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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Juglans regia L.*, folium

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HMPC decision on review of monograph *Juglans regia L.,* folium adopted on 09 July 2013	13 January 2021
Call for scientific data (start and end date)	From to 01 March 2021 to 31 May 2021
Discussion in Committee on Herbal Medicinal Products (HMPC)	September 2021 November 2021 January 2022 March 2022 July 2022
Adoption by Committee on Herbal Medicinal Products (HMPC)	20 July 2022

Review of new data on *Juglans regia* L., folium

Periodic review (from 2013 to 2021)

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

☒Pharmacovigilance data (data from EudraVigilance, national databases)

☒ Scientific/Medical/Toxicological databases: Embase, Medline, Pubmed, Toxline. Search period from 2013 to 2021 September

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Key words: Juglans regia safety, Juglans regia efficacy 967 references were found, 5 references were selected

☐ 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

☐ 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)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change 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 likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change 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	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒

Summary and conclusions on the review

During the review, 967 new references not yet available during the first assessment were identified. Five references were considered to be relevant for the review assessment.

During the review, no new information on quality had been identified.

No references were provided by interested parties during the Call for data.

New nonclinical safety data

Three new nonclinical studies were identified: one *in vitro* experiment that highlighted the anti-proliferative and apoptotic activities of constituents of chloroform extract of *Juglans regia* leaves (Salimi M *et al*., 2014), and 2 *in vivo* studies that investigated the protective effects of methanolic extract of *Juglans regia* L. leaf, on streptozotocin-induced diabetic peripheral neuropathy in rats (Nasiry D *et al.*, 2017) and the hepatoprotective effects of *Juglans regia* extract against CCl4-induced oxidative damage in rats (Eidi A *et al.*, 2013*).*

Assessor's comment: The only herbal preparation included in the EU herbal monograph of Juglans regia L., folium corresponds to comminuted herbal substance. Therefore, the studies identified were not deemed relevant to justify a revision of the monograph.

Clinical efficacy data

Two clinical trials conducted in Iran have shown a significant hypoglycemic effect using *Juglans* leaves as aqueous extract in diabetic patients (Abdoli M *et al*., 2017; Hosseini S *et al*., 2014). The insufficient sample sizes used during these studies and the bias in the analysis will need further clinical studies. This would confirm the conclusions about the efficacy and safety of this herb. However, the potential presence of juglone in the extracts for oral use is not acceptable.

Assessor's comment: No revision is considered required because medicinal products corresponding to the indications described in the above-mentioned clinical studies are not reported from the EU market. Therefore, the well-established use criteria are not fulfilled.

Clinical safety data

The overall review of pharmacovigilance data obtained from EudraVigilance (from 15 July 2013 to 15 September 2021) showed 70 case reports related to *Juglans regia,* including oral intake of food supplement or homeopathic products. Out of those cases, 15 have been declared as serious and appeared after skin-tests or injections of immunotherapy products but none of them contained *Juglans regia* L., folium.

Assessor comments: No causal link could be established between any adverse events and herbal medicinal products containing Juglans regia L., folium.

In conclusion, no revision of the EU herbal monograph is considered required because no new data on safety or acceptable new indications in clinical studies were highlighted.

References

a) References relevant for the assessment:

Abdoli M, *et al*. Anti-hyperglycemic effect of aqueous extract of *Juglans regia* L. leaf (walnut leaf) on type 2 diabetic patients: A randomized controlled trial. *Advances in Integrative Medicine* 2017, 4(3):98-102

Eidi A, *et al*. Hepatoprotective effects of *Juglans regia* extract against CCl4-induced oxidative damage in rats. *Pharm Biol* 2013, 51(5):558-565

Hosseini S, *et al*. The hypoglycemic effect of *Juglans regia* leaves aqueous extract in diabetic patients: A first human trial. *Daru* 2014, 22(1):19

Nasiry D, *et al.* Protective effects of methanolic extract of *Juglans regia* L. leaf on streptozotocin-induced diabetic peripheral neuropathy in rats. *BMC Complementary and Alternative Medicine* 2017, 17 (1):476

Salimi M, *et al*. Anti-proliferative and apoptotic activities of constituents of chloroform extract of *Juglans regia* leaves. *Cell Prolif* 2014, 47(2):172-179

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