EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Agrimonia eupatoria* L., herba

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HMPC decision on review of monograph *Agrimonia eupatoria* L., herba adopted on 28 January 2015	26 January 2022
Call for scientific data (start and end date)	From 15 February 2022 to 14 May 2022
Discussion in Committee on Herbal Medicinal Products (HMPC)	July 2022 September 2022 November 2022
Adoption by Committee on Herbal Medicinal Products (HMPC)	23 November 2022

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

BMJ Online, DOAJ, EBSCOhost, J-Stage, JSTOR, Karger, Nature, NEJM, Ovid, ProQuest, PubMed Central, Springer Link, Taylor and Francis Online, Thieme Connect, Wiley Online Library. Key words: *Agrimonia eupatoria* L., Agrimony. Access from the library of the Warsaw Medical University for the last 10 years (2012-2022), publications searched without additional filters. Search was controlled by the Google Scholar machine, with Google priority of relevance (AI), years 2013-2022, using the same key words, and the only filter was reviewed publications. In the key publications key references were checked.

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☒ Pharmacovigilance databases

☒ data from EudraVigilance

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

☐ Other

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: Inconsistency between a definition in Agrimony monograph of European Pharmacopoeia and available data on *Agrimonia eupatoria* L., herba. See below.

☒ 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, 118 new references not yet available during the first/previous assessment were identified. Out of these new references, one reference was considered to be relevant for the monograph and none of the references 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

New data on genotoxicity of Agrimoniae herba preparation

In the review period it was published an article by Pukalskienė *et al.* (2018) with new data on genotoxicity of methanolic extracts of *Agrimonia eupatoria* L. and *A. procera* herbs (as above ground parts). The extracts of both species dried herbs, collected in a flowering state from botanical garden in Kaunas, were prepared with 20 g of the herbal substance in 400 mL of methanol, with shaking over 24 h, filtration and condensation in a rotary evaporator in 40°C. The UPLC/DAD with detector in 280nm showed the main components of the *A. eupatoria* extract as rutoside, hyperoside, luteolin-7-O-glucoside and apigenin–O-hexoside. The authors conducted 3 tests for possible genotoxicity of the extract. The alkaline comet assay, a high sensitivity test detecting single, double–strand breaks and alkali-labile sites, was positive. Treatment with the methanol extract under the alkaline conditions caused an increase of T-DNA %. In further steps the authors used two standard tests used for the mutagenicity assessment. Ames test on *S. typhimurium* TA 98 for detection of frameshift mutations and on *S. typhimurium* TA100 for base pair–substitution mutations, both in the presence and absence of *in vitro* metabolic activation (Aroclor-1254). The test showed no increase count of revertant colonies over a normal range. Cytokinesis block micronucleus assay was conducted on lymphocyte cultures of blood samples taken from healthy donors. Treatment with the extract started 24 h after a culture initiation and lasted 48 h. Untreated culture serve as blank control, doxorubicine was positive control. The presence of micronuclei was evaluated by scoring of total 1000 cytochalasin B blocked binucleated cells per concentration. *Agrimonia eupatoria* methanolic extract did not cause an increase in the observed micronucleated cytokinesis-blocked lymphocytes (MNCB). The authors concluded that there is no evidence for genotoxicity on a base of the conducted *in vitro* tests, although for conclusive results animal tests should have been conducted, for further studies.

The data on mutagenicity were incomplete, not in accordance with current guidelines and did not cover the preparations in the EU herbal monograph.

New regulatory practice that could trigger a revision of the monograph

During the review procedure, no new authorised/registered herbal medicinal products containing Agrimoniae herba were identified in the European Union countries. There are no new authorised/ registered herbal medicinal products in the European Union countries influencing the content of the monograph on Agrimoniae herba, what could trigger a revision of the monograph.

Inconsistency that could trigger a revision of the monograph

The monograph 01/2011:1587 for Agrimony in the European Pharmacopoeia have been introduced in 2011; but it describes only a part of Agrimoniae herba: dried flowering tops, with the content not less than 2.0% of tannins expressed as pyrogallol. In traditional use, the whole Agrimoniae herba defined as above ground parts is still used (see first version of the assessment report).

For the moment, the inconsistency between the EU herbal monograph and the Ph. Eur. monograph does not trigger a revision of the EU herbal monograph on Agrimoniae herba.

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

Non clinical data – primary pharmacodynamics

Muruzovic *et al*. (2016) tested antimicrobial activity of *Agrimonia eupatoria* L., herba extracts with diethyl ether, acetone, ethanol and water. Among the tested extracts, the activity against Gram+ bacteria, especially on probiotic species, using acetone extract. The extract also contained maximum concentration of flavonoids, total phenols and procyanidins. The authors reported that the acetone extract demonstrated moderate activity in reducing biofilm (biofilm coverage reduced by 50% was 4.3 mg/mL for *P. mirabilis* and 4.5 mg/mL for *P. aeruginosa*).

Nicu *et al*. (2017) tested 70% ethanol extract of *Agrimonia eupatoria* L., herba, for antimicrobial activity against standard Gram+ and Gram– bacteria. Weak activity was found against G+ *S. aureus* ATCC 6538 and *S. epidermidis* ATCC 12228 MIC 625 µg/mL, and for Gram– *E. coli* ATCC 8739 MIC 1250 µg/mL and *P. aeruginosa* MIC 312.5 µg/mL.

Kincses *et al.* (2017) testing herbal teas prepared as infusion of 2g of herbal substance in 200 mL of water, observed with agrimony herb infusion an inhibitory zone 12mM in *B. cereus* culture.

Cardoso *et al.* (2018) tested 45% ethanol extract of *Agrimonia eupatoria* L., herba against 12 native *H. pylori* strains isolated from patients. The authors report that the highest concentration of the extract (75 and 50 mg/mL) presented activity on all isolated strains, independent of susceptibility to antibiotics or virulence genotype (5 mg/mL had no activity).

Komiazyk *et al* (2019) tested influence of agrimony infusion on cholera colonies and cholera toxin *in vitro*. The authors reported that the infusion displayed only modest bacteriostatic potential although observed it may modulate the effects of cholera toxin on intracellular cAMP levels what may suppress the binding of subunit B of cholera toxin to the cell surface.

Santos *et al*. (2017) tested anti-inflammatory potential of infusion, prepared with 20 g powdered Agrimoniae herba in 600 mL of water and its ethyl acetate fraction. The infusion was defatted with n-hexane, vacuum concentrated (30°C) and freeze dried (second part of the infusion was extracted EtOAc and chromatographed; HPLC-DOA-ESI/MS, 280nm). The condensated infusion fraction and EtOAc fraction were tested on carrageenan–induced rat paw edema with positive control of diclofenac sodium (10 mg.kg), for central analgesic activity, peripheral analgesic activity and antioxidant activity. The authors reported that the infusion and EtOAc fraction reduced edema by 43 and 52% (in formalin test) and in peripheral analgesic test reduced abdominal writhing by 50% (diclophenac 73%).

Tsirigotis-Maniecka *et al.* (2019) isolated from agrimony herb an polyphenolic-polysaccharide complex inhibiting blood coagulation cascade (indirect thrombin inhibitor).

Non-clinical data – secondary pharmacodynamics

Kuczmannova *et al.* (2016) studied possible antidiabetic effects of agrimony herb infusion administered to rats over a five week period. Although the direct glucose lowering effect was not found the authors observed protective effects of the treatment on relaxation ability of rats aorta. The observation was confirmed by Malheiros *et al.* (2022) suggesting isoquercitrin from agrimony extract to play a role in vasorelaxant activity in human aortas. Kubinova (2016) indicated remarkable inhibition of cholinesterases AChE and BuChE by the *A. eupatoria* extract but it was not closer characterised.

Clinical data

Ivanova *et al.* (2013) observed effects of supplementation of diet in 19 healthy volunteers (18-55 years old) with use of 200 mL of infusion of 1 g of Agrimoniae herba, 2 times daily for one month, on the metabolic markers level. Over the period significant increase of HDL cholesterol and increase of total cholesterol was observed. Plasma triglycerides and glucose level remained within reference values. LDL cholesterol and HDL/LDL ratio indicated not statistically significant change. Over 30 days tea consumption it was observed a decrease of IL-6 concentration with no change of C-reactive proteins. Serum TNFα levels changed from 8 pg/mL to below detection limit. The observation was not designed as a clinical trial. There was no control for the 30 days observation.

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References that could be relevant for the next review

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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