and Antimicrobial Activities of Some Herbal Extracts. *KOREAN J. Hort. Sci. Technol* 2010, 28: 871–876

De Mieri M, Monteleone G, Ismajili I, Kaiser M, Hamburger M. Antiprotozoal Activity-Based Profiling of a Dichloromethane Extract from *Anthemis nobilis* Flowers. *J. Nat. Prod* 2017, 80: 459–470. Available at: <https://doi.org/10.1021/acs.jnatprod.6b00980>

Dooraghi M, Solati J, Shahsavari B. Anxiolytic-Like Effects of Chamaemelum Nobile 1. Ethanolic Extract in Male Wistar Rats. *Am. J. Addict* 2010, 19: 380

Ebani VV, Nardoni S, Bertelloni F, Najjar B, Pistelli L, Mancianti F. Antibacterial and Antifungal Activity of Essential Oils against Pathogens Responsible for Otitis Externa in Dogs and Cats. Med. Basel, Switzerland 2017, 4. Available at: <https://doi.org/10.3390/medicines4020021>

Farhoudi R. Chemical Constituents and Antioxidant Properties of Matricaria recutita and Chamaemelum nobile Essential Oil Growing Wild in the South West of Iran. *J. Essent. Oil Bear. Plants* 2013, 16: 531–537. Available at: <https://doi.org/10.1080/0972060X.2013.813219>

Farhoudi R, Lee DJ. Chemical constituents and antioxidant properties of Matricaria recutita and Chamaemelum nobile essential oil growing in south west of Iran. *Free Radic. Biol. Med.* 2017, 108: S24. Available at: <https://doi.org/10.1016/j.freeradbiomed.2017.04.106>

Ghaedi M, Naghiha R, Jannesar R, Dehghanian N, Mirtamizdoust B, Pezeshkpour V. Antibacterial and antifungal activity of flower extracts of Urtica dioica, Chamaemelum nobile and Salvia officinalis: Effects of Zn<sub>2</sub>[OH]<sub>2</sub> nanoparticles and Hp-2-minh on their property. *J. Ind. Eng. Chem.* 2015, 32: 353–359. Available at: <https://doi.org/10.1016/j.jiec.2015.09.007>

Guimarães R, Barros L, Dueñas M, Calhelha RC, Carvalho AM, Santos-Buelga C *et al.* Nutrients, phytochemicals and bioactivity of wild Roman chamomile: A comparison between the herb and its preparations. *FOOD Chem.* 2013, 136: 718–725. Available at: <https://doi.org/10.1016/j.foodchem.2012.08.025>

Hashikawa-Hobara N, Otsuka A, Ishikawa R, Hashikawa N. Roman chamomile inhalation combined with clomipramine treatment improves treatment-resistant depression-like behavior in mice. *Biomed. Pharmacother* 2019, 118: 109263. Available at: <https://doi.org/10.1016/j.biopha.2019.109263>

Kazemian H, Ghafourian S, Heidari H, Amiri P, Yamchi JK, Shavalipour A *et al.* Antibacterial, anti-swarming and anti-biofilm formation activities of Chamaemelum nobile against Pseudomonas aeruginosa. *Rev. Soc. Bras. Med. Trop.* 2015, 48: 432–436. Available at: <https://doi.org/10.1590/0037-8682-0065-2015>

Kazemian H, Ghafourian S, Sadeghifard N, Houshmandfar R, Badakhsh B, Taji A *et al.* 2018. *In vivo* Antibacterial and Wound Healing Activities of Roman Chamomile (Chamaemelum nobile). *Infect. Disord. Drug Targets* 2018, 18: 41–45. Available at: <https://doi.org/10.2174/1871526516666161230123133>

Lopez Jornet P, Aznar-Cayuela C. Efficacy of topical chamomile management vs. placebo in patients with oral lichen planus: a randomized double-blind study. *J. Eur. Acad. DERMATOLOGY Venereol* 2016, 30: 1783–1786. Available at: <https://doi.org/10.1111/jdv.13770>

Rustaiyan A, Masoudi S, Ezatpour L, Danaii E, Taherkhani M, Aghajani Z. Composition of the Essential Oils of Anthemis Hyalina DC., Achillea Nobilis L. and Cichorium intybus L. Three Asteraceae Herbs Growing Wild in Iran. *J. Essent. Oil Bear. Plants* 2011, 14: 472–480. Available at: <https://doi.org/10.1080/0972060X.2011.10643603>

Sándor Z, Mottaghipisheh J, Veres K, Hohmann J, Bencsik TT, Horváth A *et al.* Evidence Supports Tradition: The *in vitro* Effects of Roman Chamomile on Smooth Muscles. *Front. Pharmacol.* 2018, 9. Available at: <https://doi.org/10.3389/fphar.2018.00323>

Sharifzadeh A, Javan AJ, Shokri H, Abbaszadeh S, Keykhosravy K. Evaluation of antioxidant and antifungal properties of the traditional plants against foodborne fungal pathogens. *J. Mycol. Med.* 2016, 26: e11-7. Available at: <https://doi.org/10.1016/j.mycmed.2015.11.002>

Tadrent W, Bachari K, Kabouche Z. Comparative compositions and antibacterial activity of the essential oils of *Anthemis nobilis* L. And *Anthemis mixta* L. (Asteraceae). *Int. J. Pharm. Pharm. Sci.* 2016, 8: 457–459

Tvarijonaviciute A, Aznar-Cayueta C, Rubio CP, Tecles F, Ceron JJ, Lopez-Jornet P. Salivary Antioxidant Status in Patients with Oral Lichen Planus: Correlation with Clinical Signs and Evolution during Treatment with *Chamaemelum nobile*. *Biomed Res. Int.* 2018. Available at: <https://doi.org/10.1155/2018/5187549>

Zhao J, Khan SI, Wang M, Vasquez Y, Yang MH, Avula B *et al.* Octulosonic Acid Derivatives from Roman Chamomile (*Chamaemelum nobile*) with Activities against Inflammation and Metabolic Disorder. *J. Nat. Prod* 2014, 77: 509–515. Available at: <https://doi.org/10.1021/np400780n>

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

The HMPC agreed not to revise the monograph, assessment report and list of references on *Chamaemelum nobile* (L.) All. (*Anthemis nobilis* L.), flos, by consensus.