20 September 2023
EMA/HMPC/320997/2023
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Sideritis scardica* Griseb.*; Sideritis clandestina* (Bory & Chaub.) Hayek*; Sideritis raeseri* Boiss. & Heldr.*; Sideritis syriaca* L.*,* herba

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HMPC decision on review of monograph *Sideritis scardica* Griseb.*; Sideritis clandestina* (Bory & Chaub.) Hayek*; Sideritis raeseri* Boiss. & Heldr.*; Sideritis syriaca* L.*,* herba adopted on 2 February 2016	26 January 2022
Call for scientific data (start and end date)	From 13 April 2022 to 14 July 2022
Discussion in Committee on Herbal Medicinal Products (HMPC)	May 2023 July 2023 September 2023
Adoption by Committee on Herbal Medicinal Products (HMPC)	20 September 2023

Review of new data

Periodic review (from 2016 to 2023)

Sources checked for new information:

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

☒ Scientific/Medical/Toxicological databases

Scientific data of the period 2016 -2023 was reviewed using Google Scholar browsing machine and sources available in library of PubMed, Reaxys, SciFinder, Scopus, The Cochrane Library,

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ScienceDirect. Search terms "Sideritis + herba", "Irowort herb", "Sideritis + scardica", "Sideritis + clandestina", "Sideritis + raeseri", "Sideritis + syriaca"

☒ Pharmacovigilance databases

☒ data from EudraVigilance (access 18.07.2023)

☒ from other sources (e.g. data from VigiBase; National sources, access 18.07.2023)

☐ 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 (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	☐	☒

Summary of new references

During the review 46 new references not yet available during the first/previous assessment were identified. Out of these new references, none were considered to be relevant for the monograph.

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

Not applicable.

New regulatory practice that could trigger a revision of the monograph

There are no new herbal substances/preparations with 30/15 years of TU or 10 years of WEU.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other issues that could trigger a revision of the monograph

Nor applicable.

New information not considered to trigger a revision at present but that could be relevant for the next review

In the study by Moussavi *et al.* (2022) *in vitro* anti-inflammatory effects of extracts and polyphenols (together with eleven isolated phenolic compounds) of *Sideritis scardica* Griseb. have been explored, with focus on neurodegenerative disease. The extracts and isolated compounds were assessed for immunomodulatory, enzyme-interacting and cytotoxic properties. The results revealed a broad-spectrum activity, which might potentially serve as a multi-target system in Alzheimer's disease, after further adequate studies.

In another study by Feistel *et al.* (2018), has been investigated the single and repeated-dose oral toxicity of a *Sideritis scardica* Griseb. 20% (V/V) ethanol extract in Sprague Dawley rats, and mutagenicity using the Ames test. No gross pathological abnormalities and no toxicity signs or mortality were detected in animals treated with the dose of 2000 mg/kg bw during 14 days of observation. To evaluate a repeated-dose toxicity, an extract has been tested over a 28-day period followed by a 14-day recovery period. No mortality and no changes in body/organ weight or food consumption have been observed. The no-observed-adverse-effect-level of the extract was determined at 1000 mg/kg bw. The results of Ames tests conducted on extracts of different polarity (water; 20% (V/V) ethanol; 50% (V/V) ethanol; n-heptane), were unequivocally negative. The study revealed no

toxicity of *Sideritis scardica* Griseb. and no concerns for its mutagenic effects, supporting its positive safety profile, and confirms the acknowledged traditional medicinal use in human.
Sideritis scardica Griseb. together with *Sideritis euboea* (which is not included in the MO) were studied recently *in vivo*, regarding their potential effects on cognition in APP-transgenic and aged, nontransgenic C57Bl/6 mice. Concluding, that daily oral treatment with *Sideritis* spp. extracts enhanced cognition in *in vivo* experiment on aged, non-transgenic as well as in APP-transgenic mice, an effect that was even more pronounced when extracts of both species were applied in combination. (Hofrichter *et al.,* 2022).

No records appeared during the search on Eudravigilance and VigiLyze.

Assessor's comment:

None of the new references are considered to be relevant for the EU herbal monograph on Sideritis scardica Griseb., Sideritis clandestina (Bory & Chaub.) Hayek, Sideritis raeseri Boiss. & Heldr. and Sideritis syriaca L., herba. Moreover, no records appeared during the search on Eudravigilance and Vigibase.

References

References that could be relevant for the next review:

Feistel B, Wegener T, Rzymski P, Pischel I. Assessment of the acute and subchronic toxicity and mutagenicity of *Sideritis scardica* Griseb. extracts. *Toxins* 10(7), 2018, 258

Hofrichter J, Krohn M, Schumacher T, Lange C, Feistel B, Walbroel B, *et al*. *Sideritis* spp. extracts enhance memory and learning in Alzheimer's β-amyloidosis mouse models and aged C57Bl/6 mice. *Journal of Alzheimer's disease* 53(3), 2016, 967-80

Moussavi N, Azizullah H, Malterud KE, Inngjerdingen KT, Wangensteen H. Immunomodulating polyphenols from *Sideritis scardica*. *Journal of Functional Foods 96*, 2022, 105197

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