



26 January 2022  
EMA/HMPC/681054/2021  
Committee on Herbal Medicinal Products (HMPC)

## Addendum to Assessment report on *Fucus vesiculosus* L., thallus

Rapporteur(s)	O. Palomino
Peer-reviewer	J. Wiesner

HMPC decision on review of monograph <i>Fucus vesiculosus</i> L., thallus adopted on 06 May 2014	15 January 2020
Call for scientific data (start and end date)	From 01 March 2020 to 31 May 2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	26 January 2022

### Review of new data on *Fucus vesiculosus* L., thallus

#### Periodic review (from 2016 to 2021)

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. Search period was set from January 2016 to November 2021. The following key words were used "Fucus", "Bladderwrack", efficacy or safety. 16 and 20 references were found, respectively.
- 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)
- Referral
- 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 (i.e. likely to lead to a relevant change of the monograph)**

<i>Scientific data</i>	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical safety data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New data introducing a possibility of a new list entry	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical studies introducing a possibility for new WEU indication/preparation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other scientific data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Regulatory practice</i>	Yes	No
New herbal substances/preparations with 30/15 years of TU	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New herbal substances/preparations with 10 years of WEU	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other regulatory practices likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Referrals likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Consistency</i>	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other relevant inconsistencies that require a change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>

**Summary and conclusions on the review**

During the review, 13 new references not yet available during the first/previous assessment were identified. Nine among them referred to the efficacy (clinical studies) of herbal preparations containing bladderwrack or fucoidan from *Fucus vesiculosus* on the treatment of metabolic syndrome, atopic dermatitis or osteoarthritis.

**Scientific data**

Clinical efficacy:

Two reviews on the efficacy of brown seaweeds in the prevention or management of metabolic syndrome have been published (Keleszade *et al.*, 2021; Gabbia & De Martin, 2020). These reviews included some clinical studies demonstrating the beneficial potential of brown seaweeds in this area. It is important to note that all studies showing positive results were conducted with a combination of two species: *Ascophyllum nodosum* and *Fucus vesiculosus* (Paradis *et al.*, 2011; Haskell-Ramsay *et al.*, 2018; Derosa *et al.*, 2019; De Martin *et al.*, 2018). The same situation can be found in the observational study by Nicolucci *et al.* (2021). Only one of the studies included in the review was conducted with a polyphenol-rich *F. vesiculosus* extract; in this study, no effects on the postprandial

peak of glycemia and plasma insulin with respect to placebo were observed; also different insulin sensitivity in Asian subjects was observed (Murray *et al.*, 2018).

The randomized placebo-controlled trial conducted by Myers *et al.* (2016) studied the effects of an extract from *Fucus vesiculosus* (85% fucoidan) in reducing symptoms of osteoarthritis (OA). A 12-week period treatment showed no significant reduction in symptoms of OA when compared to placebo group.

*Assessor's comment:*

*None of these references were considered to be relevant to justify a revision of the monograph as the quality of the studies is low (small number of patients, short duration...) and the results cannot always be referred to the administration of Fucus vesiculosus itself. Furthermore, the medicinal products corresponding to the indications described in the clinical studies are not reported from the EU market and the assayed indications could not be considered for traditional use (public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in Community herbal monographs, EMA/HMPC/473587/2011, 13 September 2011).*

#### Clinical safety:

Three references (Bovet *et al.*, 2019; Ventura *et al.*, 2020; Zhang *et al.*, 2020) were linked to bladderwrack safety when administered with other drugs, in cancer treatment or for the attenuation of doxorubicin-induced acute cardiotoxicity. No references on fucus-own toxicity were found.

The Drugs and Lactation Database (2021) published a report on the use of *F. vesiculosus* during lactation. Authors explained that, although iodine is a normal component of human milk, no data exist on the excretion of any organic components of seaweed into breastmilk. Iodine and heavy metals, which are also present in bladderwrack, are excreted into milk. Thus, the recommendation is not to use seaweed during breastfeeding because of its high iodine content and potential contamination with heavy metals.

*Assessor's comment:*

*No new safety data regarding F. vesiculosus have been found during the review. The recommendation of not using F. vesiculosus preparations during lactation was already included in section 4.6 of the original monograph.*

#### Eudravigilance data:

Pharmacovigilance data obtained from the EudraVigilance Database showed 12 individual reports between 2016 and 2021. The severity of the cases was high in six cases: five of them referred to the intake of one homeopathic preparation and the sixth one was related to a food supplement; all products were combination products used for weight control.

Six individual cases (low severity) were related to the use of a registered product containing *Rhamnus frangula*, *Rhamnus purshianus* and *Fucus vesiculosus*; adverse events were abdominal pain, diarrhoea and hypersensitivity, which resolved after discontinuation of the treatment.

*Assessor's comment:*

*No new safety data have been found regarding bladderwrack toxicity. The reports found in Eudravigilance Database were related to homeopathic preparations or combination products, which are not covered by the monograph.*

In summary, no new relevant clinical studies or new safety concerns related to the use of *Fucus vesiculosus* L., thallus were found. There are no new products in the EU market containing *F. vesiculosus* L., thallus as the single active substance.

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

13 references were considered to be relevant for the assessment.

No references justify a revision of the monograph.

In view of all the above explained data, no revision is considered required.

## References

a) References relevant for the assessment:

Bovet L, Samer C, Daali Y. Preclinical evaluation of safety of fucoidan extracts from *Undaria pinnatifida* and *Fucus vesiculosus* for use in cancer treatment. *Integr Cancer Ther* 2019, 18:1534735419876325, in press, doi: 10.1177/1534735419876325.

De Martin S, Gabbia D, Carrara M, Ferri N. The brown algae *Fucus vesiculosus* and *Ascophyllum nodosum* reduce metabolic syndrome risk factors: A clinical study. *Nat Prod Commun* 2018, 13:1691-1694

Derosa G, Cicero AFG, D'Angelo A, Maffioli P. *Ascophyllum nodosum* and *Fucus vesiculosus* on glycemic status and on endothelial damage markers in dysglycemic patients. *Phytother Res* 2019, 33:791-797

Drugs and Lactation Database (LactMed) [Internet]. *Bethesda (MD): National Library of Medicine (US)*, 2006, Seaweed, [Updated 2021 Feb 15]

Gabbia D, De Martin S. Brown seaweeds for the management of metabolic syndrome and associated diseases. *Molecules* 2020, 25(18):4182, in press, doi: 10.3390/molecules25184182

Haskell-Ramsay CF, Jackson PA, Dodd FL, Forster JS, Bérubé J, Levinton C, *et al.* Acute post-prandial cognitive effects of brown seaweed extract in humans. *Nutrients* 2018, 10:85

Keleszade E, Patterson M, Trangmar S, Guinan KJ, Costabile A. Clinical efficacy of brown seaweeds *Ascophyllum nodosum* and *Fucus vesiculosus* in the prevention or delay progression of the metabolic syndrome: a review of clinical trials. *Molecules* 2021, 26(3):714, in press, doi: 10.3390/molecules26030714

Murray M, Dordevic AL, Ryan L, Bonham MP. The impact of a single dose of a polyphenol-rich seaweed extract on postprandial glycaemic control in healthy adults: a randomised cross-over trial. *Nutrients* 2018, 10:270

Myers SP, Mulder AM, Baker DG, Robinson SR, Rolfe MI, Brooks L, *et al.* Effects of fucoidan from *Fucus vesiculosus* in reducing symptoms of osteoarthritis: a randomized placebo-controlled trial. *Biologics* 2016, 10:81-8, in press, doi: 10.2147/BTT.S95165

Nicolucci A, Rossi MC, Petrelli M. Effectiveness of *Ascophyllum nodosum* and *Fucus vesiculosus* on metabolic syndrome components: a real-world, observational study. *J Diabetes Res* 2021:3389316, in press, doi: 10.1155/2021/3389316

Paradis ME, Couture P, Lamarche B. A randomised crossover placebo-controlled trial investigating the effect of brown seaweed (*Ascophyllum nodosum* and *Fucus vesiculosus*) on postchallenge plasma glucose and insulin levels in men and women. *Appl Physiol Nutr Metab* 2011, 36:913-919

Ventura S, Rodrigues M, Falcão A, Alves G. Safety evidence on the administration of *Fucus vesiculosus* L. (bladderwrack) extract and lamotrigine: data from pharmacokinetic studies in the rat. *Drug Chem Toxicol* 2020, 43(6):560-566, in press, doi: 10.1080/01480545.2018.1518454

Zhang J, Sun Z, Lin N, Lu W, Huang X, Weng J, *et al.* Fucoidan from *Fucus vesiculosus* attenuates doxorubicin-induced acute cardiotoxicity by regulating JAK2/STAT3-mediated apoptosis and autophagy. *Biomed Pharmacother* 2020, 130:110534, in press, doi: 10.1016/j.biopha.2020.110534

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 *Fucus vesiculosus* L., thallus, by consensus.