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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Peumus boldus* Molina, *folium*

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HMPC decision on review of monograph *Peumus boldus* Molina, folium adopted on 22 November 2016	31 January 2024
Call for scientific data (start and end date)	From 01 March 2024 to 31 May 2024
Discussion in Committee on Herbal Medicinal Products (HMPC)	July 2024 September 2024
Adoption by HMPC	25 September 2024

Review of new data

Periodic review (from 2016 to 2024)

Sources checked for new information:

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

☒ Scientific/Medical/Toxicological databases

PubMed: Search period was set from June 2016 until June 2024. Search terms: "Peumus boldus" (65 references found), "boldo" (135 references), "Peumus boldus" plus "liver" (10 references), "Peumus boldus" plus "pharmacology" (34 references).

☒ 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 (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 135 new references not yet available during the first/previous assessment were identified, the majority of them not being relevant for the assessment of the safety or efficacy of boldo leaf.

During the call of data period, no data were provided by interested parties.

Assessment of new data

New scientific data that could trigger a revision of the monograph

Adverse event(s) or other safety data: A search was performed in EVDAS (EudraVigilance) database in June 2024 with the Key word "Peumus boldus" and nine cases were reported. In four cases, patients were receiving combination herbal products with a different number of herbals, together with three or more other medicinal products to treat different diseases such as diabetes or bacterial pneumoniae. Adverse effects included myalgia and vomiting, among others. None of these cases were directly related to the use of *Peumus boldus* leaf. In three other cases no relevant information was given and in another case, the patient referred to the misuse of three different herbal medicinal products (boldo, California poppy and fucus).

Another search was performed in EudraVigilance and Vigibase databases in June 2024. Key words were "Peumus boldus", "interaction". The search revealed six cases, including the case reports. Three reports referred to the same case with the following MeaDRA terms: vaginal haemorrhage, drug interaction and international normalised ratio increased.

Several individual case reports have also been published regarding liver injury or hepatotoxicity in elderly patients with biliary tract disorders. Adverse effects are weakness, anorexia and jaundice (Oliveira *et al*., 2020; Ribeiro *et al.,* 2017). Although the authors determined boldo was the probable cause of liver injury, they did not include a causality assessment score and thus it could not be classified as directly related to the adverse effects.

Assessor's comment: No clinical studies or new safety concerns related to the use of Peumus boldus Molina, folium were found. Thus, no new relevant data have been found which could affect the existing EU herbal monograph. The adverse events retrieved from the pharmacovigilance database and published case reports were mostly i) due to misuse of these preparations, ii) use of different combination products and/or simultaneous use with three or more synthetic medicinal products for the treatment of several different diseases. In all cases the exerted adverse reactions cannot be attributed to the intake of Boldi folium

As a result of this review, no revision is considered required.

New regulatory practice that could trigger a revision of the monograph

There are no new products in the EU market containing *Peumus boldus* Molina*, folium* as the single active substance out of those already included in the existing monograph.

Inconsistency that could trigger a revision of the monograph

Not applicable.

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

Taking in account that spontaneous case reports have been published regarding hepatotoxicity or liver injury and the use of boldo preparations (i.e. Oliveira *et al*., 2020 and Ribeiro *et al*., 2017), it seems to be relevant to assess the possibility of new case reports in the future.

References

Oliveira Sá A, Pimentel T, Oliveira N. Boldo-Induced Hepatotoxicity: A Case of Unexplained Jaundice. *Eur J Case Rep Intern Med*. 2020, 27;7(12):002116. doi:10.12890/2020_002116

Ribeiro RJ, Silvestre C, Duarte C. Hidden Risks of Alternative Medicines: A Case of Boldo-Induced hepatotoxicity. *J Diet Suppl*. 2017, 4;14(2):186-190. doi:10.1080/19390211.2016.1207123. Epub 2016 August 30

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