6 May 2020
EMA/HMPC/595722/2019
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Filipendula ulmaria* (L.) Maxim. (= *Spiraea ulmaria* L.), herba

Rapporteur(s)	B Kroes
Assessor(s)	Jan van der Nat
Peer-reviewer	J Wiesner

HMPC decision on review of monograph *Filipendula ulmaria* (L.) Maxim. (= *Spiraea ulmaria* L.), herba adopted on July 2011	30 January 2018
Call for scientific data (start and end date)	From 30 April 2018 to 31 July 2018
Adoption by Committee on Herbal Medicinal Products (HMPC)	6 May 2020

Review of new data on *Filipendula ulmaria* (L.) Maxim., herba

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)

☒ Scientific/Medical/Toxicological databases: Scopus, PubMed, Embase, ToxNet

☐ 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)

– information from Member States (reporting between November 2018 and January 2019):

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

☐ Referral

☒ Ph.Eur. monograph: Filipendulae ulmariae herba 04/2013:1868

Currently: request for revision: replacement of hexane in TLC identification.

☐ 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 60 new references not yet available during the first/previous assessment were identified.

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

15 references were considered to be relevant for the assessment. From these references, only 3 are about (preparations of) the herb; in the other cases other plant parts (e.g. flowers) have been studied or the relevant plant parts are unknown/not mentioned.

The EudraVigilance database contains 6 cases. In all cases the *Filipendula* was used in combination with other herbs and drugs used.

Scientific data

10 references are related to the herb's anti-inflammatory action, 1 to its use in the treatment of common cold.

Clinical Studies

From the anti-inflammatory references, only one concerns a clinical study (Drummond *et al.*, 2013). However, it was not mentioned which parts of plant were used for the *Filipendula* extract. Moreover, this extract has only been tested in a combination preparation together with two other plant extracts. The authors concluded that the results reported are inconclusive and will have to be further evaluated.

Non–clinical studies

From the anti-inflammatory references, 9 out of 10 references concern non-clinical studies.

Two references (Pukalskienė *et al.*, 2018 and Matić *et al.*, 2015) describe genotoxic activity of *Filipendula* extracts.

Pukalskienė *et al.*, 2018: methanolic extract, part of plant not mentioned, harvested at flowering stage. Increase in a DNA damage in the comet assay. The extracts did not produce reverse mutation in bacterial cells in the Ames test and were not genotoxic in the micronucleus test. A slight though significant decrease of nuclear division index values was observed.

Matić *et al.,* 2015: methanolic extracts from the aerial parts possess weak genotoxic effects in the comet assay performed on the anterior midgut of *D. melanogaster*). However,

1. Methanol was used as extraction solvent; no methanol extract is described in the monograph.
2. Genotoxicity was not tested in accordance with relevant (ICH/OECD) guidelines:
    - Only the use of the AMES test is in accordance with the recommendations of ICH guidelines on testing of genotoxicity, the other tests (*in vitro* comet; *in vitro* micronucleus-test) are not.
    - The performed AMES test has several methodological shortcomings:

- Only 2 Salmonella strains have been used (TA98 and TA100) – according to the relevant OECD guideline for testing of chemicals (471), 5 strains are needed.
- The highest concentration they used was 250 µg/plate – according to the OECD test it should be 5000 µg/plate and as mixtures you should expect even more.
- They only performed the incorporation test and not the pre-incubation test.

Assessor's comment:

Because of the extraction solvent used in the studies is not covered by the monograph and the methodological shortcomings in the genotoxicity testing (including the AMES-test), the above-mentioned studies are considered not sufficient to justify a list entry or trigger a revision of the monograph.

Regulatory practice

No new medicinal products with *Filipendula ulmaria* (L.) Maxim., herba, as the single active substance have been reported from the Member States.

The reference to the Ph. Eur monograph on *Filipendula ulmaria* (L.) Maxim., herba (Ph. Eur. 01/2008:1868 corrected 6.0) is included as a foot note in the first version of the monograph published in 2011.

In 2013 a small revision has been implemented: in the Identification section under B the illustration of powdered herbal drug has been introduced and its legend has been integrated into the text of identification B. This means that the correct reference now should be Ph. Eur. 04/2013:1868.

The monograph is currently on the EDQM working list as there is a request for revision of the Identification section under C: replacement of hexane in TLC identification.

Assessor's comment:

No new medicinal products with Filipendula ulmaria (L.) Maxim., herba as the single active substance and no new relevant (pre-)clinical data and safety concerns are reported for Filipendula ulmaria (L.) Maxim., herba. The (expected) changes in Ph. Eur. monograph 1868 are not considered relevant for the EU herbal monograph. Therefore no revision of the monograph is proposed.

References

a) References relevant for the assessment:

Berkovitz S, Bassett P, Hughes JG. A randomised double-blind comparability study of a placebo for Individualised Western Herbal Medicine. *Complementary Therapies in Medicine* 2013; 21 (3): 195-199

Bijttebier S, Van Der Auwera A, Voorspoels S, Noten B, Hermans N, Pieters L, Apers S. A First Step in the Quest for the Active Constituents in Filipendula ulmaria (Meadowsweet): Comprehensive Phytochemical Identification by Liquid Chromatography Coupled to Quadrupole-Orbitrap Mass Spectrometry. *Planta Med* 2016; 82 (6): 559-572

Broughton A. An overview of Yellow Card reporting by NIMH practitioners. *Journal of Herbal Medicine* 2011; 1 (1):15-29

Corp N, Pendry B. The role of Western herbal medicine in the treatment of gout. *Journal of Herbal Medicine* 2013; 3 (4):157-170

Denev P, Kratchanova M, Ciz M, Lojek A, Vasicek O, Blazheva D, Nedelcheva P, Vojtek L, Hyrsl P. Antioxidant, antimicrobial and neutrophil-modulating activities of herb extracts. *Acta Biochimica Polonica* 2014; 61 (2):359-367

Drummond EM, Harbourne N, Marete E, Jacquier JC, O'Riordan D, Gibney ER. An *in vivo* study examining the antiinflammatory effects of chamomile, meadowsweet, and willow bark in a novel functional beverage. *Journal of Dietary Supplements* 2013; 10 (4):370-380

Drummond EM, Harbourne N, Marete E, Martyn D, Jacquier JC, O'Riordan D, Gibney ER. Inhibition of proinflammatory biomarkers in THP1 macrophages by polyphenols derived from chamomile, meadowsweet and willow bark. *Phytotherapy Research* 2013; 27 (4):588-594

Katanić J, Boroja T, Mihailović V, Nikles S, Pan S-P, Rosić G, Selaković D, Joksimović J, Mitrović S, Bauer R. *In vitro* and *in vivo* assessment of meadowsweet (*Filipendula ulmaria*) as anti-inflammatory agent. *J Ethnopharmacol* 2016; 193:627-636

Krenn L. Meadowsweet [Mädesüß]. *Zeitschrift fur Phytotherapie* 2011; 32 (5):241-246

Matić S, Katanić J, Stanić S, Mladenović M, Stanković N, Mihailović V, Boroja T. *In vitro* and *in vivo* assessment of the genotoxicity and antigenotoxicity of the *Filipendula hexapetala* and *Filipendula ulmaria* methanol extracts. *J Ethnopharmacol* 2015; 174:287-292

Piwowarski JP, Granica S, Zwierzyńska M, Stefańska J, Schopohl P, Melzig MF, Kiss AK. Role of human gut microbiota metabolism in the anti-inflammatory effect of traditionally used ellagitannin-rich plant materials. *J Ethnopharmacol* 2014; 155: 801-809

Pukalskienė M, Slapšytė G, Dedonytė V, Lazutka JR, Mierauskienė J, Venskutonis PR. Genotoxicity and antioxidant activity of five *Agrimonia* and *Filipendula* species plant extracts evaluated by comet and micronucleus assays in human lymphocytes and Ames *Salmonella*/microsome test. *Food and Chemical Toxicology* 2018; 113:303-313

Samardžić S, Arsenijević J, Božić D, Milenković M, Tešević V, Maksimović Z. Antioxidant, anti-inflammatory and gastroprotective activity of *Filipendula ulmaria* (L.) Maxim. and *Filipendula vulgaris* Moench. *J Ethnopharmacol 2018;* 213:132-137

Samardžić S, Tomić M, Pecikoza U, Stepanović-Petrović R, Maksimović Z. Antihyperalgesic activity of *Filipendula ulmaria* (L.) Maxim. and *Filipendula vulgaris* Moench in a rat model of inflammation. *J Ethnopharmacol* 2016; 193:652-656

Shilova IV, Khoruzhaya TG, Samylina IA. Technology and Standardization of Meadowsweet (*Filipendula ulmaria*) Extract. *Pharmaceutical Chemistry Journal* 2015; 49 (5):329-333

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 *Filipendula ulmaria* (L.) Maxim. (= *Spiraea ulmaria* L.), herba by consensus.