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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Vitis vinifera* L., folium

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HMPC decision on review of monograph *Vitis vinifera* L., folium adopted on 30 May 2017	31 January 2024
Call for scientific data (start and end date)	From 01 April 2024 to 30 June 2024
Discussion in Committee on Herbal Medicinal Products (HMPC)	September 2024 November 2024 January 2025 March 2025 May 2025
Adoption by HMPC	07 May 2025

Review of new data

Periodic review (from 2018 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 was searched on July and September 2024; period covered: until September 2024,

Search terms: Vitis vinifera L., folium grapevine leaf efficacy and/or safety

☒ Pharmacovigilance databases

☒ data from EudraVigilance

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

☐ Other

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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 (to be published in 2025)

☐ 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

Other

☒ Request to introduce an herbal preparation

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
Request on behalf of an Interesting Party (European Company) suggesting to introduce an herbal preparation (dry extract (DER 4-6:1) extraction solvent water, identical to an existing one under WEU, with the same administration route (orally), with an existing indication, until now proposed only cutaneously.	☐	☒

Summary of new references

During the review, 295 new references, further filtered to 58 most relevant, not yet available during the previous assessment were identified. None of these new references were considered to be relevant for the monograph and/or could trigger revision of the monograph.

The search in pharmacovigilance databases revealed no serious case report.

Moreover, no new indications, herbal preparations and dosages were identified, towards the existing therapeutic indication in the adopted monograph.

As referred above, during the Call for data an Interested Party (a European company) requested to add the herbal preparation dry extract (DER 4-6:1) extraction solvent water, under TU with proposed indication 'symptomatic relief of itching and burning associated with haemorrhoids, after serious conditions have been excluded by medical doctor'.

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

The EU herbal monograph has been based to the monograph of French Pharmacopoeia since 1996, where spectrophotometric assay has been used with similar definition on VIGNE ROUGE/*Vitis vinifera* dried leaf harvested after fructification, when the leaves are red. Content:

– total polyphenols: min 4.0% and **–** anthocyanosides, expressed as cyanidin 3-O-glucoside ($C_{21}H_{21}O_{11}$; Mr 449.4): min 0.2% (dried drug).

A monograph on *Vitis vinifera* l., folium with an HPLC assay, has now been developed by the Ph. Eur. and will be published in April 2025 (2025: 2667).

Grapevine leaf definition is: dried leaf of *Vitis vinifera* L. harvested after fructification, when the leaves are red. Content:

– total flavonols, expressed as isoquercitroside ($C_{21}H_{20}O_{12}$; Mr 464.4): min 1.5% (dried drug);

– anthocyanosides, expressed as cyanidin 3-O-glucoside ($C_{21}H_{21}O_{11}$; Mr 449.4): min 0.4% (dried drug).

Assessor's comment:

The current monograph and supporting documents are based on the French Pharmacopoeia. The Ph. Eur. uses a different assay-methods and has different limits for the maker content. The difference *between the Ph. Eur. and French Pharmacopoeia does not trigger a revision.*

Inconsistency that could trigger a revision of the monograph

Not applicable

Other issues that could trigger a revision of the monograph

Several among new references focused to chemical studies on polyphenols' content on the grapevine leaf extracts (Armari *et al*., 2024), with antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory properties and their potential exploitation against infectious and inflammatory skin and scalp diseases, as well as to different ways of grapevine leaf extractions' bioactive metabolites (Mastellone *et al*., 2020).

The antioxidant and the DNA protective potentials of *Vitis vinifera* L. water extract against UV-A and UV-B radiation in HaCaT cells, a human keratinocytes cell line has been also studied showing antioxidant and scavenger activity on the UV-A, while the maintenance of the apoptosis with both UV-A and UV-B has been evaluated as potential anti-mutagenic effect (Marabini *et al*., 2020).

In a study by Zanella *et al.* (2021), the phenolic composition and antiviral activity of *V. vinifera* leaf extract against two human viruses: the herpes simplex virus type 1 (HSV-1) and the pandemic coronavirus 2 (SARS-CoV-2) have been studied. About 40 phenolic compounds were identified in the extract by HPLC-MS/MS analysis. Leaf extract was able to inhibit both HSV-1 and SARS-CoV-2 replication in the early stages of infection by directly blocking the proteins enriched on the viral surface, at a low concentration of 10 µg/mL.

In a recent overview, the rate of adverse events after venoactive drug (VAD) prescription and subsequent compliance and switching rates have been analysed in South Korea, using the National Health Insurance Service database, between 01/2009 and 12/2019, having included 1,551,212 patients. The adverse events, compliance, and switching rates with 8 venoactive drugs, including *V. vinifera* extract, *V. vinifera* leaf extract, naftazone, micronized purified flavonoid fraction, diosmin, diobsilate calcium, bilberry fruit dried extract, and sulodexide have been analysed. The most commonly prescribed VAD was *V. vinifera* extract (72.2%), followed by sulodexide (9.3%), and *V. vinifera* leaf dry extract (8.2%). Adverse event rates were significantly higher in the *V. vinifera* leaf dry extract group ($p = 0.009$) mostly, urticaria and gastrointestinal disturbances but in fact, the drugs were relatively well tolerated, and the adverse events were not serious (Kim *et al*., 2023).

Adverse event(s) or other safety data: A search was performed in EudraVigilance data base.
For the *V. vinifera* soft extract (DER 2.5 - 4:1) extract solvent water, for cutaneous use, several case of pruritus, rash, erythema and burning sensation have been reported. While for the dry extract of *V. vinifera* (DER 4-6:1) extract solvent water, for oral use, also several cases of adverse reactions have been recorded such as pruritus, rash, erythema, nausea, burning sensation, gastrointestinal pain, abdominal discomfort etc. These cases were related to the use of *Vitis vinifera* leaf extracts (in some cases as main component and in others in concomitant uses with other synthetic drugs – such as levothyroxin, clopidogrel, adenocoumaril, furosemide, lorazepam, etc. or with multivitamins and food supplements (ginkgo, cranberries, etc) was considered as mostly not serious and very rare serious adverse events (AEs). In some cases, elderly patients (older than 80 years of age) with existing cardiac problems had more serious problems. The special warnings and precautions for use (see

section 4.4.) as well as the undesirable effects (see section 4.8.) of the existing EU herbal monograph and supporting documents, are covering the recorded cases.

There are no new products on the market containing *Vitis vinifera* folium which could trigger a revision of the monograph.

An Interested Party (a European company) requested to add the herbal preparation dry extract (DER 4-6:1) extraction solvent water, under TU with the proposed indication 'symptomatic relief of itching and burning associated with haemorrhoids, after serious conditions have been excluded by medical doctor'. This is not a new product as it was already assessed and discussed during the establishment of the monograph in 2018.

Assessor's comment:
These adverse events are related mainly to V. vinifera soft extract (DER 2.5 - 4:1) extract solvent water and/or V. vinifera dry extract (DER 4-6:1) extract solvent water, products in which Vitis extracts were partially the main component while in other cases were in concomitant use with other drugs. Almost all reported not serious adverse events (AEs) are covered by the already adopted in the monograph precautions for use and undesirable effects.

The proposal from the Interested Party has been addressed, while in a similar request previously stated during the establishment of the monograph (Overview of Comments received on European Union herbal monograph on Vitis vinifera L., folium (EMEA/HMPC/16635/2009)), to introduce the same preparation, as now proposed - dry extract (DER 4-6:1) extraction solvent water for oral use under TU - had already been discussed during the establishment of the monograph (it was not endorse to include this extract under TU). Meanwhile, the suggested preparation has been withdrawn from the EU market. Therefore, the proposal of the interested party is not endorsed.

No revision is considered required because there are no new products on the market and no new scientific data related to non-clinical and clinical safety or clinical efficacy which could trigger a revision.

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

Not applicable

References

a) References relevant for the assessment

Armari M, Zavattaro E, Trejo CF, Galeazzi A, Grossetti A, Veronese F, *et al*. *Vitis vinifera* L. leaf extract, a microbiota green ally against infectious and inflammatory skin and scalp diseases: an in-depth update. *Antibiotics*. 2024; 13(8): 697. https://doi.org/10.3390/antibiotics13080697

Kim H, Cho S, Lee K, Lee SH, Joh JH. A nationwide study of compliance of venoactive drugs in chronic venous disease patients. *Ann Surg Treat Res* 2023;104(5):288-295

Marabini L, Melzi G, Lolli F, Dell'Agli M, Piazza S, Sangiovanni E, *et al*. Effects of *Vitis vinifera* L. leaves extract on UV radiation damage in human keratinocytes (HaCaT). *Journal of Photochemistry and Photobiology B: Biology*, 2020, 204, 111810

Mastellone G, Pacheco-Fernández I, Rubiolo P, Pino V, Cagliero C. Sustainable micro-scale extraction of bioactive phenolic compounds from *Vitis vinifera* leaves with ionic liquid-based surfactants. *Molecules* 2020, 25, 3072; doi: 10.3390/molecules25133072

Zannella C, Giugliano R, Chianese A, Buonocore C, Vitale GA, Sanna G, *et al*. Antiviral activity of *Vitis vinifera* leaf extract against SARS-CoV-2 and HSV-1. *Viruses*. 2021; 13(7):1263. https://doi.org/10.3390/v13071263

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

☐ 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