EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Symphytum officinale* L., radix

Rapporteur(s)	J. Wiesner
Peer-reviewer(s)	I. Chinou

HMPC decision on review of monograph *Symphytum officinale* L., radix adopted on 05 May 2015	26 January 2022
Call for scientific data (start and end date)	From 15 April 2022 to 14 July 2022
Discussion in Committee on Herbal Medicinal Products (HMPC)	July 2023 November 2023 January 2024
Adoption by Committee on Herbal Medicinal Products (HMPC)	31 January 2024

Review of new data

Periodic review (from 2015 to 2023)

Sources checked for new information:

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

☒ Scientific/Medical/Toxicological databases

A search was performed for the period of 01/2015-04/2023 in EBSCO Discovery database (Medline Complete, Pub Med, Embase, DynaMed) on 24.04.2023. Key words were "symphytum radix" or "symphytum officinale" or "comfrey" or "comfrey root", language English. Further searches were performed with additonal key words as "ames test", "clinical study", "toxicology" and "adverse events".

☒ Pharmacovigilance databases

☒ data from EudraVigilance

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

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☒ Other: EURD list

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 (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 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	☐	☒
Other	Yes	No

Summary of new references

During the review 48 new references not yet available during the first assessment were identified. Out of these new references four references were considered to be relevant for the monograph but not considered to trigger a revision of the monograph.

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

No Ph. Eur. monograph was available in 2015. No new monograph was established since then.

Assessment of new data

New scientific data that could trigger a revision of the monograph

No references were identified on toxicity studies (Ames test or animal reproductive and developmental toxicity studies). No references were identified concerning studies on clinical efficacy or adverse events.

Pharmacovigilance database EudraVigilance

A search was performed from the pharmacovigilance center of the BfArM between 01/01/2015 and 25/04/2023 in EudraVigilance; active substance: Mono; SYMPHYTUM, SYMPHYTUM OFFICINALE, SYMPHYTUM OFFICINALE ROOT, COMFREY ROOT LIQUID EXTRACT; Report Type:Spontaneous, Other, Not available to sender (unknown), Report from Studies; Characterisation: suspect, interacting.

In this period 208 cases were provided. The most frequent adverse events were skin and subcutaneous tissue disorders (for example, pruritus 42 cases, erythema 33 cases, rash 50 cases); allergic conditions 26 cases (17 cases hypersensititvity); respiratory, thoracic and mediastinal disorders 19 cases (13 dyspnoea).

Serious cases

All seven serious cases found were reported in connection to branded products containing a special Symphytum root extract not covered by the monograph.

Assessor´s comment:
The EU herbal monograph lists as adverse reactions: "None known". The evaluable reports found refer exclusively to a product that was not included in the monograph due to its special production steps. Based on the clearly different composition with regard to the medicinally active ingredient (composition, concentration) and the importance of the other ingredients, especially in the case of locally applied products, it is proposed not to change the previous statement in the monograph.

New regulatory practice that could trigger a revision of the monograph

Old/new market overview

A request for market overview was performed in Europa in April 2022. New herbal substances/preparations with 30/15 years of TU or 10 years of WEU were not identified.

Pharmacovigilance actions taken in member states

No information was provided by the member states.

Inconsistency that could trigger a revision of the monograph

New or revised public statements or other HMPC decisions that could trigger a revision of the monograph

New guidance document*: "Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs) including recommendations regarding contamination of herbal medicinal products with PAs" (EMA/HMPC/893108/2011 Rev. 1).*

It became apparent during the assessment of *Symphytum officinale* (monograph EMEA/HMPC/572844/2009) that the risk assessment of PAs poses considerable difficulties, since several PAs being regarded as both hepatotoxic and carcinogenic. Considering that PAs are natural constituents of a number of plants used for medicinal purposes, the HMPC decided to prepare a first public statement on the use of herbal preparations containing PAs (EMA, 2014). The existing monograph was established on a limit given for adults in the first version of the public statement published in 2014 (0.35 µg/day). The public statement was finalized in 07 July 2021 with a higher limit (1 µg/day).

Assessor´s comment:
No new risks result from the final version of the public statement, for the EU herbal monograph, however the monograph should be corrected to the final version of the public statement (sections 5.3 and 6).

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

The study of Savic *et al*. (2015) investigated the biological activity of pure allantoin and aqueous extract of the comfrey (*Symphytum officinale* L.) root (AECR) standardized to the allantoin content. Cell viability and proliferation of two cell lines were studied by using MTT test. Anti-irritant potential was determined in artificially irritated skin of young healthy volunteers, three and seven days after application of creams and gels with pure allantoin or AECR. The authors concluded that the biological activity of the comfrey root extract cannot be attributed only to allantoin but is also likely the result of the interaction of different compounds present in AECR.

The aim of the study of Jedlinszki *et al*. (2017) was to carry out pharmacokinetic studies on the diffusion and penetration of lycopsamine (a main PA of comfrey) from a Symphytum product through a synthetic membrane and human skin. Investigations were carried out on vertical Franz diffusion cell. Lycopsamine was quantified by a validated LC-MS method. The amount of lycopsamine diffused through a synthetic membrane varied between 0.11% and 0.72% (within 24 h). On human epidermis, the rate of penetration was lower (0.04-0.22%).

The study of Plaza *et al*. (2022) investigated to what extent PAs are bioavailable following topical exposure, assessing penetration of retronecine-type PAs in an in vitro human skin model. A single comfrey root formulation was spiked with three different congeners and percutaneous absorption was

measured. The measured penetration for all three PAs was low and compared favourably with existing in vitro data. These data was seen by the authors to facilitate the understanding of absorption differences following topical exposure, which in turn can be taken into account in the risk assessment.

In the study of Trifan *et al*. (2023) different PA-/mucilage-depleted/undepleted comfrey root extracts were subjected to detailed phytochemical characterization (LC-HRMS/MS) and biological evaluation. Antioxidant and enzyme inhibitory activity was determined by in vitro free radical scavenging and several enzymatic assays. The PA-depleted materials contained PAs levels below 2 ppm, whereas the removal of mucilage increased the content of rosmarinic acid, globoidnan A, globoidnan B, and rabdosiin. Neither PA-depletion nor mucilage-depletion had considerable effects on the in vitro inhibitory activity of cholinesterases, tyrosinase, amylase, and glucosidase or release of ex vivo pro-inflammatory cytokines (e.g., IL-1β, IL-8, and TNF-α) in LPS-stimulated neutrophils.

References

Jedlinszki N, Balázs B, Csányi E, Csupor D. Penetration of lycopsamine from a comfrey ointment through human epidermis. *Regul Toxicol Pharmacol* 2017, 83:1-4. doi: 10.1016/j.yrtph.2016.11.015

Plaza A, Toner F, Harris J, Ottersbach P, Roper C, Mahony C. Support for Regulatory Assessment of Percutaneous Absorption of Retronecine-type Pyrrolizidine Alkaloids through Human Skin. *Planta Med* 2022, 88(2):144-151. doi: 10.1055/a-1505-8524

Savić VLj, Nikolić VD, Arsić IA, Stanojević LP, Najman SJ, Stojanović S *et al*. Comparative Study of the Biological Activity of Allantoin and Aqueous Extract of the Comfrey Root. *Phytother Res* 2015, 29(8):1117-1122

Trifan A, Czerwińska ME, Zengin G, Esslinger N, Grubelnik A, Wolfram E *et al*. Influence of pyrrolizidine alkaloids depletion upon the biological activity of *Symphytum officinale* L. extracts. *J Ethnopharmacol* 2023, 303:116010. doi: 10.1016/j.jep.2022.116010

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

A correction of the EU herbal monograph is suggested to include the PA limits of the Final *"Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs) including recommendations regarding contamination of herbal medicinal products with PAs" (EMA/HMPC/893108/2011 Rev. 1)* in sections 5.3 and 6.

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